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# Prevalence of Stress and its Association with Body Weight among the Medical Students of Jorhat Medical College and Hospital, Jorhat

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## Abstract

**Introduction:** Medical students undergo tremendous stress during various stages of the medical education. Psychosocial stress has been implicated as a risk factor for high blood pressure, cardiovascular disease, and even cancerous conditions. Stress may lead to changes in dietary habit that may lead to weight change.

**Aim and Objectives:** This study was carried out to determine the prevalence of perceived stress among medical students and to observe any possible association between the levels of stress and (a) gender, (b) body mass index (BMI).

**Methods:** The questionnaire consisted of 10 questions were used to measure the stress (perceived stress scale). The completed form was analyzed to obtain perceived stress score. Higher the score index, higher will be the level of stress. Weight and height were measured by standard techniques.

**Result:** The prevalence of highly stressed students in our study is 36.2% and that of very highly stressed students is 39.1%. For simplicity, if we combine highly and very highly stressed level as stressed and average and low level as nonstressed students, then overall prevalence of stress will be 75.3% in the study. In this study, we have not found any significant difference in prevalence of stress among male and female. The prevalence rate of obese (03.6%) and overweight (15.9%) is not very high. But found a strong correlation between psychological stress and body weight.

**Conclusion:** We can conclude that prevalence rate of stress is very high among the medical students of Jorhat medical college but without any significant difference between male and female. The prevalence rate of obese and overweight is not very high but there is a strong correlation between stress and BMI, greater the psychosocial stress more is the body weight.

**Key words:** Body mass index, Medical students, Obese, Overweight, Psychosocial stress, Stress

## INTRODUCTION

It is usually observed that medical students undergo tremendous stress during various stages of the medical education. It characterized many psychological changes in students.<sup>1</sup> High levels of stress may have a negative effect on physical and mental health of the medical students. This can lead to mental distress and has a negative effect

on attentive functioning and learning<sup>2</sup> psychosocial stress has been implicated as a risk factor for high blood pressure, cardiovascular disease, and cancer.<sup>1-7</sup> The association between stress and weight gain is less clear. Stress may lead to changes in dietary habit that lead to weight change with various effects related to sex,<sup>8-10</sup> body mass index (BMI)<sup>11</sup> in response to stress.<sup>12,13</sup> These factors may cause some people to gain more weight under stressful circumstances while others may gain less weight or even lose weight when stressed.

Study of Firth in three British universities in 1986 showed that the prevalence of stress was 31.2%.<sup>3</sup> Study of Sherina *et al.*<sup>4</sup> and Saipanish<sup>5</sup> showed that the prevalence of stress was 41.9% and 61.4% in a Malaysian and Thai medical school, respectively. Study of Assadi *et al.* showed that the

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prevalence of psychiatric disorders among Iranian medical students was 44%. Medical school stress probably may later lead to mental health problems but students rarely ask for help for their problems. Dahlin *et al.* showed that the prevalence of depressive symptoms among Swedish students was 12.9% and a total of 2.7% of students had made suicidal attempts.<sup>2</sup> It is important for medical educators to pay attention and know the prevalence and causes of students' distress, which not only affects their health but also their academic achievement and future career. However, such studies are less done in Jorhat, Assam. Hence, this study was carried out to determine the prevalence of perceived stress among medical students and to observe its association with gender, obesity.

### Aim and Objectives

This study was carried out to determine the prevalence of perceived stress among medical students and to observe any possible association between the levels of stress and (a) gender, (b) BMI.

## MATERIALS AND METHODS

This study was conducted in the Department of Physiology of Jorhat Medical College, Jorhat, Assam.

The participants were interviewed and information regarding age, sex, exercise profile, and sleeping hours were collected using questionnaire.

A written informed consent was obtained from all the participants who responded to the questionnaire survey. The study protocol was approved by the institutional ethics committee before the start of the study.

A total of 138 medical students of first to final year MBBS were selected randomly for this study. The students who are already diagnosed as having some psychological ailments and under medication were excluded from this study.

The questionnaire consisted of 10 questions were used to measure the stress (perceived stress scale). The completed form was analyzed to obtain perceived stress score. Higher the score index, higher will be the level of stress.<sup>6</sup>

Weight and height were measured by standard techniques. Weight was measured using normal weighing scale with no shoes. Height was recorded using a measuring tape with the individual standing straight next to the wall with the heels, buttocks, shoulders, and occiput touching the wall without shoes. BMI was calculated using the formula weight (kg)/height<sup>2</sup> (m<sup>2</sup>) BMI <18.5 was considered as underweight, <25 was considered normal, 25-29.9 was overweight and 30 or above obese.<sup>7</sup>

Statistical analysis-SPSS Version 16 was used for all data processing and analysis. Independent sample *t*-test was done for comparison of two variables and correlation coefficient was calculated to see the presence of significant correlation.

## RESULTS AND OBSERVATIONS

Total 138 medical students were examined. Out of these 74 (54.3%) were female and 62 (45.7%) were male. The prevalence of high and very highly stressed students are 50 (36.2%) and 54 (39.1%) respectively. Out of these highly stressed students, 26 (52%) were female and 24 (48%) were male. Again out of the highly stressed students 28 (51.9%) were female and 26 (48.1%) were male. This is shown in Table 1. However, independent sample *t*-test has shown that there is no significant difference of stress level in male and female. This is shown in Table 2.

Table 3 shows that in our study only 03.6% (5) students were obese and only 15.9% (22) students were overweight. Most of the students (71.7%) were of normal body weight. We have tried to correlate stress and BMI and found that there is a strong correlation between stress and BMI, which is shown in Table 4.

## DISCUSSION

The prevalence of highly stressed students in our study is 36.2% and that of very highly stressed students is 39.1%. For simplicity, if we combine highly and very highly stressed level as stressed and average and low level as nonstressed students, then overall prevalence of stress will be 75.3% in the study, which is higher than a Thai study (61.4%),<sup>5</sup> a study in Egypt (43.7%),<sup>8</sup> or a Malaysian study (41.9%)<sup>4</sup> and a British study (31.2%).<sup>3</sup> This could be either due to the different instruments used in other studies or it could be a real difference.

In this study, we have not found any significant difference in prevalence of stress among male and female. Other studies have also shown that the gender differences in

**Table 1: Distribution of students according to sex and also in different categories of stress level**

Parameters	Sex		Total
	Female	Male	
Stress			
Average	19	11	30 (21.7)
High	26 (52)	24 (48)	50 (36.2)
Low	2	2	4 (2.9)
Very high	28 (51.9)	26 (48.1)	54 (39.1)
Total	75 (54.3)	63 (45.7)	138

**Table 2: Independent sample t-test**

Parameters	Levene's test for equality of variances		t-test for equality of means						
	Frequency	Significant	t	df	Significant (two-tailed)	Mean difference	Standard error difference	95% confidence interval of the difference	
								Lower	Upper
Stress									
Equal variances assumed	0.042	0.839	-0.468	136	0.640	-0.394	0.842	-2.059	1.270
Equal variances not assumed			-0.468	131.448	0.641	-0.394	0.842	-2.061	1.272

**Table 3: Distribution of students according to sex and also in different levels of BMI**

Parameters	Sex		Total
	Female	Male	
BMI			
Normal	53	46	99 (71.7)
Obese	5	0	5 (03.6)
Over WT	9	13	22 (15.9)
Under WT	8	4	12 (08.9)
Total	75	63	138

BMI: Body mass index

**Table 4: The correlation between stress and BMI**

Correlations	BMI 2	Stress 2
BMI 2		
Pearson correlation	1	0.007
Significant (two-tailed)		0.939
n	139	138
Stress 2		
Pearson correlation	0.007	1
Significant (two-tailed)	0.939	
n	138	138

BMI: Body mass index

specific stress symptoms and overall prevalence or mean scores of stress were scarce and did not turn out to be a significant factor in reporting of stress.<sup>9,10</sup>

Several studies have demonstrated heterogeneity in eating behaviors in response to stress; some people eat more when stressed while others eat less.<sup>11-13</sup> In our study, the prevalence rate of obese (03.6%) and overweight (15.9%) is not very high and may be due to health consciousness of the students or due to use of the well-equipped gym of the college. However, we have found a strong correlation between psychological stress and body weight, greater the psychosocial stress more is the body weight.

## CONCLUSION

We can conclude that prevalence rate of stress is very high among the medical students of Jorhat medical college but without any significant difference between male and female. The prevalence rate of obese and overweight is not very high but there is a strong correlation between stress and BMI.

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# Comparative Study on Fixation Techniques and Functional Outcome between Plate Osteosynthesis, Interlocking Nailing, and Titanium Elastic Nailing in both Bones of Forearm Fractures

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## Abstract

**Introduction:** The goal of treatment of fractures of both bones of forearm in adults is to regain length, axial, and rotational stability. Open reduction and internal fixation with compression plates achieve a high percentage of union in about 96-98% of cases.

**Aim:** Aim of this study is to compare the results of treating diaphyseal fractures of both bones in adult forearm using plate osteosynthesis with that of titanium elastic nail fixation and interlocking nail fixation.

**Materials and Methods:** This is a prospective study of 30 cases of diaphyseal fractures of both bone of forearm in adults treated by surgical fixation with various implants.

**Results:** Diaphyseal fractures of both bones of forearm in adults are one of the most common fractures being reported to orthopedic emergency. Early fixation of fracture followed by intense physiotherapy produced excellent results (70%). Fixation with plate osteosynthesis has stood the test of time and provides excellent fixation (80%).

**Conclusion:** Titanium elastic nail fixation is particularly useful in fractures involving middle third of radius and ulna. Providing for 3 point fixation leads to stable fixation and proper alignment of fracture fragments. Being newer techniques, these intramedullary devices require further evaluation and there is a steep learning curve.

**Key words:** Forearm fractures, Intramedullary, Radius and ulna

## INTRODUCTION

Recent advances in fracture management in humans have focused on minimally invasive fracture stabilization techniques. Over the last 40 years, anatomic reduction with plate stabilization has become the standard in adult patients with diaphyseal fractures of the radius and ulna. When operative fixation has been indicated in skeletally immature patients with these fractures, a variety of techniques has

been reported, with intramedullary fixation becoming increasingly accepted.<sup>1</sup> There is currently significant variability in the treatment of adolescents with forearm fractures.<sup>1</sup> Fractures of forearm are classified according to the level of fracture, the pattern of fracture, the degree of displacement, the presence or absence of comminution or segmental bone loss and whether they are open or closed. Each of these factors may have some bearing on the type of treatment to be selected and the ultimate prognosis.<sup>2</sup> For descriptive purposes, it is useful to divide the forearm into thirds, based on the linear dimensions of radius and ulna. Disruption of proximal or distal radioulnar joints is of great significance to the treatment and prognosis. It is imperative to determine whether the fracture is associated with joint injury because effective treatment demands that both the fracture and joint injuries are treated in an integrated fashion.<sup>3</sup>

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## Aim

Aim of this study is to compare the results of treating diaphyseal fractures of both bones in adult forearm using plate osteosynthesis with that of titanium elastic nail fixation and interlocking nail fixation.

## MATERIALS AND METHODS

This is a prospective study of 30 cases of diaphyseal fractures of both bone of forearm in adults treated by surgical fixation with various implants. It includes all diaphyseal fractures of both bones of forearm in adults. Comminuted, segmental fractures are included in this study. All compound fractures, malunited fractures, bones with medullary canal diameter of <2 mm, and fractures in children are excluded from this study.

## RESULTS

The age group varied from 20 to 70 years with the mean age of 45 years. The incidence of fracture was observed maximum between 30 and 50 years of age. Among the 30 cases, males were predominant. Right side fracture was common in our series. The most common mode of injury had been road traffic accident. 80% of patients are in Muller type A3 (Table 1). 88% of patients presents after 2 days of injury (Table 2).

Intramedullary fixation provides for short operating time, short hospital stay and early rehabilitation (Table 3). Average time of fracture healing was 8 weeks. In patients who had undergone plate osteosynthesis, it was 9 weeks whereas in patients who had undergone nail fixation it was 6 weeks. Muller type 22 C1 fracture was united by 11 weeks. Other fracture patterns healed between 6 and 9 weeks. One patient, who had undergone interlocking nail fixation, developed nonunion of fracture of radius. After a period of 15 weeks, since there was angulation of the distal fragment with no callus response at the fracture site, the nail was removed and open reduction and internal fixation with plate osteosynthesis and bone grafting was done. The fracture went on to unite after a period of further 10 weeks. 2 patients had restricted pronation and supination and both of them eventually recovered. All these patients were treated with plate osteosynthesis. 8 patients treated with plate osteosynthesis gave excellent results with regard to pronation and supination. 4 patients developed post-operative stiffness of elbow joint. All of them were treated with plate osteosynthesis. However, all these patients eventually had fair range of motion (ROM) by the end of 12 weeks following intense physiotherapy. The patient who had sustained fracture of radial styloid process during titanium nail fixation following far lateral entry point

developed stiffness of wrist joint. With active exercises, the ROM range of motion was increased. Restoration of pronation and supination activities was possible by the end of 6<sup>th</sup> week using intramedullary nailing whereas they were possible by the end of 9<sup>th</sup> week using plate osteosynthesis. Fixation with plate osteosynthesis has stood the test of time and provides excellent fixation (80%). Overall results are 73.3% of cases are graded as excellent (Table 4).

## DISCUSSION

The patients who had simple Muller's A3 fracture pattern were fixed with intramedullary nail fixation and the fractures with comminution and segmental pattern were fixed with plate osteosynthesis. Compound fractures were excluded from our study. A satisfactory device for internal fixation must hold the fracture rigidly, eliminating as completely as possible angular and rotatory motion. This can be accomplished by either a strong intramedullary nail or AO dynamic compression plate.<sup>1</sup> During plate osteosynthesis, further injury to blood supply of the bone, the periosteum was stripped sparingly with a periosteal elevator and only sufficiently for applying a plate. The fragments were carefully reduced with interdigitating bone spicules being

**Table 1: Classification of fracture**

Muller's sub type	Number of cases (%)
A3	24 (80)
B1	4 (13.3)
B2	1 (3.3)
B3	-
C1	1 (3.3)

**Table 2: Time interval between injury and surgery**

Time interval (days)	Number of cases (%)
<2	4 (13.3)
2-5	20 (66.67)
5-7	6 (20)

**Table 3: Duration of hospital stay postoperatively**

Procedure	Duration of stay (days)
Plate osteosynthesis	12
Intramedullary nail	5

**Table 4: Overall results**

Grading	Number of cases (%)
Excellent	22 (73.3)
Good	4 (13.3)
Fair	2 (6.6)
Poor	2 (6.6)

fitted properly. Our study has showed good fracture union occurred in 80% of cases. Earlier studies have reported an alarming refracture rate of 40% when the plates were removed before 1 year.<sup>3</sup> It is well established that the cortex beneath a rigid plate weakens because of stress shielding, becoming thin, atrophic, and almost cancellous in nature. If soft tissue stripping has been extensive, osteonecrosis, and revascularization weakens the cortex further. In our series involving 10 cases treated with plate osteosynthesis, we did not have refracture in any of our patients.<sup>4</sup> While using intramedullary device for fixing the adult forearm fractures involving both bones, rotational control in fractures near the metaphyseal-diaphyseal junction was difficult because of wide medullary canal. Interference fit nails do not maintain bone length if associated with bone loss. When an intramedullary fixation is used, errors in selecting the proper diameter or length of the nail and operative technique contributed to poor results. In case of the titanium elastic nail, the distal end of nail must abut subchondral bone to prevent shortening.<sup>5</sup> The lower modulus of elasticity of titanium nails allow easier insertion and provide more load sharing with the bone. Titanium elastic nails produced interference fit which was responsible for the return of forearm rotation and grip strength. Our study had showed that good to excellent union occurred with 90% of fractures fixed with titanium elastic nail and excellent union in 70% with interlocking nail fixation. We compared the results of plate fixation with that of intramedullary fixation. Apart from the incidence of infection, we did not have any complications while treating forearm fractures with plate osteosynthesis.<sup>6</sup> Three out of the 4 cases healed well on controlling the infection and one went in for eventual replacement of ulnar plate with a "K" wire. We had technical difficulties while using both titanium elastic nail and interlocking nail. While fixing fractures of radius involving distal 3<sup>rd</sup> shaft, the titanium elastic nail did not provide with adequate stability of fracture fragments because of wide medullary canal. Furthermore, if the medullary canal diameter is narrow (3 mm) the size of the nail is used is also thin, hence, it was very difficult to manipulate the proximal fragment with the nail.<sup>7</sup> That was one of the reasons for performing open reduction at the fracture site in one case. Earlier, intramedullary devices such as K-wires, square nails, and rush nails were used for fixing radius and ulna. These implants did not provide

with rotational stability at the fracture site. This lead to higher incidence of nonunion.<sup>8</sup> But both interlocking nail and titanium elastic nail, provided with excellent rotational stability of fracture fragments. We used tourniquet in fractures fixed with plate osteosynthesis. One case of tourniquet palsy occurred but recovered eventually. Since tourniquet was not used during intramedullary fixation, the chance for occurrence of this neurological complication was totally eliminated. In our study, the rehabilitation time was much shorter for fractures fixed with intramedullary nail when compared with that of plate osteosynthesis. The average time required for functional recovery is more than 9 weeks when plates are used, and about 6 weeks when intramedullary nails are used. The duration of hospital stay postoperatively was also less (on an average of 5 days for intramedullary devices and 12 days for plate osteosynthesis).<sup>9</sup>

## CONCLUSION

Even though plate osteosynthesis is still the most commonly used form of fixation in adult both bone forearm fractures, both titanium elastic nail and interlocking nail fixation are relatively newer techniques which offer a viable and more efficient alternative especially in fixation of fractures involving shafts of radius and ulna.

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# C-peptide Levels in Diagnosis of Diabetes Mellitus: A Case-control Study

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## Abstract

**Background:** C-peptide has emerged as the most clinical and practically acceptable marker of  $\beta$ -cell function. Insulin and C-peptide are cosecreted into the portal circulation in equimolar concentration.

**Materials and Methods:** A total of 50 subjects of recently diagnosed diabetes mellitus (DM) within 1 month and 50 age and sex matched nondiabetic healthy controls were studied. These diabetics were further divided into three groups depending on the fasting serum C-peptide (FC) level, low FC group comprised subjects with FC level  $<0.54$  ng/ml ( $n = 1$ ). Intermediate FC group comprised subject with FC level  $>0.54$ - $1.1$  ng/ml ( $n = 2$ ) high FC group comprised subjects with FC  $>1.11$  ng/ml ( $n = 3$ ).

**Results:** Predominant sufferers of diabetes were males 73% to 27% females. The cutoff range of C-peptide was taken as 0.8-3.58 ng/ml. In classifying, the sub types the low and intermediate group showing a low fasting and low postprandial C-peptide level indicate the benefit from early insulin therapy and the high FC group benefiting from oral hypoglycemic agents.

**Conclusion:** The classification of DM into its subtypes is the first step in approach to management. Data for various prospective studies have shown the relevance. The previously broader classification and the oversight of latent autoimmune diabetes is now becoming clearer and increasing in specificity from a treatment perspective. With a predominant Indian population suffering from a mixture of latent autoimmune diabetes in adults and Type II diabetes the measurements of fasting and postprandial C-peptide levels are now as important as diagnosing the illness itself.

**Key words:**  $\beta$ -cell, C-peptide, Diabetes mellitus, Insulin, Latent autoimmune diabetes in adults

## INTRODUCTION

India is now ranked as a country with the most number of diabetics. This is being extrapolated to under 8 crore diabetics by the year 2030.<sup>1</sup> Diabetes is one among the most financially draining chronic noncommunicable disease. The costs for treatment rising and the burden it bears on family/individual finances and society makes it essential to approach this disease in a more collective entirety.<sup>2</sup>

An emerging pandemic with rising mortality and morbidity, diabetes mellitus (DM) is now being redefined with

emphasis on a multipronged approach with equal stresses on all the factors. The prevention of Type II diabetes has been shown to be possible and requires action now. Trials have shown that sustained lifestyle changes in diet and physical activity can reduce the risk of developing Type II diabetes. For example, the Finnish diabetes prevention study showed that a better diet, increased physical activity and modest weight loss could substantially reduce the onset of Type II diabetes in middle-aged adults at high risk.

The scale of the problem requires population-wide measures.<sup>3,4</sup> Significant relevance has been placed on the etiology by the World Health Organization as does the American Diabetic Association (ADA)<sup>5</sup> emphasis is being laid to preempt and to manage diabetes through a combination of pharmacology, lifestyle diet, and exercise.

To effectively manage DM it is imperative to understand it. DM refers to a group of common metabolic disorders that share the phenotype of hyperglycemia. Several distinct

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types of DM exist and are caused by a complex interaction of genetics and environmental factors<sup>6</sup> and can also be characterized by an absolute or relative lack of insulin. Classified as Type I and Type II, respectively. Type IA diabetes (effects 18 years and younger) is a lack of insulin resulting from near total autoimmune destruction of the pancreatic  $\beta$ -cells and another subdivision Type IB also due to  $\beta$ -cells destruction. Its etiology is not ascertained yet.

Type II DM is a heterogeneous group of disorders characterized by variable degrees of insulin resistance, impaired insulin secretion, and increased glucose production. Distinct genetic and metabolic defects in insulin action and or secretion give rise to the common phenotype of hyperglycemia in Type II DM and have important potential therapeutic implications with newer pharmacologic agents that target specific metabolic derangements.<sup>6</sup>

The plethora of diabetes is its effect on a diabetic: The medical complications it leads to second, the effect it has not only on the individuals, their care givers but also the socioeconomic repercussions that ensue. Compounding this growing problem is the rising incidence among the working population that is the young adult between 30 and 39 years.<sup>3,4</sup> Childhood obesity and an immoderate lifestyle is etiology for early onset and greater incidence.

Type I diabetes is a T-cell mediated autoimmune destruction of pancreatic  $\beta$ -cell begins in childhood, it can occur at any age. This manifest when near total pancreatic islet cell destruction occurs. Glutamic acid decarboxylase (GAD) autoantibodies and ICA512 and IA-2 autoantibodies<sup>7</sup> are now being used as a more specific cytoplasmic assay in the diagnosis of Type IA autoimmune mediated pancreatic  $\beta$ -cells destruction.

A third component of Type I diabetes is an antibody positive type that occurs in older individuals (older than 30 years of age). It has been found that approximately 40% of diabetes in India is of autoimmune variety that would benefit from insulin therapy. These thin built patients presenting in third or fourth decade having low C-peptide levels, positive GAD, or ICA antibodies, without an immediate need for insulin are labeled as type 1.5 diabetes or latent autoimmune diabetes in adults (LADA).

The expert committee on the diagnosis and classification of DM does not recognize the term LADA; rather, the expert committee includes LADA in the definition of Type I autoimmune diabetes ("Type I diabetes results from a cellular-mediated autoimmune destruction of the  $\beta$ -cells of the pancreas. In Type I diabetes, the rate of  $\beta$ -cell destruction is quite variable, being rapid in some individuals

(mainly infants and children) and slow in others (mainly adults). The National Institutes of Health (NIDDK) defines LADA as "a condition in which Type I diabetes develops in adults." LADA is a genetically-linked, hereditary autoimmune disorder that results in the body mistaking the pancreas as foreign and responding by attacking and destroying the insulin-producing beta-islet cells of the pancreas. Simply stated, autoimmune disorders, including LADA, are an "allergy to self." Adults with LADA are frequently initially misdiagnosed as having Type II diabetes, based on age, not etiology.<sup>8,9</sup>

ADA recommends that antibodies positive patients to be grouped under Type I diabetes and antibodies negative patients to be grouped under Type II diabetes. The fasting and post lunch C-peptide levels are good indicators of insulin levels in the blood and pancreatic  $\beta$ -cell function. In contrast to this group, Type II diabetes have features resembling that of metabolic syndrome and increased plasma C-peptide levels with clustering of cardiovascular risk factors. Insulin and C-peptide are cosecreted into the portal circulation in equimolar concentration. However, due to hepatic extraction and peripheral metabolism of insulin, the peripheral levels of insulin do not necessarily reflect the level of secretion and it is this uncertainty that suggests peripheral C-peptide concentration may provide a more reliable picture of  $\beta$ -cell function than do peripheral insulin levels. A closer relationship existing between portal and peripheral C-peptide concentration, in association with clinical parameters it helps to accurately identify the type of diabetes. Patients having a low C-peptide response benefit by initiating early insulin therapy. This helps in preserving the  $\beta$ -cell function by decreasing the immune process of islet cell destruction. Insulin therapy may be discontinued confidently in patients having an adequate post mean C-peptide response.<sup>10,11</sup>

Hence with the above background and confusion regarding the type of diabetes in young patients (20-40 years of age) at presentation the relatively affordable C-peptide level is estimated to classify and effectively manage DM not only improving the outcome but more importantly reduce the complications caused by chronic hyperglycemia.<sup>12,13</sup>

## MATERIALS AND METHODS

The present hospital based case-control study was conducted in the department of medicine. The study period was ½ year. 50 subjects of recently diagnosed DM within 1 month and 50 age and sex-matched nondiabetic healthy controls were studied. These diabetics were further divided into three groups depending on the fasting serum C-peptide (FC) level, low FC group comprised subjects

with FC level  $<0.54$  ng/ml ( $n = 1$ ). Intermediate FC group comprised subject with FC level  $>0.54$ - $1.1$  ng/ml ( $n = 2$ ) high FC group comprised subjects with FC  $>1.11$  ng/ml ( $n = 3$ ). Various characteristics such as family history, age, weight, height, body mass index (BMI), waist-hip ratio, blood pressure, fasting and post meal blood sugar and serum C-peptide, fasting and post meal, lipid profile, of each of these groups was studied. FC and post meal serum C-peptide was correlated with each of these characteristics. Ethical Committee approved the study.

### Inclusion Criteria

- Freshly diagnosed case of DM, in the age group of 20-40 years, attending medicine outpatient department (OPD), diabetes OPD, and patients admitted to medicine ward were included in the study.
- Diagnosis of DM was made by ADA criteria for diagnosis of DM 2003.<sup>3</sup>
- Fasting plasma glucose  $126$  g/dl or 2 h post meal plasma glucose of  $140$  g/dl or symptoms of diabetes plus random blood glucose concentration  $>200$  g/dl, or 2 h plasma glucose  $>200$  mg/dl during oral glucose tolerance test.

### Selection of Controls

Nondiabetic, age and sex match healthy control subjects selected randomly from:

- Patients attending OPD for minor ailments and seasonal infections or for physical checkup.
- Adult offspring's of diabetics visiting the admitted patient.
- Unrelated individuals into suffering from DM.
- Relatives of the diabetics above 18 years of age.

### Exclusion Criteria

- Those subjects who had glucose toxicity are very high blood sugar level at presentation. And those presenting with diabetic ketoacidosis were initially excluded from the study. But later included once blood sugar become  $<200$  g<sup>0</sup>-%- $250$  mg<sup>0</sup>-%.
- Subjects who did not give informed consent.
- Previously diagnosed diabetics even if noncompliant.

### Past History

- Hypertension, coronary heart disease, cerebrovascular episode along with history of any major illness was noted.
- Smoking, tobacco chewing, and alcohol intake was noted, smoker was defined as a person who smokes at least 1 cigarette/pipe/cigar/bidi per day.
- Personal history regarding lifestyle noted.
- Family history of Type II DM in first second-degree relatives was noted.

- Menstrual history in females was noted.
- Treatment history in cases was taken in details.

### Physical Examination Methods (167, 167, 169, 170)

#### Height

Standing height was measured with the subject in are foot, back square against the wall, and eyes looking straight ahead. A set square resting on the scale and the tape measurement from the wall was used to measure height to the nearest of  $0.5$  cm.

#### Weight

Weight was measured using a platform scale to the nearest of  $200$  gm. The scale was standardized to zero before each use.

#### BMI

BMI was calculated by the formula. Weight in kilogram divided by square of height in meter.

$$\text{BMI} = \text{Weight in kilogram} / (\text{Height in meter}^2).$$

BMI  $<25$  was taken as normal

BMI  $>25$  was taken as abnormal, i.e., increased.

#### Waist circumference

Waist circumference was measured to the nearest of  $0.1$  cm using a nonstretchable standard tape. Measurements were taken over the unclothed abdomen at the smallest diameter between the costal margin and the iliac crest. The tape measures were kept horizontal. Subject was made to relax with arms held loosely by sides. Two measurements were taken.

#### Hip circumference

It was measured to the nearest of  $0.1$  cm using a nonstretchable standard tape. Measurements were taken over light clothing at the level of greater trochanter (usually the widest diameter around the buttocks). This tape measure was kept horizontal. Subject was made to relax with arms held loosely by sides. Two measurements were recorded.

#### Waist-hip ratio (WHR)

WHR  $\geq 0.90$  for males and  $\geq 0.85$  for females was taken as a risk factor. Waist circumference:

- $102$  cm in males and  $>88$  cm in females was taken as a component of metabolic syndrome X according to ATP III Guidelines.

#### Blood Pressure

A mercury sphygmomanometer was used for measuring blood pressure. Systolic blood pressure was determined when the sounds appeared in the beginning when mercury column was lowered down (Korotkoffs phase I). Diastolic

blood pressured recorded at the level when the sounds just disappeared (Korotkoffs phase 5). The patient was rested at least for 5 min and was not allowed to smoke at least for 30 min before the measurement of blood pressure. Adequate cuff size was insured and cuff was made to encircle and cover 2/3<sup>rd</sup> of length of the arm with the bladder on anterior side of arm covering the brachial artery. Its lower border was kept one inch (about 2-3 cm) above the antecubital space. The bladder was deflated slowly. Two readings were taken at least 5 min apart and exact values were recorded.

### Diagnostic of Hypertension

Hypertension was defined as presence of systolic blood pressure >140 mm of Hg and diastolic >90 mm of Hg based on average of 2 readings taken on the two or more visits after an initial screening or one who was known case of hypertension with or without antihypertensive medication.

Blood pressure >130/>85 was taken as one of the components of metabolic syndrome X.

Fundus examination was performed in all cases and retinopathy.

### Measurement of Blood Sugar

Folin-wu method was used for measurement of blood sugar (fasting and postprandial).

### Measurement of Serum Total Cholesterol

CHOD-PAP method was used for measurement of total serum cholesterol.

### Measurement of Serum High-density Lipoproteins (HDL) Cholesterol

Autozyme HDL cholesterol precipitation method 3 used for enzymatic determination of HDL cholesterol in serum.

### Measurement of Serum Triglyceride

Serum lipid profile was estimated by calorimetric method 3 in the Biochemistry laboratory at Dr. D. Y. Patil Hospital.

### Measurement of Serum C-peptide

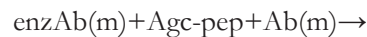
The quantitative determination of circulating C-peptide concentration in human serum was carried out by C-peptide chemiluminescence which involves assay by microplate immunoassay method. The C-peptide assay was carried out by Ranbaxy Laboratory, Bombay. Highly sophisticated and latest "Automated CLIA Analyzer" - ADVIA CENTAUR from Bayer, USA, was used for this assay.

### C-peptide chemiluminescence immunoassay

#### Principle

The essential reagents required for an immunoassay include high and specificity antibodies (enzyme

conjugated and immobilized) with different and distinct epitope recognition, in excess, and native antigen. In this procedure, the immobilization takes place during the assay at the surface of a microplate well through the interaction streptavidin coated on the well and exogenously added biotinylated monoclonal anti-insulin antibody. On mixing monoclonal biotinylated antibody, the enzyme-labeled antibody and a serum containing the native antigen reaction occurs between the native antigen and the antibodies, without competition or steric hindrance, to form a soluble sandwich complex. The interaction is illustrated by the following equation.



←

Simultaneously, the complex is deposited to the well through the high affinity reaction of streptavidin and biotinylated antibody. After equilibrium is attained, the antibody-bound fraction is separated from unbound antigen by decantation or aspiration. The enzyme activity in the antibody-bound fraction is directly proportional to the native antigen concentration. By utilizing several different serum references of known antigen values, a dose response curve can be generated from which the antigen concentration of an unknown can be ascertained.

### Specimen Collection and Preparation

The blood should be collected in a plain red top venipuncture tube without additives. The blood is allowed to clot. Then the sample is centrifuged to separate serum from the cells. Samples may be refrigerated at 2-8°C for a maximum period of 2 days.

**Sensitivity:** The assay sensitivity is found to be up to 0.025 mg/ml.

**Specificity:** C-Peptide does not cross react with insulin, proinsulin, and glucagon.

## OBSERVATION

The results are been depicted in tabular form in Tables 1-12.

## DISCUSSION

The classification of DM into its subtypes is the first step in approach to management. Data for various prospective studies have shown the relevance. The previously broader classification and the oversight of latent autoimmune diabetes is now becoming clearer and increasing in specificity from a treatment perspective. With



**Table 1: Age distribution in diabetic cases and control**

Age group (years)	n=50 (%)		Total (n=100)
	Cases	Control	
20-24	4 (8.00)	6 (12.00)	10
25-29	5 (10.00)		12
30-34	8 (16.00)	10 (20.00)	18
35-40	33 (66.00)		60
Mean age±SD	34.72±5.55	32.08±6.01	

SD: Standard deviation

**Table 2: Sex distribution cases and controls**

Sex	n=50 (%)		Total (n=100)
	Case	Control	
Male	36 (72.00)	39 (78.00)	75
Female	14 (28.00)	11 (22.00)	25

**Table 3: Presenting symptoms**

Symptoms	Cases n=50 (%)
Paresthesia	1 (2.00)
Visual complaint	1 (2.00)
Nonspecific	4 (8.00)
Ketoacidosis	5 (10.00)
Skin infection	4 (8.00)
Urinary complaint	4 (8.00)
Weakness/fatigability	6 (12.00)
Weight loss	9 (18.00)
Polyphagia	8 (16.00)
Polydipsia	8 (16.00)
Polyuria	17 (34.00)

**Table 4: BMI (kg/m<sup>2</sup>)**

BMI (kg/m <sup>2</sup> )	n=50 (%)	
	Case	Control
≤	41 (82.00)	46 (92.00%)
25-29	9 (18.00)	4 (8.00%)
Mean±SD	21.18±4.07	20.78±4.38

SD: Standard deviation, BMI: Body mass index

a predominant Indian population suffering from a mixture of LADA and Type II diabetes the measurements of fasting and postprandial C-peptide levels are now as important as diagnosing the illness itself.<sup>14,15</sup>

The investigation into incident discovery of impaired glucose tolerance will now be complete with the inclusion of C-peptide estimations in conjunction with HbA1C, fasting and post meal blood sugars and also the evaluation of urine sugars and micro albumins.<sup>16-18</sup>

With the confusion created by the BMI and the inclusion of metabolic syndrome with the Indian sufferer the C-peptide

**Table 5: WHR in cases and controls**

WHR	n=50 (%)	
	Cases	Control
Male		
≤0.90	18 (36.00)	20 (40.00)
>0.90	18 (36.00)	19 (38.00)
Female		
≤0.90	9 (18.00)	6 (12.00)
>0.90	5 (10.00)	5 (10.00)
Mean±SD	0.89±0.06	83±0.06

WHR: Waist-hip ratio, SD: Standard deviation

**Table 6: Biochemical Parameters in cases and control subjects (n=50)**

Blood sugar		
Fasting	147.70±18.44	87.04±14.05
Post meal	218.44±31.17	123.6±19.47
C-peptide		
Fasting	1.27±0.60	1.39±0.40
Post meal	2.96±2.24	5.04±1.24
Total cholesterol	161.76±34.01	154±14.35
LDL cholesterol	93.13±32.94	89.24±13.70
Serum triglyceride	131.66±38.13	111.44±16.62
HDL	41.89±7.9	43.5±6.7

LDL: Low-density lipoprotein, HDL: High-density lipoprotein

**Table 7: Mean serum C-peptide in case and control**

Mean serum C-peptide	(n=50)	
	Case	Control
C-peptide		
Fasting	1.27±0.60	1.39±0.4
Post meal	2.96±2.24	5.04±1.24

**Table 8: Clinical profile of patients with metabolic syndrome versus nonmetabolic syndrome**

Parameter	Metabolic syndrome n=18 (36.00%)	Nonmetabolic syndrome n=32 (64.00%)
Age	37.06±3.11	33.41±6.20
Systolic BP	131.69±15.69	123.06±9.58
Diastolic BP	84.83±9.38	83.41±8.14
BMI	23.29±3.40	20.0±3.98
Waist circumference	84.78±10.47	76.16±9.10
WHR	0.90±0.07	0.89±0.06
Blood sugar (F)	141.33±14.64	151.41±19.54
Blood sugar (PM)	25.22±26.11	225.88±32.51
C-peptide (F)	1.36±0.80	1.54±1.92
C-peptide (PM)	3.79±2.43	2.49±2.01
Triglyceride	145.4±35.95	123.91±37.64
LDL	101.4±35.41	88.98±31.07
HDL	37.61±4.88	44.22±8.32
Cholesterol	166.0±34.05	159.38±34.29

LDL: Low-density lipoprotein, HDL: High-density lipoprotein, BP: Blood pressure, BMI: Body mass index

levels is the better tool in planning the line of long-term management.<sup>19</sup>

As DM is a precursor to various complications that raise the mortality and morbidity in any population by properly diagnosing the status of the  $\beta$ -cell function its degradation can be slowed thereby aiding in an effective glycemic control and most importantly preempting diabetes-induced

**Table 9: Clinical, biochemical, and serological characteristic of study group (low fasting serum C-peptide group (FC-0.54 ng/dl) n1 (number of cases)**

Variable	Low FC (<0.54 ng/ml)	Intermediate FC (0.54-1.11 ng/ml)	High FC (>1.11 ng/ml)
Age	34.17 $\pm$ 5.19	35.17 $\pm$ 5.27	35.89 $\pm$ 5.54
Systolic BP	20.68 $\pm$ 3.73	19.19 $\pm$ 3.47	22.22 $\pm$ 4.38
Diastolic BP	3 $\pm$ 9.38	83.41 $\pm$ 8.14	35.17 $\pm$ 5.27
BMI	23.29 $\pm$ 3.40	20.0 $\pm$ 3.98	35.17 $\pm$ 5.27
Waist circumference	84.78 $\pm$ 10.47	76.16 $\pm$ 9.10	35.17 $\pm$ 5.27
WHR	0.90 $\pm$ 0.07	0.89 $\pm$ 0.06	35.17 $\pm$ 5.27
Blood sugar (F)	141.33 $\pm$ 14.64	151.41 $\pm$ 19.54	35.17 $\pm$ 5.27
Blood sugar (PM)	25.22 $\pm$ 26.11	225.88 $\pm$ 32.51	35.17 $\pm$ 5.27
C-peptide (F)	1.36 $\pm$ 0.80	1.54 $\pm$ 1.92	35.17 $\pm$ 5.27
C-peptide (PM)	3.79 $\pm$ 2.43	2.49 $\pm$ 2.01	35.17 $\pm$ 5.27
Triglyceride	145.4 $\pm$ 35.95	123.91 $\pm$ 37.64	35.17 $\pm$ 5.27
LDL	101.4 $\pm$ 35.41	88.98 $\pm$ 31.07	35.17 $\pm$ 5.27
HDL	37.61 $\pm$ 4.88	44.22 $\pm$ 8.32	35.17 $\pm$ 5.27
Cholesterol	166.0 $\pm$ 34.05	159.38 $\pm$ 34.29	35.17 $\pm$ 5.27

LDL: Low-density lipoprotein, HDL: High-density lipoprotein, BP: Blood pressure, BMI: Body mass index

**Table 10: Metabolic syndrome in low FC Group (n=2)**

Age	37.0 $\pm$ 2.83
Systolic BP	125.00 $\pm$ 7.07
Diastolic BP	75.00 $\pm$ 7.07
BMI	22.74 $\pm$ 4.48
Waist circumference	86.00 $\pm$ 22.63
Blood sugar (F)	145.00 $\pm$ 18.38
Triglyceride	165.00 $\pm$ 28.99
Cholesterol	180.00 $\pm$ 0.05
HDL	38.50 $\pm$ 2.12
LDL	108.00 $\pm$ 2.83

FC: Fasting serum C-peptide, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, BP: Blood pressure, BMI: Body mass index

**Table 11: Metabolic syndrome in high FC Group (n=5)**

Age	39.00 $\pm$ 2.24
Systolic BP	122.00 $\pm$ 20.20
Diastolic BP	77.2 $\pm$ 11.37
BMI	23.79 $\pm$ 3.47
Waist circumference	88.40 $\pm$ 10.01
Blood sugar (F)	149.4 $\pm$ 14.99
Blood sugar (PM)	214.00 $\pm$ 31.50
Triglyceride	168.80 $\pm$ 43.81
Cholesterol	171.2 $\pm$ 28.54
HDL	38.00 $\pm$ 5.48
LDL	107.6 $\pm$ 39.52

LDL: Low-density lipoprotein, HDL: High-density lipoprotein, BP: Blood pressure, BMI: Body mass index

retinopathy, nephropathy peripheral neuropathy and cardiovascular and cerebrovascular complications.<sup>20</sup>

The BMI in all the cases was found to be either within the normal range or below the obesity mark, <23 kg/m<sup>2</sup>. The CT abdomen showed that majority of the individuals suffering from LADA and Type II diabetes have a larger visceral fat deposit than peripheral fat deposit. Moreover, the second significant portion in the sample had large peripheral as well as visceral fat deposits. There a third percentage of individuals who have either peripheral fat or visceral fat deposit only.<sup>21</sup>

The difficulty of C-peptide estimations is that to evaluate and achieve an accurate result the individual should not have taken any form of antidiabetic medication either in the pill form or insulin in the pretending 3 months. While this is possible for new onset diabetics the trial and error method in misdiagnosed individuals can be abolished when the C-peptide estimation becomes part of the initial evaluation in suspected individuals who present with minor ailments hinting at DM.

There is definitely a practical advantage in including the C-peptide estimation in spite of its high cost. In doing so, the accurate line of management can be initiated keeping the costs of treatment to the minimum.<sup>22</sup>

## CONCLUSION

From this study, the following conclusions were arrived at:

- Predominant sufferers of diabetes were males 73-27% females.
- The cutoff range of C-peptide was taken as 0.8-3.58 ng/ml
- The sample was divided into three groups low FC <54 ng/ml 18% intermediate FC 0.54-1.1 ng/ml 36% and high FC >1.1 ng/ml 48% and their features were compared.
- There was an increase in the low-density lipoprotein in all the 48% of high FC group along with triglycerides. Whereas, the other features such as blood pressure, serum cholesterol, age, and sex differentiation were almost similar ranging only marginally.
- 75% of the high FC group was diagnosed as metabolic syndrome there by suggesting Type II diabetes and LADA are inevitably going to develop metabolic syndrome and result in insulin resistance.
- Metabolic Syndrome is predominantly a feature associated of Type II DM and also latent autoimmune diabetes in the aged.
- In classifying the sub types the low and intermediate group showing a low fasting and low postprandial

**Table 12: Treatment evaluation**

Parameters	Sulfonylureas	Sulfonylureas+biguanides	Insulin
Age	37.71±2.36	37.61±13.5317	31.88±11.24
Systolic BP	123.14±6.62	126.56±14.52	126.58±13.11
Diastolic BP	84.29±7.87	81.67±8.52	85.04±8.83
Weight	52.00±10.32	61.44±11.62	49.38±9.48
BMI	21.11±3.84	23.33±3.41	19.52±4.04
Waist circumference	79.43±8.50	84.50±9.60	75.42±10.3
WHR	0.86±0.05	0.90±0.07	0.89±0.06
Blood sugar (F)	147.71±16.76	148.89±20.70	147.63±17.9
Blood sugar (PM)	218.00±38.22	212.00±32.15	223.51±30.50
C-peptide (F)	1.19±0.35	1.62±1.00	1.45±2.15
C-peptide (PM)	3.36±1.46	4.58±2.18	1.71±1.64
Triglyceride	114.71±38.11	144.33±34.19	126.85±40.16
Cholesterol	166.43±27.10	160.72±37.81	159.50±33.70
HDL	43.20±10.59	39.61±5.69	42.75±8.45
LDL	107.00±11.67	86.46±38.94	92.68±31.92

LDL: Low-density lipoprotein, HDL: High-density lipoprotein, BMI: Body mass index

C-peptide level indicate the benefit from early insulin therapy and the high FC group benefiting from oral hypoglycemic agents.

- By identifying the subtypes aggressive control by emptying the most appropriate treatment regimen for impaired plasma glucose levels but will also assist significantly in preventing complications such as retinopathy, nephropathy, neuropathy, and atherosclerotic changes in the macro and micro vasculature.

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# Knowledge, Attitude, and Practice toward the Usage of Antibiotics among Public in Al-Ahsa, Saudi Arabia

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## Abstract

**Background:** Antibiotic resistance has become a worldwide public health problem, the World Health Organization has reported the increase in antibiotic resistance worldwide and this problem leads to an excess in the morbidity and mortality. The resistance increased due to the inappropriate use of antibiotics. In Saudi Arabia, there are no much such studies published and no data available.

**Objective:** This study was designed to assess the knowledge, attitude, and practice toward the usage of antibiotics in Al-Ahsa.

**Materials and Methods:** A cross-sectional study was conducted in Al-Ahsa, Kingdom of Saudi Arabia in the period from July to September 2016. A pretested standardized questionnaire was used to collect information on knowledge, attitude, and practice toward the usage of antibiotics, data entry was performed using SPSS Version 22 software.

**Results:** The responses of 420 of which 185 male and 235 female, 122 (29%) have high school degree, 257 (61.2%) have bachelor's degree, and 41 (9.8%) have master or Ph.D. degree. The mean age of the respondents was 31.1 years and all of the respondents from Al-Ahsa. The prevalence of nonprescription antibiotic use was 121 (28.8%) the main source of nonprescribed antibiotics were from pharmacist. 61.5% of respondents believed that antibiotics used to treat viral infection such as common cold and influenza. 28.6% of respondents discontinued the antibiotics when they felt better. Trust in doctor's decision and doctors often take time to consider carefully the need for an antibiotic were 67.4% and 32.1%, respectively.

**Conclusions:** The study shows that the population has inadequate knowledge about the probable usage of antibiotics, it is important to generate more awareness regard this issue, educational campaigns are important to increase the knowledge about the appropriate use of antibiotics.

**Key words:** Al-Ahsa, Antibiotics, Antibiotics resistant, Kingdom of Saudi Arabia, Self-medication

## INTRODUCTION

Antibiotic resistance has become a worldwide public health problem with a substantial economic and clinical burden.<sup>1</sup> The World Health Organization (WHO) has reported the increase in antibiotic resistance worldwide and this problem leads to an excess in the morbidity and mortality.<sup>2</sup>

Antibiotic resistance increased due to the inappropriate use of antibiotics, and this occurs through several things like using of antibiotics from previously prescription, from relatives friends or without prescription.<sup>3</sup> One of the factors that some physician prescribed antibiotics for a patient who present with viral infection (such as common cold, influenza, and acute tonsillitis) which are self-limiting diseases.<sup>4</sup> Approximately, two-thirds of all antibiotics used in the world are gained without a prescription and are used improbably.<sup>5</sup>

In Saudi Arabia, antibiotics are the third most common prescribed medications,<sup>6</sup> therefore, it is necessary to determine the knowledge level of our population and to educate them. Most of the people who used the

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antibiotics have deficiency in medical knowledge about antibiotics, which will make them to experience medical side effects of the antibiotics.<sup>7</sup> Problems associated with the rampant use of antibiotics include antibacterial resistance, increasing the chance of chronic diseases, and getting side effects (e.g., gastrointestinal effects).<sup>8</sup> Education to the public population the correct use of antibiotics should be corroborative.<sup>9</sup> The WHO also prompts member countries to educate patients and general population about antibiotics resistance.<sup>10</sup>

In Saudi Arabia, there are not much such studies published and no data available. Therefore, this study was designed to determine the knowledge, attitude, and practice toward antibiotic use among the public in Al-Ahsa.

## MATERIALS AND METHODS

### Study Design

A cross-sectional study was conducted in Al-Ahsa, Kingdom of Saudi Arabia, in the period from July to September 2016.

### Target Population

Adult from the age of 15-55 years in different area in Al-Ahsa, Kingdom of Saudi Arabia, were targeted to assess their knowledge, attitude, and practice toward the usage of antibiotics.

### Data Collection

A standardized questionnaire was used to collect information on knowledge, attitude, and practice toward the usage of antibiotics.

The questionnaire consisted of five sections: (i) Sociodemographic data, (ii) source of antibiotics, (iii) clinical indications for antibiotic use, (iv) knowledge on side-effects of antibiotic treatment and antibiotic resistance, and (v) expectations from doctors, doctors' habits and the doctor-patient relationships. The questionnaire was pretested and translated into Arabic language and then back-translated to English to validate the translation. The questionnaire was constructed based on similar research conducted in Sweden<sup>11</sup> but modified to suit the Saudi context. Verbal informed consent was obtained. Ethical approval for this study was obtained from the Human Ethical Committee. The sample size was determined using the Raosoft sample size calculator using a margin of error of 5%, a confidence interval of 95%, a population size of 1,063,112 people, and an expected response of 50%.<sup>12</sup> The minimum sample size estimated for the study was 385. Assuming a response rate of 50%, a larger sample size of 420 people were enrolled in the study.

### Data Analysis

Data entry was performed using SPSS Version 22 software.

## RESULTS

A total of 420 participants were included in this study, all of them from Al-Ahsa city which is located in the eastern region in Saudi Arabia.

### Demographic Data

The total of 420 persons participated in the study of which 185 (44%) male 235 (56%) female. The mean age was 31.1 years. Out of the total participants, 29% have high school degree, 61.2% have bachelor degree, and 9.8% have master or Ph.D. degree (Table 1).

### Source of Antibiotics

About 71.2% of the respondents had prescribed antibiotics by a physician while (28.8%) of the respondents had self-medicated which obtained mainly from private pharmacies by pharmacist 54 (12.9%) without a prescription. Other sources included friends 12 (2.9%), previous prescription 3.8% or by self 38 (9%) (Table 2).

### Clinical Indications for Antibiotic Use

About 24.3% of respondents agreed that antibiotics should be used to treat cough, 55.2% of the respondents incorrectly agreed that antibiotics speed up the recovery from sore throat, for influenza most of the respondents

**Table 1: Demographic characteristics**

Characteristics	n (%)
Gender	
Male	185 (44)
Female	235 (56)
Age (years)	
<20	64 (15.2)
20-29	157 (37.4)
30-39	114 (27.1)
40-49	58 (13.8)
>50	27 (6.1)
Education level	
High school	122 (29)
Bachelor's degree	257 (61.2)
Master or Ph.D. degree	41 (9.8)

**Table 2: Source of antibiotics**

Source	n (%)
Prescribed	
By physician	299 (71.2)
Nonprescribed	
By Pharmacists	54 (12.9)
By friends	12 (2.9)
By previous prescription	16 (3.8)
By self	38 (9)



67.9% agreed that antibiotics are effective in the treatment of influenza. Positive response for respiratory infections was 67.9%. 25.5% of participants did not agree that “antibiotics must be used postoperatively.” 49.8% of respondents agreed that antibiotics should be used to treat gastroenteritis. 57.1% disagreed to give antibiotics in bone infection. As for urinary and ear infections, it was 69% agree, 31% disagree and 68.8% agree, 31.2% disagree, respectively (Table 3).

### Knowledge on Side-effects of Antibiotic Treatment and Antibiotic Resistance

About 28.6% of the respondents agreed to stop taking the antibiotics when they felt better. Most of the respondents correctly agreed that if they get some kind of skin reaction from an antibiotic, they should not use the same antibiotic again, also 82.1% of the respondents agreed that if they get side effects during a course of antibiotics they should stop the antibiotics immediately. 26.7% of respondents did not agree that antibiotics can cause an imbalance in the body's own bacterial flora. 26% of participants did not agree on the statements: “The unnecessary use of antibiotics can increase the resistance of bacteria to them.” 21.4 of the respondents disagreed that the use of antibiotics can reduce the boy's own capacity to fight off infections (Table 4).

### Expectations from Doctors, Doctors' Habits, and the Doctor-Patient Relationships

About 32.1% of respondents agreed that doctors often take time to consider carefully whether antibiotics are needed or not. 67.4% of respondents indicated trusting the doctor decision. A significantly higher percentage (71.2) of participants agreed that pharmacists often tell them how antibiotics should be used. 56.4% of the respondents know if they need antibiotics or not before meeting the doctor (Table 5).

## DISCUSSION

Knowledge about the use of antibiotics among population in Saudi Arabia is limited. Therefore, this study aimed to collect data reflecting the state of knowledge, attitude, and practice of antibiotics in Al-Ahsa community. The study shows that population have inadequate knowledge about the use of antibiotics specially the indications of antibiotics. For instance, most of respondents agreed to use antibiotics to treat viral infection such as sore throat and influenza. The result is much higher when compared to a study conducted by Belkina *et al.*, 2014.<sup>13</sup> Another study about the knowledge, attitude, and practice toward antibiotic use among public in Kuwait by Awad and Aboud 2015,<sup>14</sup> showed that 27.5% of the respondents were self-medication with antibiotics to treat mainly common

**Table 3: Clinical indications for antibiotic use**

Characteristics	n (%)	
	Yes	No
Cough (75.7)	102 (24.3)	318 (75.7)
Sore throat	232 (55.2)	188 (44.8)
Influenza	285 (67.9)	135 (32.1)
Respiratory infection	285 (67.9)	135 (32.1)
Postoperatives	313 (74.5)	107 (25.5)
Gastroenteritis	209 (49.8)	211 (50.2)
Bone infection	180 (42.9)	240 (57.1)
Urinary tract infection	290 (69)	130 (31)
Ear infection	289 (68.8)	131 (31.2)

**Table 4: Side-effects of antibiotics and antibiotic resistance**

Statements	n (%)	
	Yes	No
I stop taking antibiotics when I feel better	120 (28.6)	300 (71.4)
If you get some kind of skin reaction when using an antibiotic, you should not use the same antibiotic again	344 (81.9)	76 (18.1)
If you get side effects during a course of antibiotics treatment you should stop taking them immediately	345 (82.1)	75 (17.9)
Antibiotics can cause imbalance in the body's own bacterial flora	308 (73.3)	112 (26.7)
The unnecessarily use of antibiotics can increase the resistance of bacteria to them	311 (74)	109 (26)
Use of antibiotics can reduce the boy's own capacity to fight off infections	330 (78.6)	90 (21.4)

**Table 5: Doctor-patient relationships**

Statements	Yes	No
Doctors often take time to decide if I need an antibiotic or not	135 (32.1)	285 (67.9)
I trust the doctor's decision when s/he prescribes antibiotics	283 (67.4)	137 (32.6)
Pharmacy staff often tell you how antibiotics should be used	299 (71.2)	121 (28.8)
I know if I need antibiotics or not	237 (56.4)	183 (43.60)

cold, sore throat, and cough. Lack of education about the difference between viral and bacterial infection has caused this misunderstanding. Regarding the source of antibiotics 28.8% of the respondents had self-medicated which is close to a similar study conducted in Riyadh, Saudi Arabia by Al Barakh *et al.*, 2014,<sup>15</sup> showed that 23.6% used nonprescribed antibiotics. In 2014, Belkina *et al.*<sup>13</sup> conduct a similar study showed that 38.8% of the respondents stop taking antibiotic if they feel better. In comparison with our results, in this terms, we have a better result this indicates that most of the respondents have a good awareness in this issue. Regarding the patient doctor relationship our respondents is less satisfy in compare to a research conducted in Kuwait 2015.<sup>14</sup>

## CONCLUSION

We concluded the study by highlighting the need to educate population regarding the usage of antibiotics and the complications of the misuses and what are the indications of antibiotics, use only doctor prescription to get antibiotics. We health authorities are to dedicate and arrange public campaigns and workshops to raise the awareness of the general population. Eventually improve their attitudes toward nonprescription antibiotics. We also advise the pharmacists to only sale antibiotics to the patients with prescription, because the availability of nonprescription antibiotics leads to inappropriate self-medication.

## Limitation

This study was conducted in different locations in urban areas. Therefore, the result of this study may not represent the entire city. To improve this issue, a larger scale study needs to be performed in different places, including rural areas, to obtain a diversified study population.

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# Diagnostic Importance of Fine Needle Non-aspiration and Fine Needle Aspiration Cytology in Thyroid Lesions

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## Abstract

**Introduction:** Fine needle aspiration cytology (FNAC) is the routine, minimal invasive technique, and well-established baseline investigation used to diagnose the nodular thyroid lesion. The main disadvantages were an inadequate specimen or the specimen obtained was blood. To avoid these problems, a new method called as fine needle non-aspiration cytology is performed nowadays instead of FNAC.

**Aim:** To find the diagnostic importance of fine needle non-aspiration and FNAC in thyroid lesions.

**Materials and Methods:** This was a diagnostic study done at Melmaruvathur Adhiparashakthi Medical College and Hospital in the Department of Surgery from March 2013 to January 2015. About 55 patients who presented with a thyroid swelling were subjected to fine-needle aspiration (FNA) and fine needle cytology (FNC) technique and underwent thyroidectomy. The slides were assessed according to Mair *et al.* scoring system and compared with the histopathology reports. Finally, sensitivity, specificity, positive predictive value, and negative predictive value were calculated.

**Results:** In this study, the majority of the patients were 30-39 years (36.36%) of age. Females comprised about 54.55% of the study group. The diagnostic performance of FNC and FNA technique indicated that FNC yielded more diagnostically superior case than FNA. However, diagnostically adequate cases were more with FNA. On the whole, the sensitivity for the FNC and FNA were 87.04% and 90.74%. The negative predictive value for both FNC and FNA was 12.5% and 16.67%.

**Conclusion:** Both the techniques have similar results, hence, can be used in tandem. However, both the techniques should be used in different places. In high cellular lesions, FNC should be the first choice and in less cellular lesions FNAC should be preferred. But on the whole, FNAC was found to be diagnostically adequate and superior than FNC.

**Key words:** Fine needle aspiration cytology, Fine needle cytology, Thyroid lesion

## INTRODUCTION

The most common clinical problem encountered by the surgeon in their outpatient department is thyroid nodules. About 1-10% of the thyroid nodules are malignant.<sup>1</sup> The incidence of thyroid cancer tripled from 1975 to 2009 due

to the increased incidence of papillary thyroid carcinoma. Hence, a prompt diagnosis and treatment in time are necessary in curing the thyroid carcinoma.<sup>2</sup> A widely accepted method for diagnosing thyroid lesions is fine needle aspiration cytology (FNAC).

FNAC was first developed by Martin and Ellis in 1930.<sup>3</sup> It is the routine and well-established baseline investigation used to diagnose the nodular thyroid lesion. It was a minimal invasive technique which can be easily done with increased sensitivity, specificity and accuracy.<sup>4</sup> The main disadvantages were inadequate specimen or the specimen obtained was bloody due to negative pressure which may lead to unsatisfactory smear and improper interpretation.<sup>5-7</sup>

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To avoid these problems a new method called as fine needle non-aspiration cytology (FNNAC) fine needle cytology (FNC) was developed by Briffod *et al.* in France in 1982.<sup>8</sup> It was first described in diagnosing thyroid nodules by Santos and Leiman in 1988.<sup>7</sup> The main mechanism for FNNAC was it avoids active aspiration. It relies only on capillary tension to suck the tissues. By this way, it decreases the traumatic episodes and reduces the bleeding in thyroid tissue.<sup>9,10</sup> There are many studies regarding the superiority of FNAC to FNNAC and vice versa. However, the studies were inconclusive. Hence, we evaluated the diagnostic accuracy of FNAC and FNNAC in thyroid nodule.

## MATERIALS AND METHODS

This was a diagnostic study done at Melmaruvathur Adhiparashakthi Medical College and Hospital in the Department of Surgery from March 2013 to January 2015. About 55 patients who presented with a thyroid swelling and attended the cytology clinic were included in the study. All the patients were subjected to fine-needle aspiration (FNA) and FNNA technique. Both the techniques were done by 23 gauge needle and 20 ml disposable plastic syringe. The dry smears were stained by Giemsa stain, and the wet smear was stained with Papanicolaou stain.

This study was a single-blind study, and all the slides were assessed without knowing the knowledge about the technique by which the slide was prepared. The slides were assessed according to Mair *et al.* scoring system (Table 1). The main criteria were the presence of blood/clot, amount of cellular material, degree of cellular trauma, and retention of appropriate architecture. According to this, they are grouped into three categories like smear

unsuitable, smear adequate for cytological diagnosis and diagnostically superior smear. All the patients were subjected to thyroidectomy either partial or complete, and the histopathology reports were compared to the smear results. Finally, sensitivity, specificity, positive predictive value and negative predictive value for both FNA and FNNA technique were extracted.

## RESULTS

In this study, the majority of the patient belongs to the age group of 30-39 years (36.36%) followed by 40-49 years (32.73%) (Table 2). Females comprised about 54.55% of the study group, while male comprised 45.45%. All the patients were subjected to the thyroid function test, and all the reports were found to be within normal limit except for three patients who had elevated T-3 and T-4 values.

Clinically, out of 55 cases 45 (81.82%) were multinodular goiter, 5 (9.01%) were suspicious of malignancy, 4 (7.27%) were solitary nodule and 1 (1.82%) was toxic nodular goiter. The histopathology report came as nodular goiter in 42 (76.36%) cases, Hashimoto's thyroiditis in 6 (10.91%) cases, adenomatous nodule in 5 (9.1%) cases, toxic nodular goiter in 1 (1.82%) case, and multinodular goiter with micropapillary carcinoma in 1 (1.82%) case. The FNAC and FNC report were compared in Tables 3-5.

The diagnostic performance of FNC and FNA technique indicated that FNC yielded more diagnostically superior case than FNA. However, diagnostically adequate cases were more with FNA. On the whole, the sensitivity for the FNC and FNA were 87.04% and 90.74%, but the specificity and positive predictive value for both the procedures were 100%. The negative predictive value for both FNC and FNA were 12.5% and 16.67% (Table 6).

**Table 1: The Mair *et al.* scoring system**

Criteria	Quantitative description	Point score
Background blood/clot	Large amount, great compromise of diagnosis	0
	Moderate amount, diagnosis possible	1
	Minimal amount, diagnosis	2
Amount of cellular material	Minimal to absent, diagnosis not possible	0
	Sufficient for cytodiagnosis	1
	Abundant, diagnosis possible	2
Degree of cellular degeneration	Marked, diagnosis impossible	0
	Moderate, diagnosis possible	1
	Minimal, diagnosis easy	2
Degree of cellular trauma	Marked, diagnosis impossible	0
	Moderate, diagnosis possible	1
	Minimal, diagnosis obvious	2
Retention of appropriate architecture	Minimal to absent non diagnostic	0
	Moderate, some preservation of, for example, follicle, papillae, and acini	1
	Excellent architectural display closely reflecting histology, diagnosis obvious	2

**Table 2: Age distribution**

Age	Frequency (%)
20-29	9 (16.36)
30-39	20 (36.36)
40-49	18 (32.73)
50-59	8 (14.55)

**Table 3: Comparison between the FNC and FNAC diagnosis**

Diagnosis	FNC (%)	FNAC (%)
Single nodular goiter	28 (50.91)	28 (50.91)
Multi nodular goiter	18 (32.73)	18 (32.73)
Hashimoto's thyroiditis	3 (5.46)	4 (7.27)
Adenomatous nodule	1 (1.82)	3 (5.46)
Adenomatous nodule hyperplasia	3 (5.46)	1 (1.82)
Toxic nodular goiter	2 (3.64)	1 (1.82)

FNAC: Fine needle aspiration cytology, FNC: Fine needle aspiration

**Table 4: Comparison of FNC and FNAC diagnosis with histopathology report**

Diagnosis	FNC (%)	FNAC (%)	HPE (%)
Single/multi nodular goiter	46 (83.64)	46 (83.64)	42 (76.36)
Hashimoto's thyroiditis	3 (5.46)	4 (7.27)	6 (10.91)
Adenomatous nodule	1 (1.82)	3 (5.46)	5 (9.1)
Adenomatous nodule hyperplasia	3 (5.46)	1 (1.82)	0 (0)
Toxic nodular goiter	2 (3.64)	1 (1.82)	1 (1.82)
Multi nodular goiter with microscopic papillary carcinoma	0 (0)	0 (0)	1 (1.82)

FNAC: Fine needle aspiration cytology, FNC: Fine needle aspiration, HPE: Histopathological examination

**Table 5: Diagnostic performance**

Category	FNC (%)	FNA (%)
Diagnostically superior	16 (29.1)	13 (23.64)
Diagnostically adequate	34 (61.82)	38 (69.1)
Diagnostically unsuitable	5 (9.1)	4 (7.27)

FNA: Fine needle aspiration, FNC: Fine needle aspiration

**Table 6: Diagnostic accuracy of FNC and FNAC**

Diagnostic value	FNC (%)	FNA (%)
Sensitivity	87.04	90.74
Specificity	100	100
Positive predictive value	100	100
Negative predictive value	12.5	16.67

FNAC: Fine needle aspiration cytology, FNA: Fine needle aspiration, FNC: Fine needle aspiration

## DISCUSSION

Worldwide it has been already documented very clearly that FNAC is a gold standard method in diagnosing both palpable and nonpalpable masses. FNAC is also considered as the gold standard method in diagnosing thyroid swelling. It is a safe, simple and a cost effective method with a very

low complication rate. But still, another method which is simpler with less complications than FNAC should be found because of its limitation like inadequate specimens which require repeated aspirations.<sup>11</sup> The Thyroid gland is highly vascular. Samples taken from this may contain high quantities of blood and the cellular material may be inadequate for proper cytological interpretation. Hence, the diagnostic accuracy may decrease.

The maximum incidence of thyroid disorder was between 30 and 39 years followed by 40-49 years. The same observations have been stated by other authors. In this study, the majority were females (54.55%) followed by male patients (45.56%). All the patients showed a benign disease pattern except in one patient who had a multinodular goiter with micropapillary carcinoma in histopathology report. When both the techniques were compared with the parameters of blood clots, the FNC was found to be superior than FNAC. FNC gives a clear cytological report with least hemorrhage in the slide. The presence of blood was totally prevented by capillary action (i.e.,) while doing the procedure high pressure was not applied for aspirating the material. The vice versa occurs in FNAC. This was similar to other studies.<sup>7,10,12</sup>

In the high cellular lesion, the FNC was more likely to diagnose than FNAC. But in less cellular lesions FNAC was found to be diagnostically superior than FNC. The majority of the authors found that both were having similar reports.<sup>13-15</sup> Only very few studies had the results similar to the present study.<sup>7,16</sup> The degeneration and the cellular trauma were same for both techniques. FNAC had more cellular material if some sheets of cells were destroyed it does not obscure the field of diagnosis. This was contrast to the study done by Ghosh *et al.* and Raghuveer *et al.* In their study, they reported that FNC had a better score in cellular trauma and degeneration than FNAC.<sup>13,17</sup>

In our study, micropapillary carcinoma was detected in only one patient by histopathology. It was not diagnosed by FNAC or FNC. In a previous study, it was reported that there was a slight difficulty in diagnosing the carcinoma by FNC slide.<sup>7</sup> However, in our study, both methods failed to diagnose. On the diagnostic performance, FNC was producing diagnostically superior specimen ( $n = 16$  [29.1%]) than FNAC ( $n = 13$  [23.64%]). But diagnostically adequate specimen was yielded by FNAC ( $n = 38$  [69.1%]) than FNC ( $n = 38$  [69.1%]). This was contrast to the study done by others where FNC has diagnostically superior and diagnostically adequate slide than FNAC.<sup>7,10</sup>

In this study, FNC appears to be a better technique than FNAC in only one way (least hemorrhage). Both the techniques have its own advantages and disadvantages.

Sajeev and Siddaraju also done a similar study of comparison in lymph node lesion and concluded that FNC was superior in diagnosing cellular lymph node lesions.<sup>18</sup> The sensitivity, sensitivity, positive predictive value and the negative predictive value of FNC were 87.04%, 100%, 100%, 12.5%. The sensitivity, sensitivity, positive predictive value and the negative predictive value of FNAC were 90.74%, 100%, 100%, 16.67%, respectively. These results were compared with the other studies, and similar results were found.<sup>19,20</sup>

## CONCLUSION

Both the techniques have similar results, hence, can be used in tandem. However, both the techniques should be used in different places. In high cellular lesions, FNC should be the first choice and in less cellular lesions FNAC should be preferred. But on the whole, FNAC was found to be diagnostically adequate and superior than FNC.

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# A Nursing Study on the Assessment of Needs Gratification among School Children

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## Abstract

**Introduction:** All of us have needs but certain needs are more important in childhood. Children are very much dependent on others for the gratification of their needs. If their needs are met adequately, they will develop as balanced individuals.

**Objectives:** The objectives of this study were (1) to assess the need gratification of school children, living at home and staying in hostels. (2) To compare levels of need gratification among school children, living at home and stay in hostels. (3) To find out the association between need gratification and selected demographic variables of school children living at home and stay in hostels.

**Materials and Methods:** A systemic literature search was performed to identify all relevant articles to the research questions. The bibliographic databases, CIMS, WHO, FAO, Pub, CINHALL, and around 194 national and international book references with 40 national and international journals were searched from 2008 to 2012. The search comprised all the articles on literature related to needs and problems of children, child development, the family and child care at home and in hostel. Nonexperimental, descriptive design was adopted in this study. Selected population was higher secondary schools children studying in 8-12<sup>th</sup> class standard of Bhilai Town, District Durg, and Chhattisgarh. Stratified simple random technique was considered for data collection. The sample size was 500 among them 250 children were living at home, and 250 children were staying in the hostel.

**Results and Conclusion:** Based on findings study was concluded, the hostel students had fully gratified with hostel conditions. Because of trained warden/care takers and better facilities provided by the warden/care takers regarding physiological, safety, and belonging needs.

**Key words:** Gratification, Children, Nursing

## INTRODUCTION

The investigator appearances that physical and emotional condition of a child often is not clean is tired and has no energy, comes to schools without breakfast, often does not have lunch. Seems to be alone often, needs glasses, and dental care or the medical attention. Some of the children were unwilling to participate in physical activities, study timing and recreational activities, etc., in views of all these the investigators have decided to do a comparative study on “*A nursing study on the assessment of needs gratification among school children.*”

## Objectives

1. To assess the needs gratification among school children, living at home and in the hostel.
2. To compare the level of needs gratification among school children, living at home and in the hostel.
3. To determine the association between needs gratification and selected demographic variables among school children living at home and in the hostel.

## MATERIALS AND METHODS

The research approach adopted for this study was nonexperimental survey approach, ex post facto research design used to examine the association between the demographic variables and relationship of needs and gratification among subjects living with parents and staying in the hostel. Ethnographic survey research was used to fixed answer for the self-administered questionnaire to elicit the gratification on needs

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gratification among school children living with parents and staying in the hostel.

### Sample Size

Among 500 samples, 250 Children were living at home, and 250 children were living in the hostel.

### Sampling Technique

The stratified simple random technique was considered.

Section A: It consists of questionnaire about participants housing condition and hostel condition.

Section B: It consists of rating scale to assess the levels of needs gratification among school children regarding five basic needs.

In the Table 1, all gratification tools' stability were  $\geq 0.7$  ( $r \geq 0.7$ ), and the stability of the tools were more than 50%.

### Internal Consistency

The internal consistency of the gratification tools were tested by Croneback's alpha ( $\alpha$ ). They were physiological needs.

### Stability

The stability of the tool was tested by test, retest method. The Pearson correlation coefficient ( $r$ ) between the test and retest of physiological needs gratification, safety needs gratification, and belonging needs gratification is shown in Table 2.

### Data Collection Procedure

There were 47 schools having without hostel facility for such children, among these 5 schools has been selected at random to make 50% of the available school for inclusion in the sample. From each school 10 students were selected from each class of 8<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, and 12<sup>th</sup> standards, coming from the home. Similarly, there were 10 schools

having hostel facility for such children, among these 5 schools has been selected at random to make 50% of the available school for inclusion in the sample. From each school were having hostel facility 10 students were selected from each class of 8<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, and 12<sup>th</sup> standards, staying in hostels. Permission was obtained from concerned selected schools. List of subjects was collected from each selected school. The data were collected from September 2011 to March 2012.

## RESULTS

The study subjects of home and hosteller were described according to the demographic characteristics in terms of percentages. They were matched for comparison by the prime variables of age and the class of studying. Pearson correlation coefficient was applied to analyze and interpret the relationship between the condition of home or hostel with the respective needs gratification. The needs gratification of home and hosteller were compared and interpreted by Student's independent  $t$ -test. The gratification needs of physiological, safety and belonging needs were analyzed in terms of percentages. The associations between gratifications of needs and demographic characteristics were studied by Chi-square test ( $\chi^2$ ). The above statistical procedures were performed by the statistical package predictive and analysis software statistics version-18, the so-called SPSS. The  $P < 0.05$  was considered as statistically significant under two-tailed test.

As per the objectives of a study finding were:

Section A: Distribution of students according to their demographic profiles.

Table 3 describes the demographic characteristics of the students in terms of percentages of home as well as hostel

**Table 1: Stability of gratification tools of home and hostel**

Gratification tool	Home (n=30)				Hostel (n=30)			
	"r"	Significance	r <sup>2</sup>	%	"r"	Significance	r <sup>2</sup>	%
Physiological	0.973	P<0.000	0.947	94.7	0.945	P<0.000	0.893	89.3
Safety	0.881	P<0.000	0.776	77.6	0.757	P<0.000	0.573	57.3
Belonging	0.908	P<0.000	0.824	82.4	0.786	P<0.000	0.618	61.8

**Table 2: Internal consistency of gratification tools of house and hostel**

Gratification tool	Home (n=30)				Hostel (n=30)			
	"α"	Significant	α <sup>2</sup>	%	"α"	Significant	α <sup>2</sup>	%
Physiological	0.807	P<0.000	0.651	65.1	0.867	P<0.000	0.752	75.2
Safety	0.792	P<0.000	0.623	62.3	0.704	P<0.000	0.501	50.1
Belonging	0.712	P<0.000	0.507	50.7	0.709	P<0.000	0.503	50.3

**Table 3: Distribution of students according to their demographic profiles**

Demographic profiles	Category	Number (%)	
		Home (n=250)	Hostel (n=250)
Age group (years)	14-15	100 (40.0)	100 (40.0)
	16-17	121 (48.4)	119 (47.6)
	18+	29 (11.6)	31 (12.4)
Gender	Male	106 (42.4)	97 (38.8)
	Female	144 (57.6)	153 (61.2)
Class of studying	VIII	49 (19.6)	50 (20.0)
	IX	51 (20.4)	51 (20.4)
	X	50 (20.0)	50 (20.0)
	XI	50 (20.0)	49 (19.6)
	XII	50 (20.0)	50 (20.0)
	Nuclear	122 (48.8)	170 (68.0)
Type of family	Joint	128 (51.2)	80 (32.0)
	Hindu	108 (43.2)	174 (69.6)
Religion	Muslim	62 (24.8)	41 (16.4)
	Sikhs	48 (19.2)	15 (6.0)
	Christians	32 (12.8)	20 (8.0)
	2000-12000/m	29 (11.6)	91 (36.4)
Family monthly income (INR)	13000-23000/m	93 (37.2)	65 (26.0)
	24000-34000/m	59 (23.6)	22 (8.8)
	≥350000/m	69 (27.6)	72 (28.8)
	Illiterate	2 (0.8)	39 (15.6)
Father's education	Primary	6 (2.4)	32 (12.8)
	Middle	6 (2.4)	16 (6.4)
	High school	15 (6.0)	30 (12.0)
	Higher secondary+	221 (88.4)	133 (53.2)
Mother's education	Illiterate	20 (8.0)	45 (18.0)
	Primary	36 (14.4)	43 (17.2)
	Middle	4 (1.6)	25 (10.0)
	High school	25 (10.0)	38 (15.2)
Father's occupation	Higher secondary+	165 (66.0)	99 (39.6)
	Service	116 (46.4)	95 (38.0)
	Business	120 (48.0)	73 (29.2)
	Others	14 (5.6)	82 (32.8)
Mother's occupation	Service	79 (31.6)	55 (22.0)
	Business	123 (49.2)	68 (27.2)
Relation to head of family	Others	48 (19.2)	127 (50.8)
	Son	85 (34.0)	68 (27.2)
	Daughter	124 (49.6)	121 (48.4)
No. of siblings	Others	41 (16.4)	61 (24.4)
	1	89 (35.6)	65 (26.0)
	2	124 (49.6)	72 (28.8)
	3	23 (9.2)	55 (22.0)
	4+	14 (5.6)	58 (23.2)
Primary source of help	Father/Warden	99 (39.6)	165 (66.0)
	Mother/Care taker	97 (38.8)	43 (17.2)
	Both	54 (21.6)	42 (16.8)
Closeness at home/hostel	Father/Warden	60 (24.0)	151 (60.4)
	Mother/Care taker	56 (22.4)	56 (22.4)
	Both/Any other	134 (53.6)	43 (17.2)
	Caring nature/Cooperation	53 (21.2)	73 (29.2)
Reasons of closeness	Caring nature	50 (20.0)	52 (20.8)
	Cooperation	157 (62.8)	125 (50.0)

students. The selection of the subjects was made based on the prime characteristics of the students such as age and class studying. They were matched by their age and class since they have to be compared between the home dwelling and hostel staying students.

Section B: Comparison of home and hostel students according to their age group (year).

The comparison in Table 4 reveals that the home students and hostel students were not significantly differed in respect of their age groups (year) ( $P > 0.05$ ).

Section C: Comparison of home and hosteller students according to their class.

Table 5 compares the class of studying the home and hosteller students. 50 students were selected from each class for both study groups.

Section D: Assessment of needs gratification of home and hostel students (Table 6a-c).

Section E: Comparison of needs gratification of home and hostel students.

The comparison of home and hosteller students' gratifications are shown in Table 7. The mean gratification of physiological needs of home students was 18.4, (standard deviation [SD] 7.8) and it was 20.1, (SD 7.7) for hostellers, observed difference was statistically significant ( $P < 0.05$ ). The mean safety needs gratification of home was 19.6, (SD 7.7) and the same for the hostellers was 23.2, (SD 9.5) the difference observed was highly statistically significant ( $P < 0.001$ ). The mean gratification of belonging needs of home and hosteller students were 19.3, (SD 8.3) and 23.3, (SD 8.2), respectively.

Section F: Comparison of home and hostel conditions of students. The conditions of home and hostel of students were compared to identify the difference of conditions between them.

The results of the comparison between are presented compared in Table 8. The mean condition of the home was 24.3 (SD 3.0) and it was 20.9 (SD 5.1) for hosteller students. The mean difference was highly statistically significant ( $P < 0.001$ ).

Section G: Relationship between home/hostel conditions with gratification of needs. The conditions of home and hostel were correlated with their respective gratification of needs such as physiological needs, safety needs, and belonging needs (Table 9).



**Table 4: Comparison of home and hostel students according to their age group (year)**

Age (years)	Number (%)	
	Home students	Hostel students
14-15	100 (40.0)	100 (40.0)
16-17	121 (48.4)	119 (47.6)
18+	29 (11.6)	31 (12.4)
Total	250 (100)	250 (100)

Chi-square test statistic=0.08;  $P=0.96$ ; not statistically significant**Table 5: Comparison of home and hosteller students according to their class of studying**

Class studying	Number (%)	
	Home students	Hostel students
VIII	50 (20)	50 (20)
IX	50 (20)	50 (20)
X	50 (20)	50 (20)
XI	50 (20)	50 (20)
XII	50 (20)	50 (20)
Total	250 (100)	250 (100)

**Table 6a: Assessment of gratification of physiological needs of home and hostel students**

Score	% of score	Category	Number (%)	
			Home students	Hostel students
32-40	81-100	Fully gratified	15 (6.0)	14 (5.6)
24-31	61-80	Gratified	56 (22.4)	73 (29.2)
16-23	41-60	Moderately gratified	84 (33.6)	99 (39.6)
8-15	21-40	Minimally gratified	76 (30.4)	46 (18.4)
0-7	0-20	Not gratified	19 (7.6)	18 (7.2)
Total			250 (100)	250 (100)

Chi-square test statistic=10.91;  $P=0.03$ ; not statistically significant**Table 6b: Assessment of gratification of safety needs of home and hostel students**

Score	% of score	Category	Number (%)	
			Home students	Hostel students
32-40	81-100	Fully gratified	15 (6.0)	57 (22.8)
24-31	61-80	Gratified	65 (26.0)	77 (30.8)
16-23	41-60	Moderately gratified	87 (34.8)	83 (33.2)
8-15	21-40	Minimally gratified	66 (26.4)	17 (6.8)
0-7	0-20	Not gratified	17 (6.8)	16 (6.4)
Total			250 (100)	250 (100)

Chi-square test statistic=54.57;  $P<0.001$ ; highly statistically significant

## DISCUSSION

In 1<sup>st</sup> objective, our study revealed that home students will be more gratified than hostel students with their physiological, safety, love, and belonging needs.<sup>1</sup> However, our study revealed opposite of need and gratification of

**Table 6c: Assessment of gratification of belonging needs of home and hostel students**

Score	% of score	Category	Number (%)	
			Home students	Hostel students
32-40	81-100	Fully gratified	23 (9.2)	38 (15.2)
24-31	61-80	Gratified	54 (21.6)	103 (41.2)
16-23	41-60	Moderately gratified	80 (32)	62 (24.8)
8-15	21-40	Minimally gratified	77 (30.8)	34 (13.6)
0-7	0-20	Not gratified	16 (6.4)	13 (5.2)
Total			250 (100)	250 (100)

Chi-square test statistic=38.23;  $P<0.001$ ; highly statistically significant**Table 7: The home students and hostellers were compared in respect of their gratification such as physiological needs, safety needs, and belonging needs**

Gratification	Mean±SD		t statistic	d.f	Sig.
	Home students (n=250)	Hostel students (n=250)			
Physiological needs	18.4±7.8	20.1±7.7	2.397	498	$P<0.05$
Safety needs	19.6±7.7	23.2±9.5	4.731	498	$P<0.001$
Belonging needs	19.3±8.3	23.3±8.2	5.441	498	$P<0.001$

SD: Standard deviation

**Table 8: Comparison of home and hostel conditions of students**

Variable	Mean±SD		t statistic	d.f	Sig.
	Home students (n=250)	Hostel students (n=250)			
Home/Hostel condition	24.3±3.0	20.9±5.1	8.982	498	$P<0.001$

SD: Standard deviation

**Table 9: Correlation of home and hostel condition with gratification of needs**

Home condition with gratification of	"r"	Sig.	Hostel condition with gratification of	"r"	Sig.
Physiological needs	-0.096	$P>0.05$	Physiological needs	0.329	$P<0.001$
Safety needs	-0.016	$P>0.05$	Safety needs	0.27	$P<0.001$
Belonging needs	0.015	$P>0.05$	Belonging needs	0.295	$P<0.001$

hostel students were more gratified with all three basic needs compare to home students and home children were not gratified of their needs because of nuclear family, less educated parents, working parents, lack in care of children at home, under care of untrained care takers/mates, broken family, and parents may be under stress because of over burden of work at working place and at home, no love and affection to children, more number of sibling, lower income of the family, etc.

Objective 2: To compare levels of need gratification among school children, living at home, and stay in hostels.<sup>2</sup> In 2<sup>nd</sup> objective our study revealed that the comparisons of house and hostel students' gratifications were shown in the above Table 7. The mean gratification of Physiological needs of house students was  $18.4 \pm 7.8$  and the same of the hostellers was  $20.1 \pm 7.7$ . The difference between them was statistically significant ( $P < 0.05$ ). The mean safety needs gratification of the house was  $19.6 \pm 7.7$ , and the same of the hostellers was  $23.2 \pm 9.5$ . The difference between them was statistically very highly significant ( $P < 0.001$ ). The means gratification of belonging needs of house and hostel students were  $19.3 \pm 8.3$  and  $23.3 \pm 8.2$ , respectively. The relationship between house condition with the gratification needs of house students were not significantly correlated ( $P > 0.05$ ). The house students were not gratified with their house conditions, but the hostel conditions were significantly positively correlated with physiological need, safety need, and belonging needs ( $P < 0.001$ ). The hostel students had fully gratified with hostel conditions. Because of trained care takers/warden in hostels, who gratified the need of the hostellers.<sup>3</sup>

Objective 3: To find out the association between need gratification and selected demographic variables of school children living at home and stay in hostels.

Study revealed that;

1. The physiological need gratification of hostel students was statistically significantly associated with their demographic characteristics such as religion, class, closure to hostel warden/care takers, and reasons for closeness ( $P < 0.05$ ).

Because all religion parents agreed to admit their children in school with hostels facility and they were not concern with religion of the other students, care takers, and warden.<sup>4-6</sup> Parents were agreed with the rules and regulations of the hostels as well as hosteller students accepted positively, environment of hostels. Beside these hosteller students were receiving, proper balanced and nutritious diet at a time, clean water facilities, proper ventilation, rest and steep, physical exercise, adequate time for study, and recreation along with sports facilities.<sup>7-9</sup>

Whereas, the physiological need gratification of house students were not significantly associated with their all demographic characteristics ( $P > 0.05$ ) because parents were not paying attention to words their children because of less education, less income, more number of sibling, joint family, only father may be earning member in the family, and inadequate facility at home.

The safety need gratification of hostel students were statistically associated with their demographic characteristics

such as age, class, education of mother, occupation of father and mother, closer to hostel, and reasons for closeness ( $P < 0.05$ ). Because from 8<sup>th</sup> to 12<sup>th</sup> standard of students, between the age group of 14-18 years met safety needs such as immunization facility, properly maintenance of health records, feeling of safety under the care of warden/care takers, provision for training of personal hygiene, followed rules and regulation of hostels, paying attention toward need of children, feeling of fearlessness and facing problem with full strength in the presence of care takers/warden, and because of highly education of mother, occupation of father and mother, parents think that they cannot spent time and give care in a proper way for their children. Hence, as a result, hostel is the best residential place where their children can met with their needs.<sup>10,11</sup>

Whereas, the safety need gratification of house students were statistically significantly associated with their demographic characteristics ( $P < 0.05$ ) such as class only.

3. The hosteller belonging need gratification was statistically significantly associated with their demographic characteristics such as class and education of mother ( $P < 0.05$ ).

From 8<sup>th</sup> to 12<sup>th</sup> standard of school children hostel are the residential area as a safety point of view and proper growth and development of child where children will get love and affection, play therapy with peer group relaxation therapy as well as care from care takers/warden when he/she falls sick. Because highly educated mother will do service/business and would not be able to meet need at home.

Whereas, the belonging needs gratification of house students were statistically associated with their demographic characteristics ( $P < 0.05$ ) age, class, and occupation of father. Because house students from 14 to 18 years of age studying in 8<sup>th</sup> to 12<sup>th</sup> standard received love and affection from mothers who is housewives and well educated. Because of occupation of father and good position (service/business) paid attention to met need of children.

From the above results and discussions, the research hypothesis ( $H_1$ ), "there will be significant difference between needs gratification of school children living at home and in the hostel," is accepted and concluded that the hostellers' needs gratification is significantly more than the children living in home.

The research hypothesis ( $H_2$ ), "there will be association between needs gratification and the selected demographic variables of School children living at home and in the hostel," is rejected in respect of all demographic profiles of School children living at home regarding physiological

needs gratifications. Moreover, the following demographic variables related to respective needs gratification are also rejected.

1. Safety needs gratification = Age, sex, religion, type of family, family monthly income, education of father, education of mother, occupation of father, occupation of mother, siblings, primary source of help, closer to family/hostel head, and reasons of closeness.
2. Belonging needs gratification = Sex, religion, type of family, family monthly income, education of father, education of mother, occupation of mother, relation to head of family, siblings, primary source of help, closer to family/hostel head, and reasons for closeness.

## CONCLUSION

Based on findings, the study was concluded that the hostel students had fully gratified with hostel conditions. Because of trained warden/care takers and better facilities provided by the warden/care takers regarding physiological, safety, and belonging needs.

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# Pulmonary Manifestations in Human Immunodeficiency Virus Infected Patients and Correlation with CD4 Count: A Clinical Observational Study

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## Abstract

**Introduction:** Pulmonary manifestations are common in patients with human immunodeficiency virus (HIV) infections. In this study, we attempt to evaluate the various pulmonary manifestations and its correlation with CD4 count from a tertiary center in the low prevalence state of Kerala.

**Materials and Methods:** A total of 56 patients with HIV infection presenting with respiratory symptoms were evaluated and investigated for 24 months.

**Results:** Out of the 56 patients, 36 were diagnosed to have pulmonary tuberculosis (TB). 18 had smear positive TB, 18 smear negative TB, 13 *Pneumocystis* pneumonia, 3 bacterial pneumonia, no definite etiology identified in 5. The mean CD4 count was lower in smear positive TB patients than in smear negative.

**Conclusion:** The most common opportunistic respiratory infection in HIV-infected individuals was pulmonary TB (63%). The mean CD4 count in patients with smear positive TB was significantly lower than that of smear negative TB.

**Key words:** CD4 counts, Human immunodeficiency virus infected, Pulmonary manifestations

## INTRODUCTION

The lungs are the major target organs in patient with human immunodeficiency virus (HIV) and in patients with the acquired immunodeficiency syndrome (AIDS). In developed countries, the use of highly active antiretroviral therapy (HAART) and prophylaxis against *Pneumocystis* pneumonia (PcP), *Mycobacterium tuberculosis* (MTB), and *Mycobacterium avium* complex has changed the spectrum of disease affecting the lungs. In these countries in the pre-HAART era, 65% of patients had evidence of pulmonary disease. PcP was the most common cause followed by TB,

fungi and bacterial pneumonia. Now there are fewer cases of opportunistic infections, and pulmonary symptoms are more often due to noninfectious complications.

In the developing world, the situation has not changed much. The major cause of pulmonary morbidity and mortality is still attributable to opportunistic infections, with TB being the prime culprit.

India has the third largest HIV epidemic in the world. In 2015, HIV prevalence in India was an estimated 0.26%. The states with high HIV prevalence rates include Manipur (1.40%), Andhra Pradesh (0.90%), Mizoram (0.81%), Nagaland (0.78%), Karnataka (0.63%), and Maharashtra (0.55%).

The state of Kerala comes under the category of low prevalence states. Although there have been a few studies on pulmonary manifestations of HIV infection from the high and moderate prevalence states, there are not many studies focusing on this aspect from the state of Kerala.

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This particular study, therefore, attempts to evaluate the various pulmonary manifestations in HIV-infected patients and its correlation with CD4 count from a tertiary referral center in North Kerala.

## MATERIALS AND METHODS

### Setting

Institute of chest diseases, Medical College, Calicut.

### Period of Study

24 months.

### Study Design

Observational study.

### Inclusion Criteria

All patients diagnosed to have infected with HIV presenting with respiratory symptoms.

All patients presenting with respiratory symptoms, subsequently, found to be infected with HIV.

### Exclusion Criteria

Patients who had other reasons for immunosuppression.

A total of 56 patients with respiratory symptoms were admitted and evaluated. If already diagnosed to have HIV infection, the diagnosis was confirmed by repeated testing. The study population consisted of all adults more than 15 years. Patients were evaluated using a pre-designed pro forma regarding the demographic characteristics, risk factors for HIV infection, presenting symptoms, physical findings, and laboratory parameters. Using the history and investigations available including CD4 counts, all efforts were made to reach at a possible diagnosis for the patient's symptoms. All patients were counseled and offered antiretroviral therapy, whenever indicated. On discharge from the hospital, patients were advised to follow-up as outpatients, on a regular and as needed basis.

## RESULTS

The following are the observations made in 56 patients over the study period of 2-year.

### Age

The mean age at presentation was 39.3. The maximum number of patients belonged to 21-40 age group (59%) (95% confidence interval = 44.1-70-9).

### Sex

The ratio of males to females was 3:1.75% of the study group was formed by males, 25% by females.

### Symptoms in the Study Group

The most common symptom at the presentation was cough, which was followed closely by fever and dyspnea.

### Symptoms in TB Patients

The most common symptom in patients with TB was fever (92%) and cough (89%) followed by weight loss, which was also seen in 58% of the patients.

### Diagnosis

Out of 56 patients, 36 patients had a diagnosis of pulmonary TB. Smear positive TB was diagnosed if the patient's sputum, pleural fluid or lymph node smear (along with respiratory symptoms and chest radiological abnormalities) was positive for acid-fast bacilli. Smear negative TB was diagnosed based on symptoms along with suggestive chest radiological abnormalities, positive tuberculin test (>5 mm) or a favorable response to anti-TB treatment. 18 patients had smear positive TB and 18 had smear negative TB.

PcP was diagnosed if the patients had the organism demonstrable from the sputum, or symptoms or recent onset fever, rapidly progressive dyspnea, dry cough along with suggestive radiological features and a favorable response to cotrimoxazole. 13 patients were diagnosed to have PcP, out of which in 2 patients the organisms was demonstrable from sputum. One patient who had PcP presented 1 year later with features of left pleural effusion and his sputum was positive for acid-fast bacilli.

About 3 patients had a diagnosis of bacterial pneumonia. This was diagnosed based on the clinical features and isolation of organism from the sputum along with radiological abnormalities. In 2 patients, pneumococci were isolated, and in 1 patient, *Klebsiella* species was isolated. One patient with pneumococcal pneumonia gave a history of similar episode 8 months back (recurrent pneumonia) and the other 2 patients had a history of TB and had evidence of fibrosis in their chest radiograph.

No definite diagnosis was possible in 5 patients in spite of all the available investigations. They had respiratory symptoms but no chest radiological abnormalities.

Most of the patients with smear positive TB had upper zone shadows (44%), 3 had mid zone shadows, 3 had pleural effusion, 2 had lower zone infiltrates, and one each had hydropneumothorax and miliary shadows.

In smear negative TB, the most common chest radiological abnormality seen was hilar prominence (28%) and pleural effusion (28%). 4 patients had lower zone shadows, 2 had mid zone shadows, one each had upper zone infiltrates and miliary shadows.



In PcP, 9 (69%) patients had mid zone perihilar infiltrates and 4 (31%) had lower zone infiltrates. In patients with bacterial pneumonia, 2 had mid zone infiltrates and one had evidence of right upper lobe fibrosis with secondary pneumonia.

### CD4 Count

The mean CD4 count was 85.1 cells/ $\mu$ L (48 subjects). The mean CD4 count in patients diagnosed to have TB was 88.3 cells/ $\mu$ L (32 subjects). In smear positive TB, the mean CD4 count was 64.3 cells/ $\mu$ L (17 subjects). In smear negative TB it was 115.6 cells/ $\mu$ L (15 subjects). There was statistically significant difference between two groups ( $P = 0.03$ ). The mean CD4 count in patients with PcP was 70.2 cells/ $\mu$ L (10 subjects). In patients diagnosed to have bacterial pneumonia, the mean CD4 count was 66 cells/ $\mu$ L (3 subjects).

In patients with TB, when the CD4 count was compared with the radiological picture, there was no significant difference in the different groups except in the group with miliary shadows whose mean CD4 count was relatively higher (172 cells/ $\mu$ L) although there was no statistical difference between the various groups.

### Deaths

Six patients (10.7%) died during their course in hospital. Two were diagnosed to have smear positive TB, 3 patients had PcP, one had smear negative TB. The mean CD4 count in these patients was 46.7 cells/ $\mu$ L. This was significantly lower when compared to the patients who were discharged alive ( $P = 0.04$ ).

## DISCUSSION

Opportunistic infections remain the major cause of morbidity and mortality in HIV-infected individuals in India. In resource limited settings such as ours, knowledge about the prevalence of various opportunistic infections would help in making decisions regarding empirical treatment and also in prioritizing treatment for these patients.

Out of 56 patients included in this study, some of the patients already had been diagnosed to have HIV infection from elsewhere and presented with respiratory symptoms at our outpatient department. Others were diagnosed to have HIV infection while being worked up for their respiratory symptoms. The study population mostly belonged to the six districts of North Kerala to which the hospital caters. Being a tertiary care center, most of the patients with milder symptoms would have obtained treatment from their local health facilities.

The mean age at presentation was 39.3 maximum number of patients belonged to the 21-40 age group (59%). 39% of the study population belonged to the age group of 41-60. The National AIDS Control Organization (NACO) also suggests that AIDS is affecting mainly young people in the sexually active group. The majority of the HIV infections (87.7%) are in the age group 15-44 years.

Males dominated the study population with a male female ratio of 3:1. The NACO figures also mention a similar ratio. In a study conducted by the dermatology department, Medical college Thiruvananthapuram, the male/female ratio was 2.3:1 and the maximum number of patients was seen in age group 21-40 (77.68%).<sup>1</sup>

The most common symptoms with which the subjects presented was cough (93%), followed by fever (80.7%) and dyspnea (68.4%). In two studies from North India,<sup>2,3</sup> the most common symptoms were fever and weight loss. However, their study population included all HIV patients irrespective of their pulmonary symptomatology. The most common symptoms in patients diagnosed to have TB were fever (92%), cough (89%), and weight loss (58%). Rupali *et al.*<sup>4</sup> have suggested that TB is the most common cause of prolonged fever in HIV-infected adults in India. Hira *et al.* has inferred that clinical features of HIV associated TB in decreasing order of frequency were chronic fever, chronic cough, lymphadenopathy, and hepatosplenomegaly.<sup>5</sup>

Nearly 66% of patients had a relapse of TB. It is a well-known fact that rate of recurrence both due to endogenous reactivation and exogenous reinfection are increased in HIV-infected patients. A HIV positive person infected with MTB has a 50-60% life time risk of developing TB disease as compared to an HIV negative person who has only a 10% risk. This is especially important in India where it estimated that 40% of the adult population harbors MTB. Furthermore, HIV-infected persons who become newly infected with MTB rapidly progress to active TB disease.

Lymphadenopathy (73%) and candidiasis (72%) were the most common physical findings. TB could be proved from 4 cases of cervical lymphadenopathy. Hepatosplenomegaly was detected in 12 subjects. In a study from Thiruvananthapuram,<sup>7</sup> candidiasis was detected in exactly 72% of the cases whereas in 2 studies from North India, the figures are much less (40.3% and 39.3%).

Anemia was detected in 48% of the patients. This is similar to the figure of 50.5% suggested by Sharma *et al.*

TB was the most common cause for respiratory symptoms in this study group. In India, most of the studies find that TB is the most common opportunistic pulmonary infection

although many suggest that extrapulmonary TB may be more common than pulmonary TB. TB accounted for the symptoms of 63% of the patients. Comparing with other studies, Sharma *et al.* - 71%,<sup>2</sup> Sircar *et al.* - 54.8%,<sup>3</sup> Rajendran and Devasia - 37.8%,<sup>7</sup> Kumarasamy *et al.* - 49%,<sup>9</sup> Chacko *et al.* - 52%.<sup>10</sup> But in all these studies, both pulmonary and extrapulmonary TB were included and the study population consisted of all HIV, irrespective of their symptoms unlike our study where only patients with respiratory symptoms were evaluated. Both smear positive and smear negative TB were evaluated. Both smear positive and smear negative TB were equally identified in our study population (50% each). The NACO guidelines for HIV TB suggest that TB is harder to diagnose in HIV-infected people than in those not infected with HIV. In late HIV, 35-50% of HIV positive people are detected to have pulmonary TB on sputum sample examination, which means that the *Mycobacterium* may not be detected in the sputum in large numbers of TB patients with late stage HIV.

PcP was diagnosed in 23% of the patients. The cysts of *Pneumocystis jirovecii* were visualized in only two patients. The rest of the patients were diagnosed based on their clinical and radiological features and their response to treatment. The presence of PcP in other related studies are Kumarasamy *et al.* - 6%, Rajendran and Devasia - 1.8%, Sharma *et al.* - 7.4%, and Rupali *et al.* - 7%. Bacteria could be isolated from the sputum in only three patients (5%) in our study. In other studies, Chacko *et al.* - 44%, Nair *et al.* - 13.2%, Rajendran and Devasia - 2.3%, the occurrence of bacterial pneumonia has been variable. This might be due to the variation in the facilities available at these centers. The low occurrence of PcP might be due to the fact that in the above mentioned related studies, all systems were included unlike ours where only patients with respiratory symptoms were included. More recent reports have noted that PcP comprises a significantly greater percentage of cases of pneumonia than it did in the past. This trend dramatically contrasts with that observed in industrialized nations, where a reduction in the number of cases of PcP has occurred as a result of the widespread use of primary *P. jirovecii* prophylaxis and HAART. Throughout the developing world, the rate of coinfection with MTB and PcP is high, ranging from 25% to 80%.<sup>11</sup>

No definite diagnosis could be made in 5 patients (9%). The chest radiograph was also normal in these patients. The reason could be that they could be not diagnosed because of nonavailability of further investigations. Another possibility is that in patients with HIV infections, symptoms and pulmonary function test abnormalities may arise even before or independent of overt pulmonary complications. This may be reflecting a heightened susceptibility of these patients to the effects of cigarette smoking. (Table 1)<sup>12</sup>

The mean CD4 count in this study was 85.1/ $\mu$ L. 95.6% of the patients had a CD4 count <200 cells/ $\mu$ L. In the study by Sharma *et al.*, this accounted for 82.6% of the patients. In patients with TB, the mean CD4 count was 88.3 cells/ $\mu$ L (Table 2). The CD4 counts of smear positive TB were significantly lower than that of smear negative TB patients ( $P = 0.03$ ). This is supported by a study by Jones *et al.* where acid fast smears were more often positive in patients with low CD4 cell counts.<sup>13</sup> The CD4 count was also very low in patients with miliary TB. The mean CD4 count in patients with bacterial pneumonia and PcP were >80 cells/ $\mu$ L in our study. Ramalingam suggests that the mean CD4 count among normal South Indians is significantly lower than that in western population and parallels that of the Chinese.<sup>14</sup> This may be the reason for the lower CD4 counts in our study population.

In spite of the low CD4 count, most patients with smear positive TB presented with classical upper zone shadows (44%). Most of the patients with smear negative TB had hilar shadows or pleural effusion (56%) (Table 2). Again contrary to the usual findings, the patients with hilar prominence had a relatively high CD4 count\* (172 cells/ $\mu$ L). Pleural effusion was seen in both smear positive and negative TB patients over wide range of CD4 counts. Upper zone infiltrate typical of PTB reactivation is usually associated with early HIV infection and so seen at higher CD4 counts. Lower or midzone infiltrates, adenopathy, interstitial pattern or normal radiograph are associated with advanced HIV disease and so at a lower CD4 count<sup>15</sup> (Table 3). The large discrepancy seen in this study could be due to the fact that CD4 counts in some of the patients were evaluated months after they had been diagnosed to have TB and started on treatment. We believe that exceptionally high

**Table 1: CXR distribution in tuberculosis**

CXR distribution	Smear positive	Smear negative	Total
Upper zone	8	1	9
Mid zone	3	2	5
Lower zone	2	4	6
Hilum	0	5	5
Pleural effusion	3	5	8
Hydropneumothorax	1	0	1
Miliary	1	1	2
Total	18	18	36

CXR: Chest X-ray

**Table 2: Relation between CD4 count in smear positive and smear negative TB**

TB cases	Number	Mean CD4 count (cells/ $\mu$ L)
Smear positive	18	64.3
Smear negative	18	115.6

TB: Tuberculosis

**Table 3: Relation between CD4 count and CXR distribution in smear positive and smear negative TB**

CXR distribution	Smear positive	Average CD4 count (n)	Smear negative	Average CD4 count (n)
Upper zone	8	59.1 (6)	1	98 (1)
Mid zone	3	71 (3)	2	39 (1)
Lower zone	2	96.5 (3)	4	101 (4)
Hilum	0	-	5	172 (5)
Pleural effusion	3	60.6 (3)	5	93.3 (3)
Hydropneumothorax	1	70 (1)	0	-
Miliary	1	21 (1)	1	25 (1)
Total	18	64.3 (17)	18	115.6 (15)

CXR: Chest X-ray, TB: Tuberculosis

CD4 count is due to the improvement in counts with anti TB treatment.

Patients diagnosed to have PcP mostly has bilateral mid zone infiltrates (69%). In patients diagnosed to have bacterial pneumonia, pneumococci were isolated in two patients and *Klebsiella* species in one. In literature too, *Streptococcus pneumoniae* is responsible for the majority of bacterial pneumonias in HIV-infected patients.

Six patients (10.7%) died during their course in the hospital. They had very low CD4 count compared to those who were discharged (46.7 cells/ $\mu$ L) ( $P = 0.004$ ). In the study by Sharma *et al.*, 21 patients (15.6%) died in hospital, most of them due to TB (16 patients) and PcP (4 patients). All patients who died in hospital except for one, had CD4 count  $<200$  cells/ $\mu$ L.

The pulmonary manifestations detected in this study may be very low compared to the actual prevalence of these complications. In a study by Wallace and Hannah at autopsy, all patients with HIV infection had pulmonary disease. Only one third of the diagnoses had been made when the patient was alive.<sup>16</sup>

## CONCLUSION

The most common cause for respiratory symptoms in HIV-infected individuals was pulmonary TB (63%). The other opportunistic infections in the study group were PcP (23%) and bacterial pneumonia (5%). The mean CD4

count in patients with smear positive TB was significantly lower than that of smear negative TB in these patients. No definite radiological pattern could be predicted for patients with TB according to their CD4 count. The patients who died in the hospital (10.7%) had a significantly low CD4 count.

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# Drainage of Liver Abscess: Comparison between 20 Fr Polyvinyl Chloride versus 10 Fr Pigtail Catheter

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## Abstract

**Background:** Liver abscesses, refractory to medical therapy requires percutaneous drainage by catheter placed under ultrasonography guidance is considered as the treatment of choice. Pigtail catheter is most commonly used for this purpose which gets repeatedly blocked, requires regular flushing and takes a long time to evacuate the abscess.

**Materials and Methods:** In this study, we compared the relative safety and efficacy of a new procedure of draining the large peripheral right lobe liver abscesses using wide bore 20 Fr polyvinyl chloride (PVC) catheter in place of 10 Fr pigtail catheter on 50 patients. Student's *t*-test was used to assess the quantitative and Chi-square test for qualitative differences. The  $P < 0.05$  was considered statistically significant.

**Results:** About 20 Fr PVC wide bore catheter is found to be more efficient in draining the pus of large liver abscess as compared to the pigtail. Complications and recurrence rate were more common with pigtail. The hospital stay and hence expenditure was more with the pigtail catheter.

**Conclusion:** Wide bore (20 Fr) PVC catheter is safe, valuable and rapid way of evacuating the massive solitary peripheral liver abscesses and should be favored to narrow bore 10 Fr. pigtail catheter.

**Key words:** Drainage, Liver abscess, Pigtail catheter, Polyvinyl chloride catheter

## INTRODUCTION

A liver abscess is a pus-filled mass inside the liver. Common causes are abdominal infections such as appendicitis or diverticulitis due to hematogenous spread through the portal vein. A large pyogenic liver abscess presumed to be the result of appendicitis.<sup>1</sup>

There are three major forms of liver abscess, classified by etiology: (1) Pyogenic liver abscess, which is most often polymicrobial, accounts for 80% of hepatic abscess cases. (2) Amoebic liver abscess due to *Entamoeba histolytica*

accounts for 10% of cases. (3) Fungal abscess, most often due to *Candida* species, accounts for <10% of cases.<sup>2</sup>

Major bacterial causes of the liver abscess include *Streptococcus*, *Escherichia*, *Staphylococcus*, *Klebsiella*, anaerobes including *Bacteroides*, *Pseudomonas*, and *Proteus*. However, most of the cases are polymicrobial.<sup>1,3</sup>

Around 15% of amoebic liver abscesses (ALA) may be refractory to medical therapy. In such cases, percutaneous drainage by 10 Fr pigtail catheter placed under ultrasonography (USG) guidance is presently considered as the treatment of choice. Pigtail catheter is a tubular, flexible instrument, passed through body channels for withdrawal of fluids from body cavity.<sup>4,5</sup>

The disadvantage with the pigtail catheter is that it gets repeatedly blocked, requires regular flushing and takes a long time to evacuate the abscess.<sup>6</sup> Hence, in this study, we compared the relative safety and efficacy of a new

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procedure of draining the large peripheral right lobe liver abscesses using wide bore 20 Fr polyvinyl chloride (PVC) catheter in place of 10 Fr pigtail catheter.

## MATERIALS AND METHODS

This prospective study was conducted in the Department of General Surgery, Teerthankar Mahaveer Medical College and Research Centre for 1 year. 50 patients after written informed consent with single large liver abscess were admitted in our hospital and were considered candidates for this study. The age group selected for the study is 18-70 years. The patients reported with the complaint of right upper quadrant pain, hepatomegaly and low-grade fever. These patients were admitted and were subjected to USG and if it showed a single, large (size >7 cm in any dimension or volume >250 cc), liquefied and peripheral (liver parenchyma <1 cm on USG or no discernible parenchyma) liver abscess in right lobe of liver, patient was enrolled in the study.

Patients with ruptured amoebic liver abscess, vitally unstable patient, multiple non-communicating abscess cavities, abscess in the left lobe of liver, abscess having thicker peripheral parenchyma, and patients lost to early follow-up were excluded from the study.

Patients were randomly selected to undergo percutaneous drainage of abscess by 10 Fr pigtail catheter or 20 Fr PVC catheter (25 patients in each group). Percutaneous treatment was performed within 48 h after admission. 10 Fr pigtail catheter drainage was done by standard procedure by ultrasonologist under USG guidance. 20 Fr PVC Catheter was inserted under vision by open technique in the 8<sup>th</sup> intercostal space as seen on CT plates to provide a window to the abscess with thinnest area of surrounding liver parenchyma. Following the catheter insertion, X-ray chest and abdomen were done. For the first 12-24 h, hourly watch was kept on the temperature, pulse, respiration, and abdominal girth to check for signs of hemorrhage or peritonitis. This procedure is done in operation theater; this caution is taken so that if there is pneumothorax, we can immediately insert an ICD tube. The pus collected was sent for culture and antibiotics were given accordingly.

After discharge from the hospital, patients underwent follow-up evaluations in the outpatient clinic at least once a week during treatment and biweekly until 6 months from the beginning of the treatment. Patients outcome, including length of hospital stay, complications related to the procedure and treatment failure were recorded.

Student's *t*-test was used to assess the quantitative and Chi-square test for qualitative differences. The *P* < 0.05 was considered statistically significant.

## RESULTS

The prospective study was conducted in our medical college for the duration of one year in which 50 patients of liver abscess were treated by two different catheters (10 Fr pigtail and 20 Fr PVC) with 25 each. The male to female ratio was 2:1.

Table 1 shows comparison of mean percentage reduction in dimension of the abscess between the two groups. On 3<sup>rd</sup>, 6<sup>th</sup> and 9<sup>th</sup> days after surgery the reduction in size of abscess was significantly more with PVC catheter as compared to pigtail catheter. This shows that the 20 Fr. PVC wide bore catheter is more efficient in draining the pus of large liver abscess as compared to the pigtail.

Figure 1 describes the complications related to both the procedure, where there was pneumothorax in three patients of 20 Fr. PVC catheter group as compared to one patient in which pigtail catheter was used. Bilous fistula formation was found only in pigtail catheter patients. The recurrent blockage was mainly present in pigtail catheter because of narrow diameter as compared to PVC catheter.

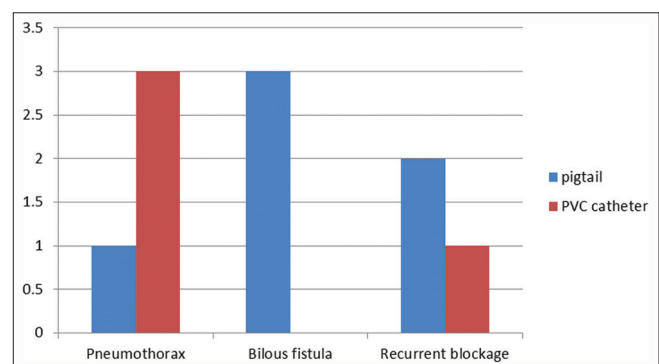
Table 2 shows mean duration of stay in hospital was 11.02 days among pigtail group that was comparable with 10.44 days among PVC drain group, and the difference was not statistically significant.

Table 3 shows the difference in the rate of recurrence after percutaneous catheter drainage. It was observed that 9 cases in Pigtail group had recurrence as per the USG

**Table 1: Comparison in change in size of abscess by two catheters**

No. of days	Reduction in size (cm)		P value
	Pigtail	PVC catheter	
3 <sup>rd</sup>	24.68±20.1	40.14±11.29	Significant
6 <sup>th</sup>	34.12±10.7	60.13±12.14	Significant
9 <sup>th</sup>	42.96±15.2	52.76±3.12	Significant

PVC: Polyvinyl chloride



**Figure 1: Comparison of complications by two catheters**



**Table 2: Comparison of mean duration of hospital stay**

Mean±SD		P value
Pigtail	PVC catheter	
11.02±4.30	10.44±3.1	Non-significant

PVC: Polyvinyl chloride, SD: Standard deviation

**Table 3: Comparison of recurrence rate (%)**

Mean±SD (%)		P value
Pigtail	PVC catheter	
9	1	Significant

PVC: Polyvinyl chloride, SD: Standard deviation

findings at 1 month, whereas there was only 1 recurrence seen in 20 Fr. PVC catheter group.

## DISCUSSION

The main difference in the treatment of pyogenic and ALA is that the pyogenic abscess is usually multiple and small, whereas amoebic liver abscess is solitary and large.<sup>7</sup> Amoebic abscess has a lot of necrotic liver parenchyma, and therefore, is not drained efficiently by the 10 Fr pigtail catheters. Hence, this study was conducted to find out whether large size catheter would be the better option and would drain the pus faster with less chances of blockage of tubes. Radiological imaging (computed tomography [CT] scan, USG) was done for all the patients of the PVC-catheter arm to demarcate the three dimensional anatomy of the abscess.

According to literature,<sup>8-10</sup> the preliminary size of the abscess cavity never affects the ultimate result. However, in this study, we found that large abscesses are more difficult to evacuate completely in one attempt. The reasons for failure of percutaneous catheter drainage, as reported in some of the earlier series, have been either thick pus not amenable to percutaneous drainage. This problem can be overwhelmed by using larger bore catheters like 20 Fr PVC.

Patients treated with pigtail stayed for a longer time than PVC catheter in the hospital. The shorter hospital stay could also be related to the fact that, unlike the practice in previous studies, we did not wait for total radiologic resolution (nonvisualization of the abscess cavity) before discharge.

In our study, complications occurred in ten patients out of 50 (10%). Three patients had recurrent blockage (2 with pigtail and 1 with PVC catheter) and had to be flushed regularly. Three patients developed a bilious fistula post pig-tailing which resolved without any

active intervention in 15 days. Four of the patients developed pneumothorax (1 with pigtail and 3 with PVC catheters). These patients had to undergo ICD insertion intraoperatively. With the help of CT scan the catheter was inserted through the eighth intercostal space in the mid-axillary line which is considered as a safe way of avoiding such complications.<sup>11</sup>

The flow of various body fluids through catheters has been demonstrated to follow the Poiseuille's law. According to this law, catheter diameter is a theoretic component of flow rate, with wide bore catheters having an advantage over the ones with smaller diameter.<sup>19</sup> Our review of the literature suggests similar success for small- and large-diameter catheters. Park *et al.*<sup>12</sup> tabulated the average number of days of drainage for small and large catheters from reported series. Unexpectedly, drainage times were less with the small-diameter catheters than with the large-diameter catheters. The most plausible explanation for this paradox is that less-viscous collections were drained with small catheters. In the other cases, the viscosity of the material drained was great enough so that even the large-diameter catheters did not enhance drainage proportionately.

In a preclinical and *in vitro* study by Niinami *et al.*,<sup>13</sup> 19 Fr tubes were compared with 28 Fr tubes. When the ability to catheter water at a set pressure of 10 mmHg was measured, the larger tube had a drainage capacity nine-fold higher than the smaller. Demonstration of cavity lesion on imaging after completion of treatment and on follow-up does not mean to re-start the treatment rather relies on symptoms and appearance of new lesion.

## CONCLUSION

We conclude that 20 Fr PVC drainage of large hepatic abscesses provides quicker aid to the patient and diminishes the total expenditure as well as duration of treatment and thereby the related morbidity. Wide bore (20 Fr) PVC catheter is safe, valuable and rapid way of evacuating the massive solitary peripheral liver abscesses and should be favored to narrow bore 10 Fr pigtail catheter.

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# Clinical Study of Hypocalcemia following Thyroid Surgery

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## Abstract

**Introduction:** Postoperative hypocalcemia is a common and most often transient event after extensive thyroid surgery. It may reveal iatrogenic injury to the parathyroid glands and permanent hypoparathyroidism.

**Aim:** To study the incidence of hypocalcaemia following total thyroidectomy and to study the various clinical presentations of post thyroidectomy hypocalcaemia.

**Methods:** Patients undergoing total thyroidectomy were included in the study.

**Results:** In 51 patients, 18 patients were had post operative hypocalcemia. Patients who underwent re-surgeries like completion thyroidectomy shows 100% incidence of post thyroidectomy hypocalcaemia.

**Conclusion:** Post thyroidectomy transient hypocalcaemia is a frequent complication which can be prevented with preoperative preparation of patients with extreme caution and preoperative meticulous dissection, prompt identification of parathyroids and postoperative frequent monitoring of serum calcium and early treatment can prevent significant morbidity.

**Key words:** Hypocalcemia, Incidence, Postoperative complications, Thyroidectomy

## INTRODUCTION

Thyroid disorders and surgical management for thyroid disorders are more common in any surgeon's daily life. Post-operative complications after thyroid surgery are variety and reported more frequently with budding and learning surgeons. Hypocalcemia after bilateral surgical resection of thyroid is a potential early complication.<sup>1</sup> From 9.2% to 25% of transient hypocalcemia are reported in literature and the incidence of permanent hypocalcemia ranges from 0.5% to 2%.<sup>2</sup> Careful meticulous dissection to identify and sparing at least 2 parathyroid glands under direct vision is mandatory to avoid post-operative reduced calcium levels and its complications, that post-operative

hypocalcemia is more frequent following bilateral resection of lobes than unilateral 9% and 1.9% respectively.<sup>3</sup> The immediate manifestations of hypocalcemia are mostly neuromuscular symptoms and occasionally psychotic states. Ectodermal changes leading on to alopecia, eczema, and cataract may occur as early as 6 months after operation. Persistent hypocalcemia may cause intracranial lesions and cardiac arrhythmias. Permanent hypocalcemia causes substantial impact on health of patient along with considerable financial loss.<sup>4</sup> Early recognition and prompt initial treatment of post-thyroidectomy hypocalcemia are crucial for successful outcome in the post-operative period following thyroidectomy. There are many predictors are under study till now to establish and effective protocol to be followed in the post-operative period in the thyroidectomy surgeries to manage post-thyroidectomy hypocalcemia successfully.<sup>5</sup> However, the availability of tests in small scale hospitals and the cost factor decides that serum calcium estimation postoperatively is the most ideal tool for early diagnosis and management of post-thyroidectomy hypocalcemia.

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## Aim

To study the incidence of hypocalcemia following total thyroidectomy and to study the various clinical presentations of post-thyroidectomy hypocalcemia.

## MATERIALS AND METHODS

This prospective study was conducted in the Department of General Surgery, Tirunelveli Medical College. Informed consent and Institutional Ethics Committee approval was obtained. All patients undergoing thyroidectomy surgeries were included in the study. Data will be collected from the patients undergoing total thyroidectomy by meticulous history taking, careful clinical examination, appropriate radiological, hematological investigations including serum calcium and serum albumin, operative findings and follow-up of the cases will be done after surgery for post-operative hypocalcemia. Patients undergoing hemithyroidectomy/lobectomy, primary parathyroid pathologies, age <12 years, previous irradiation to neck, patient already on calcium supplementation were excluded from the study.

## RESULTS

In this study, we followed 51 patients who were undergone total thyroidectomy on various indications. After thorough history taking, we excluded patients undergoing surgeries other than total thyroidectomy like hemithyroidectomy near total and subtotal thyroidectomy, in the age group of above 12 years. We excluded patients with pre-operative altered calcium levels to avoid previous altered parathyroid functions and excluded patients with previous history of radiation and also excluded patients already on calcium supplementation. We followed all patients met our study criteria with serial estimation of serum calcium levels postoperatively by day 1, day 2 and day 4 and also records history about various presentations of post-operative hypocalcemia such as perioral numbness, carpopedal spasm, trousseau sign, Chvostek's sign, electrocardiogram changes of hypocalcemia, and other neurological symptoms.

In this study, we followed 47 female patients and 4 male patients underwent total thyroidectomy. This gross difference in sex distribution is due to almost all thyroid disorders are more common with females as described by many literatures (Table 1).

About 16 patients are in 12-30 years followed by 31-40 years, 16 patients. 12 patients are in 41-50 years (Table 2).

According to pre-operative indications of thyroidectomy of these 51 patients, 8 patients are posted for thyroidectomy

for suspecting malignancy, 13 patients are posted for thyroidectomy for toxic features after controlling toxicity, 30 patients are posted for thyroidectomy for complaints like swelling or goiter or pressure effects (Table 3).

Of these 51 total thyroidectomy 2 patients are posted for completion thyroidectomy (re-surgery) followed after previous hemithyroidectomy or subtotal thyroidectomy with pre-operative benign fine needle aspiration cytology report and post-operative histopathological finding shows papillary malignancy for one patient and recurrent toxicity for another patient (Table 4).

Of the 51 total thyroidectomized patients, post-operative follow-up shows the following histopathological examination (HPE) reports. 5 patients underwent total thyroidectomy shows papillary thyroid carcinoma in their specimen, 10 patients showing thyroid adenoma, 4 patients HPE report reveals toxic multinodular goiter (MNG) and 3 patients specimen shows graves' disease. Hashimoto thyroiditis reported in post-thyroidectomy specimens of 19 patients and lymphocytic thyroiditis in 1 patient and 9 patients with nodular or colloid goiter (Table 5).

**Table 1: Description of study patients**

Sex of study population	Number of patients
Male	04
Female	47
Total	51

**Table 2: Age distribution of study patients**

Age distribution of study population (years)	Number of patients
12-30	16
31-40	16
41-50	12
More than 50	07
Total	51

**Table 3: Pre-operative indications for total thyroidectomy**

Pre-operative indications for total thyroidectomy	Number of patients
Malignancy	08
Toxic features	13
Swelling/goiter	30
Total	51

**Table 4: Distribution of nature of surgery**

Nature of surgery	Number of patients
Re-surgery/completion thyroidectomy	02
Total thyroidectomy	49

In our study period, we documented 18 patients out of 51 patients of the study population had experienced signs and symptoms of hypocalcemia in their post-operative period.

It denotes approximately 35% of study population experienced hypocalcemia in their post-operative period (Table 6).

Of these 3 males out of 4 male patients experienced hypocalcemia in their post-operative period, this approximates 75%. Out of 47 female patients 15 patients shows signs and symptoms of hypocalcemia, this approximates 32% (Table 7).

According to age distribution 4 patients in the age group of 12-30 years and 6 patients in the age group of 31-40 years, and 3 patients in the age group of 41-50 years and 5 patients in the age group of more than 50 years are affected by post-operative hypocalcemia.

Around 25% of 12-30 years patients' experienced post-operative hypocalcemia, 27% of 31-40 years experienced hypocalcemia, and 25% of 41-50 years experienced hypocalcemia and 71% of more than 50 years experienced post-operative hypocalcemia. Patients underwent total thyroidectomy with pre-operative diagnosis of malignancy

**Table 5: Post-operative final diagnosis based on HPE report**

Diagnosis	Number of cases studied
Thyroid malignancy	05
Thyroid adenomas	10
Toxic MNG	04
Graves' disease	03
Hashimoto thyroiditis	19
Lymphocytic thyroiditis	01
Nodular/colloid goiter	09
Total no of cases	51

HPE: Histopathological examination, MNG: Multinodular goiter

**Table 6: Post-thyroidectomy hypocalcemia in the study population**

Post-operative hypocalcemia in study	Number of patients
Yes	18
No	33

**Table 7: Distribution of post-thyroidectomy hypocalcemia in gender**

Sex of study population	Number of patients	Post-thyroidectomy hypocalcemia
Male	04	03
Female	47	15

experienced 75 % of post-operative hypocalcemia and approximately 46% of patients with toxic features experienced post-operative hypocalcemia, only 20% of patients with swelling or goiter are reported with post-operative hypocalcemia (Table 8).

Patients who underwent re-surgeries like completion thyroidectomy shows 100% incidence of post-thyroidectomy hypocalcemia (Table 9).

According to final post-operative HPE based diagnosis, the incidence of post-thyroidectomy hypocalcemia experience in our study was 5 out of 5 thyroid malignant patients experienced post-thyroidectomy hypocalcemia and 20% of thyroid adenomas, and 50% of toxic MNG patients and 67% of graves' disease patients and 21% of hashimoto thyroiditis patients and 33% of nodular or colloid goiter patients experienced post-operative hypocalcemia (Table 10).

In our study, 18 patients out of 51 patients experienced post-operative hypocalcemia, majority of them manifested the symptoms on post-operative day 2 such that 61%, remaining patients presented on post-operative day 1 (Table 11).

**Table 8: Age distribution of patients having post-operative hypocalcemia**

Age distribution of study population (years)	Number of patients	Post-thyroidectomy hypocalcemia
12-30	16	4
31-40	16	6
41-50	12	3
More than 50	07	5

**Table 9: Distribution of post-operative hypocalcemia in pre-operative indications for thyroidectomy**

Pre-operative indications for thyroidectomy	Number of patients	Post-thyroidectomy hypocalcemia
Malignancy	08	6
Toxic features	13	6
Swelling/goiter	30	6

**Table 10: Distribution of resurgeries in post-operative hypocalcemia**

Nature of surgery	Number of patients	Post-thyroidectomy hypocalcemia
Re-surgery/completion thyroidectomy	02	02
Total thyroidectomy	49	16



**Table 11: Distribution of diagnosis in post-operative hypocalcemia**

Diagnosis	Number of cases studied	Post-thyroidectomy hypocalcemia
Thyroid malignancy	05	05
Thyroid adenomas	10	02
Toxic MNG	04	02
Graves' disease	03	02
Hashimoto thyroiditis	19	04
Lymphocytic thyroiditis	01	00
Nodular/colloid goiter	09	03

MNG: Multinodular goiter

## DISCUSSION

Thyroid diseases are more common in females, as in many literatures. Our study population also reflects the same. Male 8% and female contributes 92% of thyroid disorders. In our study, results show that thyroid diseases that may need thyroid surgeries are frequent in the middle age group between 30 and 40 years.<sup>6</sup> However, the post-thyroidectomy hypocalcemia incidence is more common in the advancing age group, i.e., more than 50 years. A study conducted by Erbil *et al.*<sup>7</sup> named the impact of age, vitamin D level and incidental parathyroidectomy on post-operative hypocalcemia after total or near total thyroidectomy reveals that in advancing ages the level of vitamin D fall postoperatively, increases tremendously, so the incidence 25 times greater for the patients of more than 50 years of age. Benign diseases show less incidence of post-thyroidectomy hypocalcemia than the malignant diseases, this attribute to the extensive surgical dissection performed in malignant disorders to obtain tumor clearance. In a study conducted by Sakouti *et al.*<sup>8</sup> regarding the incidence of transient and permanent hypocalcemia after total thyroidectomy for thyroid cancer reveals higher incidence of hypocalcemia after total thyroidectomy in malignant diseases of the thyroid. The incidence increases more with surgeries combined with radical neck dissection. The incidence of post-thyroidectomy hypocalcemia is more in the toxic thyroid diseases than non-toxic diseases; this also attributes to the extensive surgical dissection in the toxic disorders to avoid recurrence of the disease. The same reason can explain the 100% incidence of post-thyroidectomy hypocalcemia in the resurgeries in our study, and in resurgeries some literatures postulate that extensive fibrosis can be a reason for vascular compromise that results in hypoparathyroidism. Indications for total thyroidectomy in our study population shows majority of them are resected for thyroid mass or goiter.<sup>8</sup> In our study period, we concentrated mainly on immediate post-operative hypocalcemia and due to the poor compliance of patients permanent hypocalcemia was not analyzed. Our

study shows the incidence of post-operative hypocalcemia was approximately 35%. In literature, it was reported from 27% to 80%.<sup>8</sup> During the study period, we did parathyroid autotransplantation for 4 patients who are found to be with accidental injury to the parathyroid glands found on table and post-thyroidectomy hypocalcemia did not manifest in that patients. In a study conducted by Lo *et al.*<sup>9</sup> where their team follow routine parathyroid autotransplantation incidence of hypocalcemia was less, patients presenting with hypocalcemia are whom parathyroid autotransplantation was not done. Zendenius *et al.*<sup>10</sup> reported in his study that he did 100 case series with total thyroidectomy and parathyroid autotransplantation and concluded there was no permanent hypocalcemia in his study group. For prevention of post-thyroidectomy hypocalcemia many authors followed identification of parathyroid intraoperatively by various methods, some of them are Esselstyn<sup>11</sup> used parathyroid blush on table, Silverberg used methylene blue staining of parathyroids, Gavilan *et al.*<sup>12</sup> used intravenous methylene blue for identification of parathyroids, Sofola *et al.*<sup>13</sup> used polarized spectral imaging, Pederson *et al.*<sup>14</sup> used portable gamma camera with sestamibi radiotracer, and Yao *et al.* touching print preparations, still the studies are going on.<sup>15</sup>

## CONCLUSION

Post-thyroidectomy transient hypocalcemia is a frequent complication which can be prevented with pre-operative preparation of patients with extreme caution and pre-operative meticulous dissection, prompt identification of parathyroids and post-operative frequent monitoring of serum calcium and early treatment can prevent significant morbidity. Parathyroid autotransplantation should be considered in accidental injury to parathyroids during the procedure. For small scale hospitals, serial monitoring of serum calcium levels preoperatively and postoperatively combined with careful monitoring of signs and symptoms of hypocalcemia is an efficient and cost-effective tool to detect post-thyroidectomy hypocalcemia.

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# Comparative Study of Topical Local Anesthesia using Transtracheal (Transcrisoid) Injection and “Spray as You Go” Technique during Awake Fiberoptic Intubation of Oral Cancer Patients Posted for Elective Surgery

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## Abstract

**Background:** The successful conduct of awake fiberoptic intubation is dependent on effective local anesthesia. The aim of study was to compare transtracheal injection and “spray as you go” technique for anesthetizing airway.

**Material and Methods:** A total of 100 oral cancer patients of the American Society of Anesthesiologist Grade I and II with Mallampati Class III and IV are posted for elective surgery. All overnight fasted patient consent taken and received sedation followed by 0.1% xylometazoline nasal drop in nasal nares followed by 2 ml 2% lignocaine jelly and 3-4 spray of 10% lignocaine spray done. Thereafter two group Group “A” ( $n = 50$ ) patients received 4 ml of 4% lignocaine by transtracheal (transcrisoid) injection and Group “B” ( $n = 50$ ) patients received 4 ml of 4% lignocaine through fiberoptic bronchoscope by “spray as you go” technique. After that during fiberscope cough count done and also grading of overall intubation condition (as assessed by anesthesiologist) done. Furthermore, intubation time recorded in both groups. Patients monitoring was done throughout procedure.

**Results:** In Group “A” mean cough count was 14 and Group “B” shows 22 and also mean intubation time in Group “A” was 68 second and Group “B” 92 s. Statistically Group “A” are better than Group “B.”

**Conclusion:** The transtracheal injection technique of topical local anesthetic application better than “spray as you go” technique for providing effective local anesthesia during awake fiberoptic intubation.

**Key words:** Awake fiberoptic intubation, Difficult airway, Topical local anesthesia

## INTRODUCTION

Oral cancer is most common cancer amongst the male in India.<sup>1</sup> Oral cancer patient is challenging for anesthesiologist because of difficult intubation.<sup>2</sup> However, today there are too much improvement in airway management nowadays new gadgets like fiberoptic

bronchoscope available for difficult airway management. The American Society of Anesthesiologist (ASA) and many European authors recommended awake fiberoptic intubation where difficult intubation is anticipated which can lead to the life-threatening “can’t intubate, can’t ventilate” scenario.<sup>3</sup> Awake fiberoptic is often unpleasant procedure. Hence, before awake fiberoptic intubation, the upper airway is commonly anesthetized by local lignocaine spray or gel, the modalities of applying local anesthetic to the larynx and lower respiratory tract include injection via fiberoptic bronchoscope, i.e., “Spray as you go” technique, transtracheal (transcrisoid) injection and nebulization.<sup>4</sup>

Aim of this study was to compare local anesthetic application technique, i.e., transtracheal injection and “Spray as you go”

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technique for patient undergoing awake fiberoptic intubation. It was also proposed to study the acceptability and suitability of these techniques to anesthesiologist with objective measurement of cough and intubation time.

## MATERIALS AND METHODS

ASA Status I and II 100 oral cancer patients between age group of 20-50 years were included in study. All the patients had an anticipated difficult airway with Mallampati Class III and IV and were undergo awake fiberoptic intubation. After informed consent, patients were randomized into two groups each received 4 ml of 4% lignocaine with either of two different methods:

Group "A" ( $n = 50$ ) via transtracheal (transcricoid) injection.

Group "B" ( $n = 50$ ) via fiberoptic bronchoscope, i.e., "spray as you go."

All the patients which included in study were overnight fasted. In operation theater, an intravenous access was established and monitoring instituted, viz., electrocardiogram (ECG), oxygen saturation and noninvasive blood pressure (NIBP). Through intravenous injection glycopyrrolate 0.2 mg, injection midazolam 1 mg and injection fentanyl 100 ug were given. Further 2 drops of 0.1% xylometazoline were instilled in each nostril. Thereafter nasal passage was lubricated with 2 ml of 2% lignocaine jelly and posterior pharyngeal wall anesthetized with 4 sprays of 10% lignocaine spray. Then laryngotracheal anesthesia before intubation of trachea done. Group "A" patients were given 4 ml of 4% lignocaine transtracheal through cricothyroid membrane puncturing with 22 G needle and Group "B" patients given 4 ml of 4 % lignocaine through fiberoptic bronchoscope port on vocal cords after cord visualization. Fiberoptic bronchoscope done by same anesthesiologist was to avoid subjective errors in results. The lubricated portex endotracheal tube was passed through mares after visualization of carinal bifurcation. The endotracheal tube was slid off the fiberoptic bronchoscope and midtracheal placement was confirmed under direct vision. During entire procedure following observation made.

1. Incident of cough, i.e., cough count
2. Intubation time (i.e., time from introduction of fiberoptic bronchoscope till the first measurement of end tidal carbon dioxide were recorded)
3. Pulse, NIBP, oxygen saturation, ECG.

To assess anesthesiologist was asked to grade the overall intubation conditions in each case.

Grading of overall intubation condition (as assessed by anesthesiologist).

Grade I: No adverse events, cough/stridor, cooperative and well tolerated.

Grade II: Coughed once or twice, cooperative with reassurance, tolerated the tube well.

Grade III: Coughed repeatedly, no stridor tube accepted.

Group IV: Coughed repeatedly, stridor present, uncooperative, did not allow scope to pass beyond glottis.

From above grading, results were analyzed statistically using "Chi-square test" and probability values  $P < 0.05$  were taken as significant.

## RESULTS

Table 1 shows demographic data of both Group "A" and Group "B," from that both groups were similar demographically without significant difference.

Table 2 shows cough count of both groups. Mean cough count for Group "A" was 14 and Group "B" was 22. From this cough count for Group "A" was significantly lower than Group "B" ( $P < 0.05$ ).

Intubation time also recorded for both groups. Table 3 shows mean intubation time for Group "A" which was 68 second and for Group "B" was 92 s, so intubation time significantly low for Group "A."

Furthermore, intubation condition grading done by anesthesiologist, Table 4 shows intubation condition grading for Group "A" it was Grade I 37 compared to 24 for Group "B," which is significantly better in Group "A" ( $P < 0.01$ ) as compared to Group "B."

## DISCUSSION

This study was done for comparison of transtracheal injection and "spray as you go" technique of topical local

**Table 1: Demographic data**

Demographic data	Group "A"	Group "B"
Age in years	40±2.2	42±1.8
Weight in kg	58.2±1.4	56±1.3
Sex (M:F)	32:18	28:22

**Table 2: Cough count in each group**

Cough	Group "A"	Group "B"
Cough count (mean)	14	22

**Table 3: Intubation time in each group**

Intubation time	Group "A"	Group "B"
Intubation time in seconds	68 (42-164)	92 (47-255)

**Table 4: Intubating condition**

Grade	Group "A"	Group "B"
Grade I	37	24
Grade II	06	11
Grade III	05	09
Grade IV	02	06

anesthetic application during awake fiberoptic intubation. In this study, we used cough count and intubation time required during fiberoptic intubation for assessment of topical local anesthetic application.

The result of this study comparison done with other study which shows certain similarities. In this study Group "A," i.e., transtracheal injection shows less cough count than Group "B," i.e., "spray as you go" technique this result when compared with Webb *et al.*<sup>5</sup> they also found same result as this study, i.e., transtracheal (transcricoid) injection of lignocaine produced less cough than "spray as you go" technique.

Graham *et al.*<sup>6</sup> using phonopneumography found that transtracheal method produced less cough and stridor during bronchoscope as compared to "spray as you go" technique and nebulization technique that result similar to this study result but only difference is they used 4 ml of 2.5% cocaine and in this study we used 4 ml of 4% lignocaine.

In this study intubation time required for transtracheal injection less than "spray as you go" technique which is

compared with Schaefer *et al.*<sup>7</sup> and Ovassapian<sup>8</sup> study. They also found mean intubation time 64 s in transtracheal injection method which was similar to this study.

## CONCLUSION

From this study, we concluded that during awake fiberoptic intubation using topical local anesthetic by transtracheal injection is better than "spray as you go" technique.

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# Clinical Characteristics, Etiology of Pediatric Constipation and Effectiveness of Polyethylene Glycol in the Management

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## Abstract

**Introduction:** Constipation is a common pediatric problem worldwide. This study aims to describe the clinical characteristics, etiology of pediatric constipation in Misurata Teaching Hospital, Libya, according to gender and age group and to assess the efficacy of polyethylene glycol (PEG) plus as oral monotherapy for fecal impaction and as a maintenance.

**Methods:** All patients with constipation managed at our pediatric gastroenterology clinic between April 2015 and September 2016 were included. Demographic data, clinical characteristics, final diagnosis, and effect of treatment were recorded. Data were analyzed according to gender and age groups (infants, preschool, school age, and adolescents).

**Results:** During the study period, 74 patients were enrolled, the number (%) according to age was the following infants: 28 (37.8%), preschool: 28 (37.8%), school age: 14 (18.9%), and adolescents: 4 (5.5%). Majority of patients 56 (75%) are below 6 years of age ( $P = 0.0003$ ). Males made up 52% and there were no statistical gender differences in any age group. The most common symptom was dry and hard stool (93.2%). Infrequent defecation (50%) the patients. Fecal incontinence was more common in school-aged children (69%) compared to pre-school-aged and adolescent. Abdominal pain was seen in almost 34% of patient and with per-rectal bleeding was more prevalent in school age children. Functional constipation was the most common etiology. Disimpaction on PEG was achieved in 50 (96%) of 52 children who presented with fecal impaction (71.3% of all children) without additional interventions, median time to disimpaction was 3.4 days (range: 3-7 days). Only 4 (5.4%) reimpacted, others are improved with no adverse events were reported on 3 months follow-up.

**Conclusion:** Functional constipation is the most common cause of childhood constipation. Clinical characteristics in children vary according to age group and gender. Older children had higher prevalence of long-standing fecal incontinence and abdominal pain. PEG is safe and highly effective as a single orally administered laxative to be used for disimpaction without recourse to invasive interventions and it is significantly effective as maintenance therapy and prevent reimpaction.

**Key words:** Children, Constipation, Fecal impaction, Infants, Polyethylene glycol

## INTRODUCTION

Constipation is a common problem in children. The worldwide prevalence varies between 0.7% and 29.6%.<sup>1</sup> Constipation is the reason for 3-5% of physician visits by children<sup>2</sup> and accounts for almost one-fourth of pediatric gastroenterology consults.<sup>3</sup> Constipation has a significant

impact on the use and cost of medical services.<sup>4</sup> Childhood constipation is a family issue that negatively affects children's physical, social, emotional, and school functioning.<sup>5</sup> As normal bowel habits differ with age,<sup>6</sup> features of constipation are expected to differ between age groups. Prevalence and symptoms of constipation are often different in very young children than in older children. For example; constipation prevalence is not the same through childhood. It peaks at the age of toilet training.<sup>7</sup> A longer duration of constipation before the diagnosis has been associated with complications (e.g., fecal incontinence) and poorer long-term outcome (persistent of symptoms and continuous need for laxatives).<sup>7</sup> The clinical profile of childhood constipation has been well described in many studies;<sup>7-10</sup> In our country, the prevalence of pediatric constipation is unknown. Although

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no epidemiological studies have been performed to accurately identify the true size of the problem, we believe that constipation is not uncommon in our society. Since, the establishment of a pediatric gastroenterology clinic in our hospital, constipation was noted as the most common cause for consultation. Because no studies have been published on constipation in children from our hospital, we performed a prospective analysis to evaluate the etiology and clinical characteristics of patients with constipation according to age group and gender.

The recommended approach is to empty the constipated bowel and keep it empty.<sup>11,12</sup> Unfortunately, the current means of achieving disimpaction add to the distress caused by the complaint. The administration of repeated enemas, suppositories, and manual evacuation under general anesthesia are distressing for the child.

Once an impaction exists, efforts to remove it by catharsis from above are not only ineffectual but may worsen the abdominal pain and may compound the retention problems in children. Polyethylene glycol 3350 (PEG) is a particularly suitable molecule upon which to base an oral laxative because a solution of PEG exhibits a linear dose-response relationship when ingested,<sup>13</sup> retaining water in the bowel to potentially produce an almost unlimited laxative action, as demonstrated by the high volume PEG bowel lavage solutions. This is in contrast with laxatives like lactulose or senna, which, as prodrugs need metabolism in the large bowel to an active moiety. The ingestion of increasing amounts of these laxatives will saturate the metabolic capability of the colon; hence, the dose-response curve shows a plateau after which increasing the dose does not produce any greater effect. Once disimpaction is achieved, a maintenance treatment is required to prevent the need for repeated attempts at disimpaction.

## MATERIALS AND METHODS

Consecutive children with constipation (organic and functional) who presented to the Pediatric Gastroenterology Clinic at Misurata Teaching Hospital, Misurata, Libya between April 2015 and September 2016 (18 months period) were included in the study and followed until 30<sup>th</sup> November 2016.

Data collected include age, sex, duration of constipation, symptoms and signs such as bowel motion frequency, consistency, presence of blood, pain with defecation, stool withholding behavior, fecal incontinence (soiling), and the presence of fecal impaction or an abdominal mass. The likely cause that reported by the parents considered as risk factors include, time of weaning, changing formulae, toilet

training, school entry, a dietary history that focused on the acceptance of fibers (fruits and vegetables) and fluids, and family history of constipation. Clinical evaluation (history and physical examination) of all patients was done by the same physician (the author). The digital anorectal examination is indicated in children when the diagnosis of functional constipation remains uncertain or in children with intractable constipation, to exclude underlying medical conditions. Laboratory and radiological investigations were performed according to the patient's presentation. Investigation for celiac disease and hypothyroidism is suggested in intractable constipation and in cases where there is evidence of altering growth. Hirschsprung's disease was confirmed only after rectal biopsy. Routine elimination of cow's milk formula to establish the diagnosis of cow's milk protein allergy was not recommended in our practice. Neurological disorders were diagnosed with appropriate investigations with pediatric neurology input.

The large variation in prevalence is mainly due to different methods of data collection and criteria of constipation were used in different studies. To solve the problem of nonuniformity in diagnostic criteria, we follow the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN)/North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) guidelines which recommend the Rome III criteria for the definition of functional constipation be used for all ages.<sup>8</sup>

### Rome III Diagnostic Criteria for Functional Constipation in Children

Symptoms must occur at least once per week for at least 2 months and include two or more of the following in children:

- Two or fewer defecations in the toilet per week
- At least one episode of fecal incontinence per week
- History of retentive posturing or excessive volitional stool retention
- History of painful or hard bowel movements
- Presence of a large fecal mass in the rectum
- History of large-diameter stools that may obstruct the toilet.

During disimpaction phase, PEG was administered orally (dose, 4 g powder dissolved in at least 150 mL water or juice) according to an escalating daily dose regimen until disimpaction was achieved (Table 1). This was a dose regimen that had been shown to be effective in many studies.<sup>14,15</sup> This regimen used an escalating dose of PEG to maximize compliance, with a higher dose given to children in the 5-14 years age group than to 1-4 years olds. Followed by maintenance treatment of constipation over a 3-month period.

### Statistical Analysis

For data analysis and comparison, we categorized the patients according to gender and age: Infants (0-24 months), preschool (25-72 months), school age (73-120 months), and adolescents (121-216 months).

The SPSS Statistics (version 18) was used. Results were expressed as the means with ranges. Categorical data were tested using Fisher's exact test, and continuous data were tested using the *t*-test.  $P < 0.05$  were considered significant.

## RESULTS

During the study period, our clinic saw 244 patients of whom 80 had constipation, comprising 31.9% of our gastroenterology clinic consults. 74 were included in the analysis after exclusion of 6 patients with organic causes.

### Patient's Distribution by Age, Sex, Duration of Constipation and Treatment Exposure

Of the 74 patients, 39 patients (52.6%) were male (Figure 1). No statistically significant gender differences were seen in any age groups ( $P = 0.816$ ). Infants and preschool children ( $n = 28$ , 37.8% each of them) were the most commonly affected age groups, followed by school-age children ( $n = 14$ , 18.9%), and adolescents ( $n = 4$ , 5.4%). The average duration of constipation before consultation significantly increased with age (5.5, 10.8, 17.8, and 26 months for infants, preschool, school age, and adolescents, respectively) (Table 2). Half of them (37 patients, 50%) reported taken at least 1 laxative medication, most commonly was lactulose.

### Clinical Characteristics of Bowel Motions and Associated Symptoms

Regarding bowel motion characteristics, hard, and dry stool were the most common symptom seen in all age groups, affecting 93.2% of constipated children. On the other hand,

infrequent bowel motion ( $<3$  bowel motions per week) was seen in almost half of our patients. The prevalence of infrequent defecation showed a nonsignificant increase as children got older. Fecal incontinence (soiling) was most commonly seen in school-age children (69.3%) and was significantly different compared to preschool children ( $P < 0.001$ ). Except for infants who did not report urinary problems, urinary complaints were more prevalent in older children (6.9%, 7.7%, and 25% of preschool, school age, and adolescents, respectively). Abdominal pain was seen in almost 34% of patients (10.7%, 34.5%, 76.9%, and 50% in infants, preschool, school age, and adolescents, respectively) (Table 3 and Figure 2). Abdominal pain and per-rectal bleeding were more prevalent in school-age children.

Functional (non-organic) constipation was the most common diagnosis in all age groups. 9 of our patient had family history of constipation (1.1%). Surgical motility-

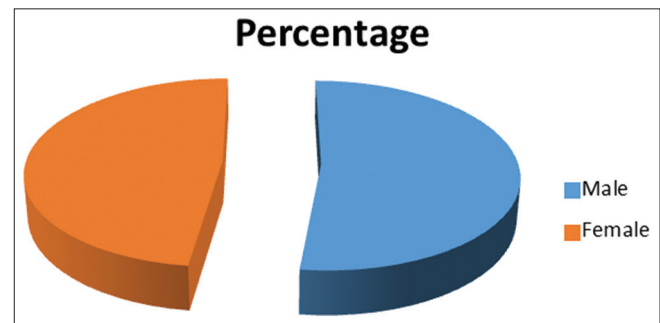


Figure 1: Sex distribution of childhood constipation

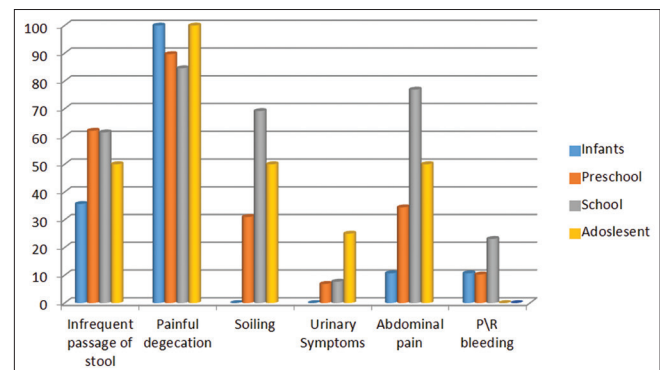


Figure 2: Clinical characteristic of bowel motion and associated symptoms of pediatric constipation

Table 1: PEG (Macrogol 4000) dosing regimen

Number of PEG sachets daily divided to 2 doses							
Age (years)	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
1-5 years	2	4	4	6	6	8	8
5-14 years	4	6	6	8	8	10	10

PEG: Polyethylene glycol

Table 2: Patients distribution by age, sex, and duration of treatment exposure

Demographic variable	Infant 0-24 months	Preschool 25-72 months	School age 73-120 months	Adolescents 121-216 months	Total	P
Patient	28 (37.8)	28 (37.8)	14 (18.9)	4 (5.5)	74 (100)	-
Male	18 (64.3)	11 (37.9)	8 (53.8)	2 (50)	39	NS
Female	10 (35.7)	17 (62.1)	6 (46.2)	2 (50)	35	NS
Average duration of constipation (months)	5.5 (2-12)	10.8 (2-42)	17.6 (4-52)	26 (6-36)	-	Significant between all age groups $<0.05$

**Table 3: Clinical characteristic of bowel motion and associated symptoms**

Clinical characteristics	Infant 0-24 months	Preschool 25-72 months	School age 73-120 months	Adolescents 121-216 months	Total	P
Infrequent passage of stool	10 (35.7)	18 (62.1)	8 (61.5)	2 (50)	38 (51.4)	NS
Painful defecation	28 (100)	26 (89.7)	11 (84.6)	4 (100)	69 (93.2)	NS
Soiling	0 (0)	9 (31)	9 (69.2)	2 (50)	21 (28.4)	Significant between all age groups <0.05
Urinary symptoms	0 (0)	2 (6.9)	1 (7.7)	1 (25)	4 (5.4)	
Abdominal pain	3 (10.7)	10 (34.5)	10 (76.9)	2 (50)	25 (33.8)	
PR bleeding	3 (10.7)	3 (10.3)	3 (23.1)	0 (0)	9 (12.2)	

related organic causes (Hirschsprung's disease) were the leading causes for organic constipation, followed by neurological disorders. Celiac disease was considered in five patients (constipation with faltering growth or family history of constipation), but celiac serology was normal, hypothyroidism, and allergy to cow's milk protein was not reported in our patients (Table 4).

Disimpaction on PEG was achieved in 50 (96%) of 52 (71.3% of all children) without additional interventions. A maximum dose of 6 sachets (for 1-5 years old) or 8 sachets (for 5-14 years old) was required; median time to disimpaction was 3.4 days (range: 3-7 days). 4 of children (5.4%) reimpacted whilst taking PEG, others are improved with good adherence. No adverse events were reported on 3 months follow-up.

## DISCUSSION

We have conducted the first prospective study to evaluate the prevalence of constipation among children treated in a pediatric gastroenterology clinic in Misurata Teaching Hospital, Libya. Patients were categorized into four pediatric age groups: Infants, preschool, school-age children, and adolescents. Our study showed that older children had less frequent bowel motions, a longer duration of symptoms, and a higher prevalence of long-standing constipation complications (fecal incontinence and abdominal pain). Infants and Preschool children were the most commonly affected age groups. We believe that the low number of adolescents does not reflect a low prevalence rate in this age group, but a referral bias, as our clinic treats children 14 years old and younger.

Fewer than three bowel motions per week is a commonly used definition of constipation, using only this definition will lead to underdiagnosis of constipation.<sup>9</sup> In a study of 178 children with constipation in Iowa, 58% had <3 bowel movements per week,<sup>16</sup> and in another study 41.3% of children with symptoms of constipation were found to have infrequent stools.<sup>7</sup> Children <2 years of age had constipation with symptoms of passage of hard or pebble

**Table 4: Etiology of constipation in study subjects**

Etiology	n (%)
Functional	74 (92.5)
Motility-related organic causes Hirschsprung's disease	2 (2.5)
Congenital anomalies (Spina bifida)	1 (1.3)
Neurologic disorders (CP, unexplained D. D.)	2 (2.5)
Autism	1 (1.3)
Celiac disease	0 (0)
Hypothyroidism	0 (0)
Cow's milk protein allergy	0 (0)

like stools with straining, withholding or painful defecation. The diagnosis would be missed in 50% if infrequent stools were the only criteria used for diagnosis. In our study, infrequent defecation was reported by only half of our patients.

Room III criteria which include hard, dry stool, and painful defecation appear to be more sensitive indicators. More than 90% of constipated children in all age groups described their bowel motions as dry, hard, and painful this is consistent with the work of Loening-Baucke,<sup>10</sup> who concluded that using stool consistency and painful bowel motion to define constipation is more sensitive than using symptom duration or frequency of bowel motions.

Retentive fecal incontinence (associated with constipation) has been reported in up to 85% of constipated children.<sup>13</sup> In our study, school-age children exhibited the highest rate (69.2%) of fecal incontinence, which was significantly different compared to preschool children ( $P < 0.05$ ).

The urinary system is anatomically adjacent to the gut and shares neurological control, rectal pathology leads to urinary symptoms through mechanical compression of the stool mass over the bladder in addition to a voiding dysfunction caused by pelvic floor muscle spasms. Constipation may cause urinary tract infections and enuresis due to uninhibited bladder contraction.<sup>7,9</sup> Urinary symptoms have been reported in 9-13% of children with a diagnosis of constipation, and urinary incontinence 10.5%, and it has been implicated in the pathoetiology of enuresis.<sup>17</sup> Asymptomatic constipation may exacerbate



urinary symptoms in children with enuresis.<sup>18</sup> Urinary symptoms were seen in 5.4% of patients in our study, a rate that is less compared with the previous studies.<sup>19,20</sup> Urinary morbidities were seen more often in adolescent compared to other age groups ( $P < 0.05$ ).

Non-specific abdominal pain has been reported in 33% of children with constipation in one study.<sup>21</sup> In our study, almost 33.8% of our patients had abdominal pain, which is the same, and the prevalence rate was higher in school-aged group ( $P < 0.05$ ) compared to other age groups. The small number of adolescents in this cohort limits the generalization of our results to this pediatric population.

The suspected underlying cause of functional constipation according to parent's report was considered in our study (Table 5), this study supports findings from the previous studies that a positive history of toilet training and low consumption of dietary fibers and fluids are significantly associated with constipation in children.<sup>22-24</sup> Interestingly, it was noted in this study that toilet training was found to be significantly associated with a higher constipation rate, Perhaps coercive toilet training in toddlers can lead to reluctance to defecate. A positive family history has been found in 28-50% of constipated children and a higher incidence reported in monozygotic than dizygotic twins,<sup>25</sup> in our study only 9 of patients had a family history of constipation (1.1%).

Although radiological confirmation of the diagnosis of fecal impaction was not part of the protocol for this study, the children recruited had symptoms of fecal impaction, such as infrequent, painful defecation, vomiting, abdominal pain, and many also had palpable abdominal fecal masses. There is considerable controversy about the need to conduct rectal examinations in children to confirm the diagnosis of and success of treatment for fecal impaction. At our hospital, rectal examinations are not routinely conducted on constipated children; thus, there was probably less certainty about diagnosis and successful outcome of treatment than if a rectal examination had been carried out.

Functional constipation was the most common cause of chronic constipation, 94.8% in our study. The rates of

functional constipation in our cohort are similar compared to reported rates.<sup>26</sup> The clinician has an important role in identifying the small fraction of children with organic causes of constipation. Organic causes of constipation are more likely among young infants, and among infants, and children presenting with atypical features or "alarm signs" (Table 6).

Treatment for chronic constipation is based on the concept that chronic constipation causes the colon to be unresponsive to stool burden, due to distension, it follows that effective treatment requires consistent and complete emptying of the colon, so that it becomes conditioned to work on its own a concept known as "bowel retraining". There are four general steps in bowel retraining, we were followed:

- Disimpaction.
- Prolonged laxative treatment and behavior therapy to achieve regular evacuation and avoid recurrent constipation.
- Dietary changes (primarily increasing fiber content) to maintain soft stools.
- Gradual tapering and withdrawal of laxatives as tolerated.

The goal of therapy is the passage of soft stools, ideally once per day, and no less than every other days. This goal of frequent defecation is important to overcome constipation, although less frequent defecation patterns are common and acceptable in children without a history of constipation. Weeks to months of laxative and behavior therapy may be necessary before this goal is achieved. The child's parents must be effectively educated about bowel retraining and behavior modification so that they can carry out the sustained treatment.

Guidelines for management of infants and children with constipation were developed by the NASPGHAN, and ESPGHAN.<sup>8</sup> These guidelines were followed in our practice, include a management with:

## PEG

Macrogol 4000, is an osmotic laxative, it is more palatable and has fewer adverse effects than other

**Table 5: Risk factors for childhood constipation**

Risk factor	Infant 0-24 months	Preschool 25-72 months	School age 73-120 months	Adolescents 121-216 months	Total	P
Low fibers and fluid	3 (10.7)	9 (31)	11 (84.6)	4 (100)	27 (36.5)	-
Weaning	9 (32.1)	0 (0)	0 (0)	0 (0)	10 (13.5)	
Change formula	3 (10.7)	0 (0)	0 (0)	0 (0)	3 (4.1)	
School entry	0 (0)	0 (0)	3 (21.4)	0 (0)	3 (5.4)	Significant between all age groups <0.05
Finicky eating	5 (17.9)	6 (20.7)	0 (0)	0 (0)	11 (14.9)	
Toilet training	0 (0)	4 (13.8)	0 (0)	0 (0)	4 (5.4)	



**Table 6: Alarm signs and symptoms in constipation**

Constipation starting extremely early in life (<1 mol)
Passage of meconium >48 h
Family history of HD
Blood in the stools in the absence of anal fissures
Failure to thrive
Bilious vomiting
Severe abdominal distension
Decreased lower extremity strength/tone/reflex
Tuft of hair on spine
Sacral dimple
Gluteal cleft deviation

agents, it is preferred by most experts for disimpaction and treatment of chronic constipation, although it is not yet labeled for this use it is approved for short-term management of constipation.<sup>8</sup> Adverse effects include diarrhea (10%), bloating or flatulence (6%), and abdominal pain (2%).<sup>27</sup> These symptoms tend to be mild, transient, and responsive to dose reduction.<sup>28</sup> In the interim, NASPGHAN has published a statement with frequently asked questions about the use of PEG in children.<sup>29</sup>

The typical dose is 0.4-0.8 g/kg/day (up to 17 g). The effective dose in an individual patient is not predictable, and many patients require relatively high doses for initial treatment of constipation, with somewhat lower maintenance dose.

A total of 52 children (71.2% of all our patient) disimpacted successfully with PEG, this was achieved in 96% of children, the median time to disimpaction for the children, overall was 3.4 days, with a range of 3-7 days.

Disimpaction was judged if feces became watery (type 7 on the Bristol stool form scale.<sup>30</sup> Within 7 days of commencing treatment. The dose required to achieve watery stools was continued to ensure complete disimpaction of the bowel, only one 10-year-old boy and one 8-year-old girl failed to disimpact within the time allowed. The adverse effects reported to be seen when taking the relatively high doses needed for disimpaction taken in consideration and, we advice to reduce the dose than that which was consumed. In our study, none of the adverse events was reported. After 12 weeks on treatment with PEG as maintenance, only one child taking PEG, senna was needed as additive rescue medication.

On entry to the study, about half of the children (50%) reported taking at least 1 laxative medication, the most common of which was lactulose and use enemas at time of fecal impaction, also one patient report disimpaction with

manual removal under general anesthesia, and reimpacted again within short period, all were responding very well to PEG with only low risk of recurrence (5.4%) and reimpaction as we mentioned before.

Children who have problems with constipation should be treated with care and consideration, it cannot be right to administer an invasive treatment to a child, as the insertion of a nasogastric tube, administration of enemas or suppositories, or manual removal of feces, if an equally or more effective noninvasive alternative exists. Although the invasive rectal approach leads to faster disimpaction within hours, it is invasive, unpleasant and carry not only physical risks to the child but also the risk of significant psychological trauma.

This study shows that PEG is safe and highly effective as a single, orally administered laxative in the treatment of fecal impaction in children and was easily be administered at home, no additional treatment was required to clear fecal impaction in children in this study, which means that the use of invasive treatments can be eliminated or at least substantially reduced in the treatment of impacted feces in children, also this will result in much lower cost to the health-care system and also eliminate the stress of hospital admission to the child and to the family. The studies cover the different scenarios of treatment: Oral resolution of impaction and maintenance therapy for relief of constipation, and in comparison with other laxatives were summarized in (Table 7).

## CONCLUSION

To the best of our knowledge, this is the first study describing the clinical profile of childhood constipation in our hospital according to age group and gender, the clinical characteristics differed according to age group and gender, and according to the results of this successful treatment protocol using PEG in disimpaction and maintenance therapy, we have to outline the current trends in the assessment and treatment of constipation and introduce the current evidence base for the therapies currently in wide use, within the context of recent NICE and ESPGHAN/NASPGHAN guidance to our primary care to decrease the burden on referrals to gastroenterology clinic, and the indication of seeking advice of pediatric gastroenterologist should be restricted only if:

- Organic cause of constipation is suspected.
- Disimpaction orally was unsuccessful.
- Soiling/abdominal pain continues despite treatment.
- Children <1 year with fecal impaction.
- Children not responding to maintenance therapy.

**Table 7: Efficacy of PEG**

PEG 4000		
Authors	Study group	Methods+key outcomes
Thomson <i>et al.</i> (2007) <sup>31</sup>	51 children	Methods: Double-blind crossover RCT PEG+E or placebo for 2 weeks Results: Mean number of defecations higher for PEG+E group versus placebo ( $P<0.001$ ). Also PEG+E reduced pain on defecation ( $P=0.041$ ), straining on defecation ( $P<0.001$ ), stool consistency ( $P<0.001$ ), and percentage of hard stools ( $P=0.001$ ). Adverse events were all mild or moderate and were similar for those children on PEG+E and placebo
Candy <i>et al.</i> (2006) <sup>32</sup>	63 children	Methods: Initial open cohort study of PEG+E (disimpaction) then double-blind RCT of PEG+E (Movicol) vs. Lactulose (maintenance) Results: Disimpaction successful in 92% children. Maximum dose=4 sachets-4-year old) or 6 sachets (5-11-year olds); median time to disimpaction was 6 days Maintenance: Greater mean stool frequency in PEG+E group ( $P=0.007$ )
Dupont <i>et al.</i> (2005) <sup>33</sup>	96 children	Method: Random allocation, open-label cohort study Results: More than 90% of children recovered normal bowel habits. Fecal mass in the rectum and abdominal pain was markedly reduced and appetite improved
Youssef <i>et al.</i> (2002) <sup>34</sup>	40 children	Methods: Prospective, double-blind, parallel RCT 4 doses of PEG 3350 Results: Disimpaction in 75% of children overall but significant difference between two higher doses vs. lower doses (95% vs. 55%, $P<0.005$ ). All groups had an increased number of bowel movements during the 5-day study versus baseline
Loening-Baucke <i>et al.</i> (2006) <sup>35</sup>	79 children	Methods: Double-blind RCT PEG 3350 versus magnesium hydroxide Results: Significant improvement in both groups, (frequency of bowel movements, reduced frequency of incontinence, and resolution of abdominal pain). Compliance=95% (PEG) versus 65%= milk of magnesia. At 12 months, 62% of PEG-treated children and 43% of MoM-treated children improving.
Pashankar <i>et al.</i> (2003) <sup>36</sup>	83 children	Methods: Cohort study for at least 3 m PEG given at 0.8 g/kg/day then adjusted to give 2 soft painless stools/day Results: Mean duration=8.7 months. Mean PEG dose was 0.75 g/kg daily. No major adverse effects. All children preferred PEG to other laxatives, Good daily compliance in 90% of children
Wang <i>et al.</i> (2012) <sup>27</sup>	105 children	Methods: RCT, PEG vs lactulose 1 week of treatment Results: 72.4% clinical remission rate, lactulose 41.4%

PEG: Polyethylene glycol

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# Blood Culture in Clinically Suspected Typhoid Fever

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## Abstract

**Background:** Typhoid fever, caused by the bacterium "*Salmonella enterica* serovar *typhi*" is still today a globally threatening disease even after the disease has been known for so many years. This is more so in developing countries such as Bangladesh, Pakistan, Nepal, African countries, and India of course. Ours being a tertiary care medical college hospital in rural area, we ventured to go for a study as to how typhoid diagnosis and treatment are done in these areas where typhoid is prevalent. Having found that almost cent percent cases of enteric fever are clinically diagnosed and empirically treated, we did a study by doing blood culture for 67 newly diagnosed cases of typhoid fever by clinical methods.

**Materials and Methods:** A total of 67 adult patients of fever of both sexes, clinically diagnosed as typhoid, without a history of prior antibiotic therapy, usually by the third day of fever, were chosen for the study. All these patients were subjected to blood culture for salmonella, and the results were analyzed.

**Results:** The results of the study showed that out of 67 clinically diagnosed typhoid patients only 8 had culture positive typhoid and 3 had culture-positive paratyphoid A.

**Conclusion:** The practices of diagnosing and empirically treating typhoid fever though hugely practiced in rural, semi-urban and even urban areas of developing countries, is definitely improper, and learned medico-social community and appropriate health authorities should come forward and find out an acceptable solution.

**Key words:** Blood culture, Clinical diagnosis of typhoid, Typhoid

## INTRODUCTION

By typhoid fever, we mean an acute febrile infectious disease whose causative organism is the bacterium "*Salmonella enterica* serovar *typhi*."<sup>1</sup> Studies<sup>2</sup> are done in urban Slums in three South-East Asian countries, viz., India, Pakistan, and Bangladesh. In India, the incidence is 493.5 cases per 100,000 population per year. In Bangladesh, it is 18.7 per thousand per year in pre-school children and 2.1 per 1000 per year in older patients. In Pakistan, the same is 451.7 cases per 100,000 per year in children aged 2-15 years. These high incidences

obviously suggest that further studies are required to explore typhoid situations particularly in developing countries. In Africa, typhoid is less understood than in Asia. This is due to lack of proper infrastructure to conduct clinical or epidemiological studies there. Crump *et al.* could get only the crude incidence rate in Africa, viz., 50 cases per 100,000 population per year where the total population is about 820 million.<sup>3</sup> However, Buckle *et al.* got a higher incidence rate in Africa, that is 724.6 cases per 100,000 population per year.<sup>4</sup> A confounding factor in these studies is the presence of non-typhoidal salmonellosis that mimics typhoid which is progressively rising and may be fatal in some cases.<sup>5</sup>

Regarding diagnosis, typhoid imposes confusion in Afro-Asian countries. Detection of causative organism in blood by polymerase chain reaction is probably the most suitable method. Next to that, bone marrow culture is the most sensitive and reliable method. Recently, the third method is being used in only a few developed

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countries because its sensitivity is 100%. In it, typhoid-specific immunoglobulin A is estimated in blood using ELISA through amplification of signal by isolation and incubation of peripheral blood lymphocytes.<sup>6</sup> Unfortunately, all the above-mentioned methods are too expensive, tedious, complicated or time-consuming to be applied in developing countries even in urban areas, let alone in remote places and villages. The Widal test has been marked unreliable as also the newer generation serology tests such as typhidot and tubex.<sup>7-9</sup>

We performed a study on knowledge, attitude, and practices of general practitioners in several underdeveloped places in India and found the noticeable poverty of infrastructure for diagnosis and management of typhoid.<sup>10</sup> Under these circumstances, we have ventured to study the sensibility and acceptability of blood culture as a diagnostic tool in this part of globe wherefrom we might get a deeper insight to develop new novel but feasible and acceptable diagnostic strategies which need to be implemented in this type of background.

## MATERIALS AND METHODS

A total of 67 patients (40 males and 27 females) with complaints of fever of more than 3 days duration were enrolled for the study. The patients were in the age range from 18 to 76 years. Most of the patients were from rural and semi-urban backgrounds. The patients who had been treated with any antibacterial drug for the recent ailment were excluded from the study population.

About 10-15 ml of blood was collected with standard aseptic precautions from each patient and was inoculated into 40-45 ml of brain heart infusion broth. Incubation was done at 37°C. Subculturing was performed on days 1, 2, 3 and 7 days on MacConkey agar plates which were incubated at 37°C for 18-24 h. Lactose nonfermenting colonies, if any, on subculture plates were picked up and were examined by microscopy after Gram-staining of the smears. Standard biochemical tests including motility test were performed for identification of *Salmonella* spp.

## RESULTS

Table 1 shows age and sex-wise distribution of isolates in blood culture of patients. Figure 1 shows age and sex-wise distribution of patients. Figure 2 shows sex-wise distribution of isolates in blood culture of patients.

## DISCUSSION

This study envisaged toward determining the blood culture reports for detection of *S. typhi* shows that out of 18 patients in the age group of 18-30 years *S. typhi* was isolated in 3 patients and only 1 *S. paratyphi* was detected. In the 31-40 years, age group where the total number of patients was 19, 2 and 1 were the *S. typhi* and *S. paratyphi*, respectively.

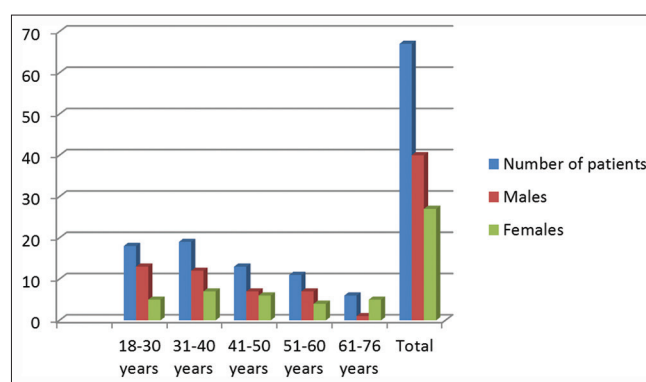


Figure 1: Age and sex-wise distribution of patients

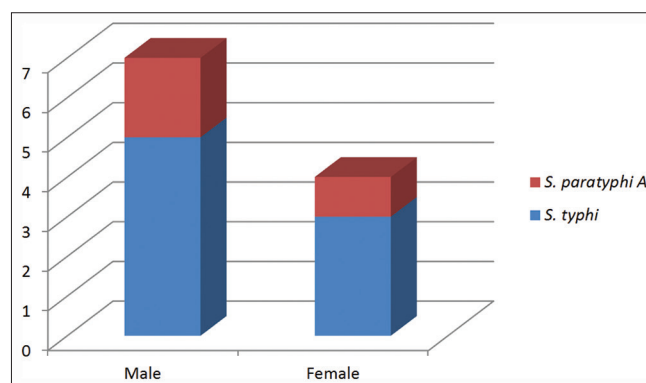


Figure 2: Sex-wise distribution of isolates in blood culture of patients

Table 1: Age and sex-wise distribution of isolates in blood culture of patients

Age group (years)	Number of patients	Males	Females	S. typhi isolated		S. paratyphi A isolated	
				Male	Female	Male	Female
18-30	18	13	5	2	1	1	-
31-40	19	12	7	1	1	-	1
41-50	13	7	6	1	-	1	-
51-60	11	7	4	1	1	-	-
61-76	6	1	5	-	-	-	-
Total	67	40	27	5	3	2	1

*S. typhi*: *Salmonella typhi*; *S. paratyphi*: *Salmonella paratyphi*



Similarly, in the age group 41-50 years out of 13 patients, 1 was *S. typhi* and 1 was *S. paratyphi*. Again, in the 51-60 years age group, 2 were detected *S. typhi* and none belonged to *S. paratyphi*, the total number of patients being 11. In the oldest age group (>60 years), which consisted only 6 patients, none was detected positive for either *S. typhi* or *S. paratyphi*. In total, out of 67 patients of all adult age groups (>18 years) 8 patients belonged to *S. typhi* and 3 patients to *S. paratyphi*. This shows that blood culture is positive in only 16.4% cases of clinically suspected typhoid/paratyphoid patients.

Diagnosis of typhoid fever is normally made in all developed countries principally by blood cultures and also by stool/urine culture and serological testing.

In one study, out of 273 blood cultures from clinically typhoid fever patients, *S. typhi* was detected in 7 (2.6%) and *S. paratyphi* was detected in 4 (1.5%) patients.<sup>11</sup> In the same study, in Widal test, TO antigen was positive (i.e., dilution >1/80) in 47% of febrile patients, and 26% TH antigen positive (cutoff value >1/160). 24.4% had positive results for both TO and TH. To perform blood culture a bacteriological laboratory has to be present on site or else, it can be transported to the main laboratory. However, interestingly for proper blood cultures, it is essential to inoculate the media immediately after drawing blood, keeping proper temperature of the specimen, the media, and the inoculated media. Furthermore, blood for culture should be drawn very meticulously and in highly aseptic manner for which a properly trained and experienced technician is extremely difficult to obtain. The volume of blood required for blood culture is also highly variable and hence confusing. For example, 10-15 ml of blood is required for culture in adults and school children, whereas only 2-4 ml of blood is sufficient in preschool children and toddlers. This is because children show a much greater number of bacterial colonies compared to adults. One cannot compromise on volume of blood to be inoculated because that effort drastically brings down the sensitivity of the test. Therefore, obtaining this amount of blood is sometimes so difficult that only for that reason the blood culture test has to be discarded and an alternate reliable and acceptable diagnostic method may have to be sought after. Keeping the specimen collecting bottle highly aseptic is also another challenge in conducting a proper blood culture. Even the slightest flaw in the process may lead to highly noticeable pseudo-bacteremia. The volume of the culture media required is also extremely crucial. If that volume is not strictly maintained the possibility of false positive or false negative reports is expected.

*S. typhi* infection frequently occurs in endemic areas because of poor sanitary hygiene. Open passage of stool and urine by infected persons or carriers and then carriage of bacteria

by insects, principally flies and cockroaches to food is an important mode of transmission of typhoid in developing countries. Even then, consumption of contaminated water is the principal cause in the developing countries, compared to developed countries where contaminated food due to droplet infection imparted by so-called healthy carriers is the commonest cause of typhoid fever. Hence, improvement of hygiene and cleanliness of the whole country particularly the rural areas and urban slums is the most important preventive step against typhoid. Construction of sanitary latrine in each and every household and frequently in the roadside should be the first step to prevent typhoid in this country. Beggars and vagabonds are very common in this subcontinent, for most of them begging are a profession or religious ritual. They do not have any habitat and they also won't spend a farthing to use a paid toilet.

Thus, extremely poor hygienic environment in developing countries, particularly in rural areas and urban slums, remains a disastrous cause of yearlong endemicity in these sects of the globe.

Interestingly, even then there is least scope of scientific diagnostic or treatment approach or the feasibility of that. There is no blood culture facility for typhoid throughout the rural and semi-urban areas of the country; even though the said test (viz., blood culture) is supposed to be the gold standard in the diagnosis of typhoid fever.

We have shown in our study that out of 67 patients who were clinically marked as typhoid fever, only 11 patients (16.4%) did have a positive culture out of which only 8 patients (11.9%) had true typhoid fever and 3 patients (4.5%) had paratyphoid fever.

In practice, however, all these patients would have got treatment for typhoid fever, sometimes with wrongly chosen antibiotics and more often with a wrong dose of the antibiotic chosen leading ultimately to drug resistance and many untoward side-effects.

Under these situations, it is obviously understood that in our conditions, which is also a vast area of the globe and hence not negligible; there are a great responsibility and burden to the scientific communities who should come forward, get united and find a solution to these challenges so that brethren of this vast weaker society get justified and enlightened service suitable for their environment but acceptable by general scientific community.

## CONCLUSION

As an inference, it can be told that being a small study, but at the same time, covering a very sensitive community,

our study shows that a very minor portion (16.4%) of the patients deemed clinically as typhoid and treated likewise are actually typhoid fever (including paratyphoid fevers also). This improper treatment which is hugely prevalent does not seem becoming in a scientific world. The enlightened scientific community having come to know this medico-social malady should come forward to find out a remedy suitable for these environmental situations.

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# Diagnostic Importance of Alvarado and RIPASA Score in Acute Appendicitis

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## Abstract

**Introduction:** One of the most common surgical emergencies encountered in the day to day practice both in developed and developing countries in the world is acute appendicitis. The incidence may range from 13% to 77%. The diagnosis is purely based on clinical history, examination and ultrasonography. Many studies are available about the diagnostic methods used for acute appendicitis in western population. Only very few studies were seen about the accuracy of scoring system in Indian population.

**Aim:** To compare the accuracy of Alvarado and RIPASA score in diagnosing appendicitis.

**Materials and Methods:** This was a prospective study conducted at Melmaruvathur Adhiparashakthi Medical College and Hospital in the Department of Surgery from March 2014 to January 2015. About 105 patients with symptoms and signs of acute appendicitis were subjected to Alvarado and RIPASA scoring chart and taken for emergency appendicectomy. The diagnostic accuracy of the scoring system was derived.

**Results:** In this study, 75% of patients were of <40 years of age and 57 (54.29%) patients were female. The most common presenting symptoms in our study were right iliac fossa pain (100%), and sign was rebound tenderness (100%). Histopathologically, about 81.8% of cases were diagnosed as appendicitis. According to Alvarado score <7 and RIPASA score <7.5 80 (76.19%) and 93 (88.57%) patients were diagnosed as appendicitis. The Alvarado score had increased specificity, positive predictive value, and positive likelihood ratio than RIPASA score. The sensitivity and negative predictive value were more for RIPASA score. According to Chi-square test, both Alvarado and RIPASA score was found to be statistically significant.

**Conclusion:** The best method to diagnose the acute appendicitis is by proper clinical examination. Both Alvarado and RIPASA score was statistically significant. But by using RIPASA score the mortality and morbidity due to appendicitis can be reduced.

**Key words:** Appendicitis, Alvarado score, RIPASA score

## INTRODUCTION

One of the most common surgical emergencies encountered in the daily practice both in developed and developing countries in the world is acute appendicitis.<sup>1</sup> Acute appendicitis is a common cause of abdominal pain which needs prompt diagnosis and treatment. This may lead to marked increase in mortality and morbidity.<sup>2</sup> The incidence may range from 13% to 77% with an average of 50%.<sup>3</sup> The

diagnosis is purely based on clinical history and examination combined with raised white cell count. Acute appendicitis is a common problem, but the diagnosis is quite difficult in women. Because the gynecological and genitourinary inflammatory condition may present with similar signs and symptoms. To improve its diagnostic accuracy usually, there is a delay in doing an appendicectomy which may lead to appendicular perforation and sepsis. This may lead to a marked increase in the mortality and morbidity.<sup>4</sup>

The gold standard method for confirmation of diagnosis is by histopathology. However, ultrasound is available for diagnosis but it is operator dependent. Usually, it is over-diagnosed or under diagnosed.<sup>5</sup> The next level is contrast computed tomography (CT) scan. The contrast CT scan has a high sensitivity and specificity but it is too costly and cannot be performed in routine.<sup>6,7</sup> The cheaper,

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faster, and non-invasive diagnostic tool in diagnosing acute appendicitis is a clinical scoring system. Several scoring systems were developed, but the two common scoring systems are Alvarado system and RIPASA system. These two scoring systems are based on the clinical and laboratory evidence. The Alvarado scoring system was developed for people in the western countries, and the RIPASA score was developed for people in the South East Asian population.<sup>2</sup>

Many studies are available about the diagnostic methods used for acute appendicitis in western population. Only very few studies were seen about the accuracy of scoring system in Indian population. Hence, we carried a prospective study to compare the accuracy of Alvarado and RIPASA score in diagnosing appendicitis.

## MATERIALS AND METHODS

This was a prospective study done at Melmaruvathur Adhiparashakthi Medical College and Hospital in the Department of Surgery from March 2014 to January 2015. About 105 patients irrespective of the age and sex who presented with following symptoms and signs and diagnosed as acute appendicitis were included in the study. The basic demographic data about the patient were collected. Inclusion criteria symptoms: (1) right iliac fossa pain, (2) anorexia, (3) nausea, and (4) vomiting. Clinical signs and laboratory investigations: (1) right iliac fossa tenderness, (2) rebound tenderness, (3) guarding, (4) Rovsing's sign, (5) fever (6) elevated white cell count, and (7) urine analysis normal. Then for all patients, the Alvarado and RIPASA scoring chart were done. All the patients were taken for emergency appendicectomy, and the specimen was sent for histopathology examination. Finally, the histopathology reports were compared with the scoring system. Sensitivity, specificity, positive predictive value, negative predictive value, and the likelihood ratios for the scoring system were derived with respect to histopathology, as the gold standard for diagnostic confirmation.

## RESULTS

In this study, 75% of patients were of <40 years of age. Out of 105 patients, 48 (45.71%) patients were male and 57 (54.29%) patients were female. Positive cases of acute appendicitis on histopathology were 86 (81.8%). The most common presenting symptoms in our study were right iliac fossa pain (100%) followed by anorexia (91.4%), nausea, vomiting (74.3%), and fever (33.33%) (Figure 1). The most common signs were rebound tenderness (100%) followed by guarding (57.14%) and Rovsing sign (49.52%) (Figure 2). About 87 (82.86%) patients had raised leukocyte count.

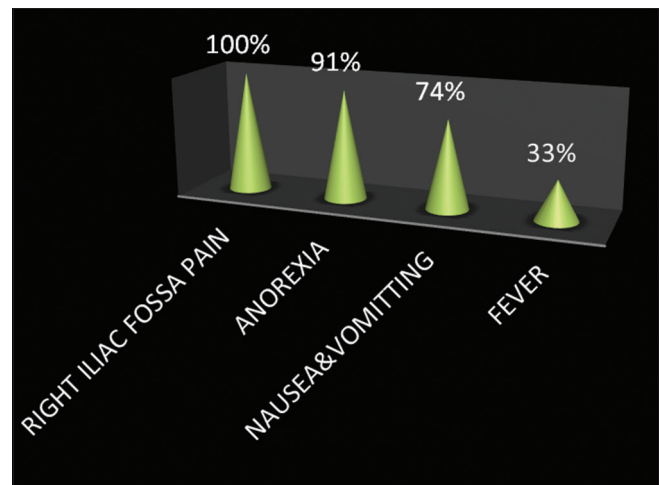


Figure 1: Presenting symptoms

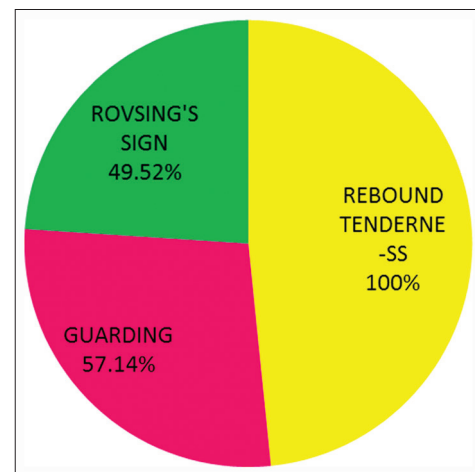


Figure 2: Presenting signs

According to Alvarado score <7, 80 (76.19%) patients were diagnosed as acute appendicitis. Out of these 80 patients, 70 patients were diagnosed as acute appendicitis by histopathology findings (Table 1). According to RIPASA score <7.5, 93 (88.57%) patients were diagnosed as appendicitis clinically, but only 80 patients were confirmed by histopathology report (Table 2). When the accuracy was calculated the Alvarado score had increased specificity, positive predictive value and positive likelihood ratio than RIPASA score. The sensitivity and negative predictive value were more for RIPASA score. According to Chi-square test, both Alvarado and RIPASA score were found to be statistically significant (Table 3).

## DISCUSSION

Inflammation of the appendix is called as appendicitis. The lifetime prevalence rate for acute appendicitis is 1 in 7. In 1554, Fernel was the first person to give a description on acute appendicitis. The classical signs for



**Table 1: Comparison of Alvarado score with histopathology report (n=105)**

Alvarado score	HPE Appendicitis (n=86)	No Appendicitis (n=19)
Alvarado score $\geq 7$ (n=80)	70	10
Alvarado score $< 7$ (n=25)	16	9

HPE: Histopathology examination

**Table 2: Comparison of RIPASA score with histopathology report (n=105)**

RIPASA score	HPE Appendicitis (n=86)	No Appendicitis (n=19)
RIPASA score $\geq 7$ (n=80)	80	13
RIPASA score $< 7$ (n=25)	6	6

HPE: Histopathology examination

**Table 3: Comparing the diagnostic accuracy of Alvarado and RIPASA score**

Diagnostic accuracy	Alvarado score	RIPASA score
Sensitivity (%)	81.4	93.02
Specificity (%)	47.37	31.58
Positive predictive value (%)	87.5	86.02
Negative predictive value (%)	36	50
Positive likelihood ratio	1.55	1.36
Negative likelihood ratio	0.39	0.22
Diagnostic prevalence (%)	81.9	81.9
Chi-square value	7.0975	9.3052
P value	0.007719	0.002285
Statistical significance	Significant	Significant

diagnosing appendicitis were described by McBurney in 1889. Only contrast enhanced CT can give an accurate diagnosis with very high sensitivity and specificity for diagnosing, but this is time-consuming and not feasible in developing countries like ours. If there is any delay in diagnosing, that may lead to increased morbidity and mortality. To avoid this, a simple way of diagnosing appendicitis should be formed. Hence, this study was done to find the accuracy of Alvarado and RIPASA scoring system which is useful in diagnosing appendicitis as early as possible in daily life.

In this study, most of the patient (75%) belongs to the age group  $< 40$  years. This was similar to the other studies.<sup>7-12</sup> Right iliac fossa pain and rebound tenderness were observed in all the patients in our study. This was consistent with the study done by Verma *et al.* and Samad *et al.*<sup>9,13</sup> In a study done by Korner *et al.* and Karan *et al.*, nausea and vomiting was the only symptoms that were found to be statistically significant. But in our study right iliac fossa pain, nausea and vomiting were the two symptoms found to be statistically significant. Similar to their study, right iliac fossa tenderness was found to be statistically significant in our study.<sup>14,15</sup>

In this study, the most common type of appendicitis reported by histopathology was periappendicitis which was consistent with other studies. The negative appendectomy rate (18.09%) was found to be slightly increased in this study. It was variable in other studies.<sup>7,9,10,13</sup> The Alvarado score was found to have more sensitivity than specificity in our study as consistent with other studies. The positive predictive value was similar to other studies like 83.5%, 87.5%, 85.3%, 87.4%.<sup>16-19</sup> In the present study, the negative predictive value was low for Alvarado score when compared to RIPASA score, but the positive predictive value was high. Positive likelihood ratio was also found to be higher than RIPASA score in our study. The Alvarado score was found to be statistically significant.

Similarly, the RIPASA score results were found to be statistically significant. The sensitivity was found to be more, than specificity in the present study. The present value was found to be similar to other studies.<sup>2,13,20</sup> When compared the accuracy of Alvarado and RIPASA score, the sensitivity was found to be more but the specificity was found to be low for RIPASA than Alvarado score. The negative predictive value was more for RIPASA score than Alvarado score. But both were found to be statistically significant. This was similar to the other studies.<sup>2,13,20</sup>

## CONCLUSION

The best method to diagnose the acute appendicitis is by proper clinical examination. RIPASA score with a cut-off total score of  $\geq 7$  is a best non-invasive tool to diagnose acute appendicitis. However, the negative predictive value was found to be high. Both Alvarado and RIPASA score was statistically significant. But by using RIPASA score the mortality and morbidity due to appendicitis can be reduced.

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# Dermatoglyphic Pattern in Relation to ABO, Rh Blood Group and Gender among the Population of Chhattisgarh

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## Abstract

**Introduction:** Dermatoglyphics provides a scientific method for identification of an individual and it is constant and idiosyncratic till demise. It might play an important role during identification of criminals, biometric, aadhar card, etc.

**Objectives:** This study was conducted to conclude relation between dermatoglyphics, ABO, Rh blood group, and gender among the population of Chhattisgarh.

**Materials and Methods:** In this study, total 260 subjects selected (130 male and 130 female) within age group of 18-35 years. All subjects were belongs to central region of India, i.e., Chhattisgarh. Fingerprint was taken using the INK method as illustrate by Cummins and Mildo. Fingerprint patterns (loops, whorls, and arches) and blood data were collected.

**Results:** In this study, 38.46% of subjects belong to O blood group followed by A, B and AB were 95.77% subject having Rh-positive and 4.23% having Rh-negative. Loops higher (female, B blood group and Rh-positive), Whorls higher (male, A blood group and Rh-negative) and arches higher (male, AB blood group, Rh-positive). Where loops lowest (male, AB blood group and Rh-negative), whorls lowest (female, B blood group and Rh-positive) and arches lowest (female, B blood group, Rh-negative).

**Conclusions:** This study shows association between distribution of dermatoglyphic, ABO, Rh blood group, and gender.

**Key words:** ABO blood group, Arches, Dermatoglyphic, Fingerprint, Gender, Loops, Rh blood group, Whorls

## INTRODUCTION

Dermatoglyphics (fingerprint/dactylography) is derived from the Greek word “Derma = Skin, Glyphe = Carve.” Dermatoglyphics defined as the scientific study of natural occurring epidermal ridges and their configuration on the volar region of digits, palms, and soles apart from flexion crease and secondary folds. The term dermatoglyphics was 1<sup>st</sup> coined by Anatomist Harold Cummins in 1926, and he found that the design of ridges on the sole and

foot are gritty by heredity and accidental or environmental influence in their intrauterine life.<sup>1</sup> The development of dermatoglyphic initiate from 12<sup>th</sup>-16<sup>th</sup> week of intrauterine life and accomplished by the 20<sup>th</sup> week of intrauterine life.<sup>2</sup> Dermatoglyphics are constant and idiosyncratic even in monozygotic twins from birth till demise. Fingerprint is personal identification of a human being.<sup>3,4</sup> Fingerprint are helpful in medico-legal case for recognition of suspect, victims and another person who touches the surface and for the diagnosis of inheritable disease. Fingerprint scans also used in digital mission of India, biometric, validate electronic registration, cashless, library access, and forensic purpose.<sup>5</sup> Sir Francis Galton in 1892 published a book known as fingerprint and classified fingerprint primary pattern as loop (60-65%), whorl (30-35%), and arches (5%).<sup>6</sup>

ABO blood group system was discovered at University of Viena by Austrian Scientist Karl Landsteiner. Till

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dated, 19 groups have been identified which vary in their frequency of distribution. ABO and Rh blood group system are of major important.<sup>7</sup> In 1930, he belatedly received the Nobel Prize for his discovery. ABO further classified into 4 principal types: A, B, AB, O. There are two antigens and two antibodies responsible for ABO type. Rh blood group is one of the most complex blood groups in human and it is further classified into Rh-positive and Rh-negative due

to the presence of absence of D antigen.<sup>8</sup> Various disease are usually influence particular blood group like duodenal ulcer in O and gastric ulcer in A blood group.<sup>9,10</sup> The aim of this study to find correlation between gender, ABO and Rh blood group with dermatoglyphic pattern in human beings.

## MATERIALS AND METHODS

This study was conducted in the Department of Anatomy and surgery at Government Medical College, Ambikapur, Surguja, Chhattisgarh, India. Total 260 subjects of equal number of male and female were selected randomly for this study. All Subjects were belongs to central region of India, i.e., Chhattisgarh and their age ranged between 18 and 35 years. All the subjects were healthy and excluded the subject having hand or finger deformities and blood group disease. Subjects have to fill the consent form. Fingerprints were taken using the INK method as illustrate by Cummins and Mildo in 1961.

The material used for this study is Faber-Castell blue color INK pad, A4 size white paper, cardboard, gauze pads, magnifying lens, pencil, and pen. Each white paper filled with basic detail of subject such as name, sex, age, date, blood group, right palm finger, and left palm finger.

### Methods

Each subject asked to wash their hands and dry with the help of towel. After that, press each right and left-hand fingertip separately in the stamp pad. Prints of all the 10 digits were taken in 10 separate blocks on a white A4 size paper. Finally, fingerprint patterns (loops, whorls, and arches) observed with the help of magnifying lens and blood group data were collected.

## RESULTS

A total of 260 subjects were selected randomly from the central region of India, i.e., Chhattisgarh. Among 260 subjects 130 were male and 130 were female.

Table 1 shows the distribution of subjects according to blood group and gender and was recorded as that

**Table 1: Distribution of subjects according to blood group and gender**

Blood group	Male n=130 (%)	Female n=130 (%)	Total n=260 (%)
A	40 (30.76)	45 (34.61)	85 (32.69)
B	25 (19.23)	20 (15.38)	45 (17.30)
AB	17 (13.07)	13 (10.00)	30 (11.53)
O	48 (36.92)	52 (40.00)	100 (38.46)
Total	130	130	260

**Table 2: Distribution of subjects according to blood group and Rh factors**

Blood group	Rh-positive (%)	Rh-negative (%)
A	82 (31.53)	3 (1.15)
B	44 (16.92)	1 (0.38)
AB	28 (10.77)	2 (0.77)
O	95 (36.53)	5 (1.92)
Total	249 (95.77)	11 (4.23)

**Table 3: Distribution of fingertip pattern in the digit of both hands**

Pattern of finger print	Total (%)
Loops	1364 (52.46)
Whorls	820 (31.54)
Arches	416 (16.00)
Total	2600 (100)

**Table 4: Distribution of fingertip pattern according to gender**

Pattern of finger print	Male (%)	Female (%)	Percentage
Loops	644 (49.54)	720 (55.38)	1364 (52.46)
Whorls	445 (34.23)	375 (28.85)	820 (31.54)
Arches	211 (16.23)	205 (15.77)	416 (16.00)
Total	1300 (100)	1300 (100)	2600 (100)

**Table 5: Distribution of fingertip pattern of right and left hand in 260 subjects according to ABO and Rh blood group in 2600 fingers digits**

Pattern of finger print	Blood group A (%)		Blood group B (%)		Blood group AB (%)		Blood group O (%)		Total (%)
	Rh-positive	Rh-negative	Rh-positive	Rh-negative	Rh-positive	Rh-negative	Rh-positive	Rh-negative	
Loops	430 (52.44)	18 (60)	250 (56.82)	7 (70)	130 (46.43)	10 (50)	506 (53.26)	13 (26)	1364 (52.46)
Whorls	270 (32.93)	11 (36.66)	130 (29.55)	2 (20)	90 (32.14)	8 (40)	282 (29.68)	27 (54)	820 (31.54)
Arches	120 (14.63)	1 (3.33)	60 (13.64)	1 (10)	60 (21.43)	2 (10)	162 (17.05)	10 (20)	416 (16)
Total	820	30	440	10	280	20	950	50	2600 (100)

mainstream of subjects 100 (38.46%) go to blood Group “O” and followed by Group A 85 (32.69%), B 45 (17.30%), and AB 30 (11.53%).

Table 2 shows the distribution of subjects according to Blood group and Rh factors and it shows that maximum 249 (95.77%) subjects go to Rh-positive factors of blood group and 11 (4.23%) go to Rh-negative factors of blood group.

Table 3 shows the distribution of fingertip pattern in the digit of both hands and it shows that the maximum percentage, i.e., 52.46% (1364 digits) observed loops and followed by whorls i.e., 31.54% (820 digits) and arches, i.e., 16.00% (416 digits).

Table 4 shows the distribution of fingertip pattern according to gender and we observed that out of 1300 male finger digits 644 (49.54%) digits having loops, 445 (34.23%) digits having whorls and 211 (16.23%) digits having arches and in 1300 female finger + digits 720 (55.38%) digits having loops, 375 (28.85%) digits having whorls and 205 (15.77%) digits having arches.

Table 5 shows the distribution of fingertip pattern of Right and left hand in 260 subjects according to ABO and Rh blood group in 2600 finger digits. Incidence of loops was maximum in Rh-positive and Rh-negative subjects of ABO blood group followed by fingertip pattern of whorls and arches excluding blood group O-negative of whorls where the occurrence of whorls was 54%.

Table 6 shows distribution of fingertip pattern according to Rh blood group and Table 7 shows distribution of fingertip pattern of right and left hand in 260 subjects according to ABO and Rh blood group in 2600 fingers digits.

## DISCUSSION

This study reveals the relation between distribution of dermatoglyphic (dactylography, fingerprint), blood group and gender. This study was done on 260 subjects (equal no. of male and female), and we got maximum of subjects belongs to O blood group, i.e., (38.46%) followed by blood Group A (32%), B (17.30%), and AB (11.53%). Greater

**Table 6: Distribution of fingertip pattern according Rh blood group**

Pattern of finger print	Rh-positive (%)	Rh-negative (%)
Loops	1316 (52.85)	48 (43.63)
Whorls	772 (31)	48 (43.63)
Arches	402 (16.14)	14 (12.72)
Total	2490 (95.77)	110 (4.23)

**Table 7: Distribution of fingertip pattern of right and left hand in 260 subjects according to ABO and Rh blood group in 2600 fingers digits**

Pattern of finger print	Blood group A (%)		Blood group B (%)		Blood group AB (%)		Blood group O (%)		Total
	Rh-positive	Rh-negative	Rh-positive	Rh-negative	Rh-positive	Rh-negative	Rh-positive	Rh-negative	
Loops	430 (52.44)	18 (60)	250 (56.82)	7 (70)	257 (57.11)	130 (46.43)	506 (53.26)	13 (26)	1364 (52.46)
Whorls	270 (32.93)	11 (36.66)	130 (29.55)	2 (20)	132 (29.33)	90 (32.14)	282 (29.68)	27 (54)	820 (31.54)
Arches	120 (14.63)	1 (3.33)	60 (13.64)	1 (10)	61 (13.55)	60 (21.43)	162 (17.05)	10 (20)	416 (16)
Total	820	30	440	10	450	280	950	50	2600 (100)

**Table 8: Comparative and chronological studies of dermatoglyphic according to ABO blood group among the various study of world**

Studied by	year	Loops		Whorls		Arches	
		Highest in blood group	Lowest in blood group	Highest in blood group	Lowest in blood group	Highest in blood group	Lowest in blood group
Mahajan <sup>12</sup>	1986	B	O	O	AB	AB	B
Kshirsagar <i>et al.</i> <sup>11</sup>	2003	B	O	O	AB	AB	B
Bharadwaja <i>et al.</i> <sup>14</sup>	2004	A	O	AB	A	B	AB
Mehta and Mehta <sup>7</sup>	2011	O	AB	B	O	AB	B
Deopa <i>et al.</i> <sup>16</sup>	2014	O	A	AB	B	A	AB
Singh <i>et al.</i> <sup>13</sup>	2016	B	AB	O	AB	AB	O
Present study	2017	B	AB	A	B	AB	B

part of the subjects, i.e., 95.77% were Rh-positive and few, i.e., 4.23% were Rh-negative.

The universal distribution of pattern of fingerprint was of the order in individual with A, B, AB and O blood group, i.e., higher frequency of loops, moderate of whorls and low of arches. The same finding was seen in Rh-positive and Rh-negative individuals.<sup>11,12</sup>

In this study, loops were higher in B blood group (57.11%) followed by A (52.70%), O (51.9%) blood group and lowest in AB blood group (46.67%) which correlates with the study of Singh *et al.*,<sup>13</sup> Mahajan<sup>12</sup> and while Kshirsagar *et al.*<sup>11</sup> found the highest percentage of loops in AB blood group. Comparative and chronological studies of dermatoglyphic according to ABO Blood group among the various study of the world showed in Table 8.

In this study, the percentage of loop was highest in Rh-positive (52.85%) and lowest in Rh-negative (43.63%), which correlated with Mehta and Mehta,<sup>7</sup> Kshirsagar *et al.*,<sup>11</sup> and Bharadwaj *et al.*<sup>14</sup> were whorls highest in Rh-negative (43.63%) and lowest in Rh-positive (31%), which correlated with Kshirsagar *et al.*<sup>11</sup> and Bharadwaj *et al.*<sup>14</sup> and contrary Mehta and Mehta.<sup>7</sup> The percentage of arches were highest in Rh-positive (16.14%) and lowest in Rh-negative (12.72%) which contrary Mehta and Mehta,<sup>7</sup> Kshirsagar *et al.*<sup>11</sup> and Bharadwaj *et al.*<sup>14</sup>

In our study, the percentage of loops higher in female (55.38%) and lowest in male (49.54%) which correlated Rastogi and Pillai,<sup>15</sup> where the percentage of whorls highest in male (34.23%) and lowest in female (28.85%) which correlated Rastogi and Pillai<sup>15</sup> and percentage of arches highest in male (16.23%) and lowest in female (15.77%) which contrary Rastogi and Pillai.<sup>15</sup>

## CONCLUSION

This study revealed association between dermatoglyphic, blood group and sex:

- Majority of subjects belongs to Rh-positive and O blood group.
- Loops are the frequently and arches are uncommon fingerprint.
- Loops were highest in B blood group and lowest in AB blood group. Whorls highest in A and lowest in B blood group. Arches were highest in AB and lowest in B.
- Loops higher in female and lowest in male, whorls highest in male and lowest in female and arches highest in male and lowest in female.
- Loops were highest in Rh-positive and lowest in Rh-negative. Whorls highest in Rh-negative and lowest in Rh-positive. Arches were highest in Rh-positive and lowest in Rh-negative.

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# Methicillin-resistant *Staphylococcus aureus* in Eastern India: Some Molecular Epidemiological Perspectives

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## Abstract

**Background:** *Staphylococcus aureus* is the most important nosocomial pathogen causing skin and soft tissue infection. Methicillin-resistant *S. aureus* (MRSA) is now established in both community-acquired and hospital-acquired infections. The defining feature of MRSA is the staphylococcal cassette chromosome *mec* (SCC*mec*), which is a mobile genetic element, carrying the central determinant for broad-spectrum beta-lactam antibiotic resistance encoded by the *mecA* gene, whereas the presence of panton-valentine leukocidin (PVL) gives more virulence to the MRSA.

**Aim:** To assess molecular epidemiology of MRSA in Eastern India.

**Design:** Descriptive cross-sectional study.

**Materials and Methods:** In this study, from 940 samples in a tertiary care hospital in rural India, over 6 months, 20 MRSA isolates were identified. These isolates were typed to study the diversity in the structures of SCC*mec* elements and *ccr* types. Statistical analysis was performed by SPSS software.

**Results:** Isolates carrying SSC*mec* Type IV were found to be dominant (60%), whereas a small proportion was SSC*mec* Type V (10%). Some composite strains were found. PVL gene was found to be associated with community-associated MRSA (CA-MRSA) genotypes.

**Conclusion:** Genotypical blurring of CA-MRSA and hospital-acquired MRSA was seen. Composite SCC*mec* strains found showing need for new nomenclature methods.

**Key words:** Epidemiological typing, Methicillin-resistant *Staphylococcus aureus*, Staphylococcal cassette chromosome

## INTRODUCTION

The resistance of *Staphylococcus aureus* to beta-lactam antibiotics is associated with the expression of penicillin binding protein 2a. This protein is encoded by the *mecA* gene, which is situated on a mobile genetic element, staphylococcal cassette chromosome *mec* (SCC*mec*).

Five different SCC*mec* types have been identified in methicillin-resistant *S. aureus* (MRSA) strains. SCC*mec* Types I, II, and III are mainly found in hospital-acquired MRSA (HA-MRSA), whereas SCC*mec* Types IV and V are mainly associated with community-acquired MRSA (CA-MRSA).<sup>1</sup>

During 1990s epidemic MRSA-15 (EMRSA-15) emerged in the hospital settings as per the reports from the UK. Later, this classical EMRSA-15 has been isolated from community settings as well and characterized as SCC*mec* Type IV CA-MRSA. The majority of the CA-MRSA causing infections in Indian subcontinent have been identified as SCC*mec* IV. A variant of EMRSA-15 which produces panton-valentine leukocidin (PVL) toxin has been isolated

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and characterized by pulsed-field gel electrophoresis method from the Indian population both in hospital and community settings.<sup>2</sup>

SCC*mec* contains the *mec* complex (*mecA* and its regulators) and the *ccr* gene complex, which encodes site-specific recombinases, responsible for the mobility of SCC*mec*. Several different *ccr* genes have been identified: *ccrA1* and *ccrB1* in SCC*mec* Type I, *ccrA2* and *ccrB2* in SCC*mec* Types II and IV, *ccrA3* and *ccrB3* in SCC*mec* Type III, *ccrA4* and *ccrB4* in SCC*mec* Type IV, and *ccrC* in SCC*mec* Type V.<sup>3</sup>

Epidemiological typing of the infectious agent can be considered as one of the important weapons in the armamentarium of the infection control specialists as this pin points the epidemiological clone of MRSA prevalent in the community. Unfortunately, there is not much published data available about the epidemiological type of MRSA from this part of India. Hence, the objective of this study was to characterize the MRSA strains.

### Objective

The objective of this study was to assess the epidemiological type of MRSA among the isolates from clinical samples in a tertiary care hospital in rural Eastern India.

## MATERIALS AND METHODS

All clinically isolated *S. aureus* over the 6 months study period were tested for methicillin-resistance according to CLSI guidelines.<sup>4</sup> Staphylococci were identified morphologically and biochemically by standard laboratory procedures. *S. aureus* was identified by tube coagulase, along with mannitol fermentation on mannitol salt agar (Himedia). Methicillin-resistance was confirmed using a cefoxitin disk on Mueller-Hinton agar (Oxoid).

### Isolation of Genomic DNA

The DNA was isolated from all the isolates growing in nutrient broth at 37°C overnight, using Genei bacterial DNA isolation kit as per manufacturer's instruction and was confirmed by visual examination of ethidium bromide agarose gel.

### 16S Ribotyping

Partial amplification of 16SrDNA was done using a universal primer set 27F (5'-AGAGTTTGTATCMTGGCTCAG-3') and 1492R (5'-TACGGYTACCTTGTTACGACTT-3'). All samples were amplified under the same conditions: Denaturation at 94°C for 30 s, annealing at 50°C for 40 s, and extension at 72°C for 90 s with 35 cycles of amplification. After separation in a 1% agarose gel and retrieval with a Qiagen Gel Extraction kit, amplicons were subjected to Sanger sequencing in Applied Biosystem

sequencer machine using primer 27F. Sequencing reaction was performed using BigDye Terminator Cycle Sequencing Kit following the manufacturer's protocol.

### Phylogenetic Analysis

Assessment of PVL and *mecA* gene: Polymerase chain reaction (PCR) was performed with the primers designed to detect the *lukS-PV* and *lukF-PV* genes, which encode for PVL toxin based on the method described by Lina *et al.* with some modifications<sup>5</sup> and the *mecA* gene, which confers methicillin-resistance to the MRSA strain.

### SSC*mec* Typing

All the MRSA isolates were typed by SCC*mec* typing for SCC*mec* IV and V and presence or absence of PVL gene. The SSC*mec* typing was performed by PCR analysis using the primers set described by Govindan *et al.* (Table 1). In this study, only the most common and prevalent CA-MRSA types in India, i.e., SSC*mec* Type IV and Type V were included. Total 3 primer sets were used to amplify the necessary genes for SSC*mec* Type IV and Type V screening. SSC*mec* Types IV isolates were next subjected to screening for the presence of IS 1272 element for reconfirmation. Frequency distribution of various types of MRSA such as PVL positives, SCC Type IV and V were analyzed using SPSS.

## RESULTS

About 940 clinical specimens in the period December 2014 to June 2015 were taken in this study, out of which 122 were identified as *S. aureus*. Among the 122 *S. aureus* isolated, 20 were MRSA by phenotypic testing. Out of the 20 MRSA isolates 12 were HA-MRSA and 8 were CA-MRSA by phenotypic criteria. Molecular results: All the 20 isolates were found to be positive for *mecA* gene (Figure 1) as internal control. The isolates in this study were predominantly of SCC*mecA* Type IV (12/20) having the *ccrB2* (Figure 2) and *dcs* region (Figure 3) in their genetic makeup, which were further checked for presence of IS-element, and were confirmed by presence of band at 1.4 KB region. Two isolates were of Type V, showing the *ccrC* gene (Figure 4), and 6 isolates carried *ccrC* gene and also the *ccrB2*, without *dcs* region. PVL was present in three isolates among all (Figure 5), which were community acquired SCC*mec* A Type IV category (Table 2).

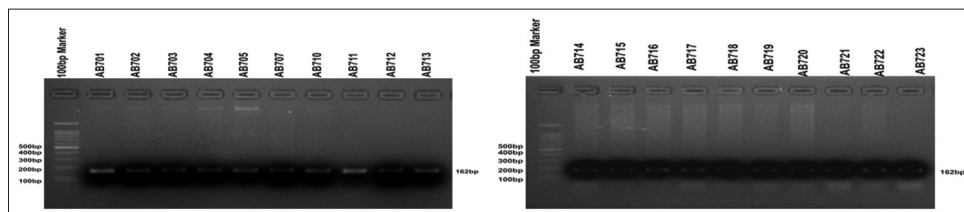
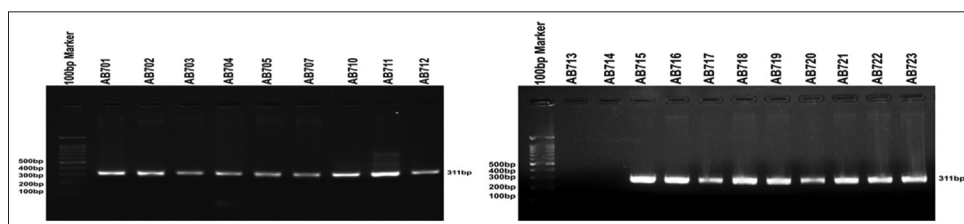
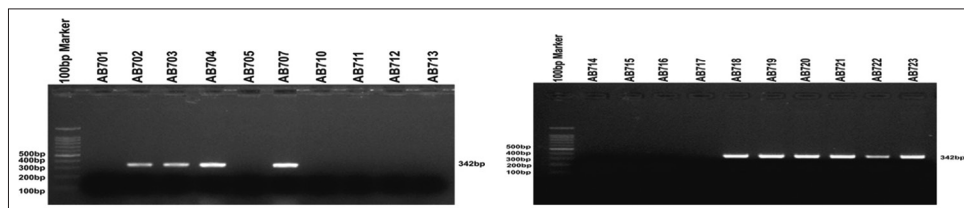
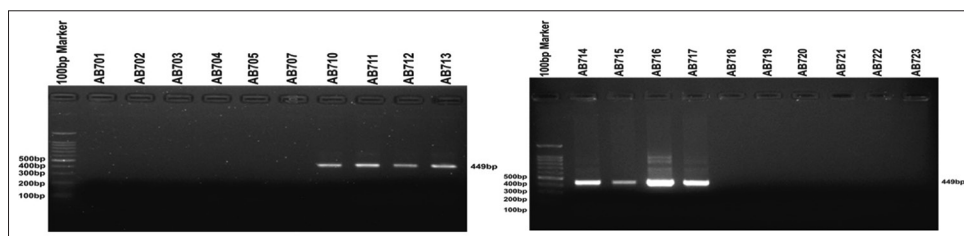
## DISCUSSION

The prevalence of MRSA in India<sup>6-8</sup> in various studies in last 5 years ranges from 48% to 53%. The prevalence during our study period of 6 months was 17% approximately. This may be because the study was conducted in a

**Table 1: Primers used in the study**

Gene	Forward primer	Backward primer	References
<i>MecA</i>	5'-ACTGCTATCCACCCTCAAAC-3'	5'-CTGGTGAAGTTGTAATCTGG-3'	Govindan <i>et al.</i> <sup>2</sup>
<i>ccrB2</i>	5'-AGTTTCTCAGAATTCGAACG-3'	5'-CCGATATAGAAAGGGTTAGC-3'	
<i>ccrC</i>	5'-GTACTCGTTACAATGTTTGG-3'	5'-ATAATGGCTTCATGCTTACC-3'	
<i>Dcs</i>	5'-CATCCTATGATAGCTTGGTC-3'	5'-CTAAATCATAGCCATGACCG-3'	
PVL	5'-ATCATTAGGTAAAATGTCTGGACATGATCCA-3'	5'-GCATCAASTGTATTGGA-3'	
IS	5'-AACGCCACTCATAACATATGG-3'	5'-TATACCAAACCCGACAAC-3'	

PVL: Panton-valentine leukocidin

**Figure 1: Detection of *mecA* gene in methicillin-resistant *Staphylococcus aureus* isolates****Figure 2: Detection of *ccrB* genes in methicillin-resistant *Staphylococcus aureus* isolates****Figure 3: Detection of *dcs* gene in methicillin-resistant *Staphylococcus aureus* isolates****Figure 4: Detection of *ccrC* genes in methicillin-resistant *Staphylococcus aureus* isolates**

hospital serving a rural population with limited access to cosmopolitan cities. Furthermore, this may not reflect the true prevalence as the study was conducted on samples collected over 6 months only. The majority of the MRSA were found to be SCC*mec* Type IV (60%). Two others were SCC*mec* Type V (10%), but 6 were composed of an SCC with *ccrC* as well as an SCC*mec* with a class B2 *mec* gene complex (30%). Such composites of two or more

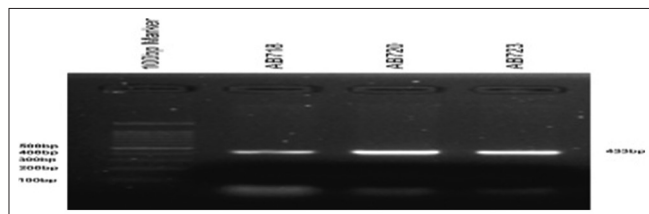
scc elements carrying two *ccr* gene complexes have been identified in other studies and have posed nomenclature problems (such as *S. aureus* ZH47).<sup>9</sup>

All strains were evenly distributed among the phenotypically identified HA-MRSA and CA-MRSA which once again shows that that this distinction is now blurred and not useful. The previous research shows that genotypically

**Table 2: Break up of genes detected in the MRSA isolates**

Number of isolates (n=23)	SCCmec type	ccr gene complex		MecA gene complex present	PVL gene present
		ccrB2	ccrC		
12	IV	+	-	+	3
2	V	-	+	+	0
6	Novel ( <i>Staphylococcus aureus</i> strain ZH47)	+	+	+	0

PVL: Pantan-valentine leukocidin, MRSA: Methicillin-resistant *Staphylococcus aureus*

**Figure 5: Detection of panton-valentine leukocidin gene in methicillin-resistant *Staphylococcus aureus* isolates**

the original CA-MRSA were seen to be SCC Type IV and V. Hence, the MRSA in our study can be assumed to be derived from the community strains as all contain genes which are present in Type IV or Type V or both. Hence, the phenotypically defined hospital-acquired strains have their origins in the community, and have evolved, maybe via horizontal gene transfer of virulence factors.<sup>10</sup> The importance of hand hygiene once again is to be emphasized for prevention of such evolution of CA-MRSA to more invasive strains. The more virulent EMRSA derived from CA-MRSA<sup>11,12</sup> has already been found in some studies in India. PVL was identified in only three strains of SCCmec Type IV only. PVL has been shown as acquired by EMRSA strains in other studies. None of the PVL gene possessing isolates in our study were from pneumonia patients, So PVL being a necrotizing toxin in staphylococcal pneumonia caused by CA-MRSA could not be verified.<sup>13</sup>

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# Antibiotic Profile for Blood Stream Infections in Hemodialysis Patients

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## Abstract

**Background:** Blood stream infections (BSIs) remain a significant factor influencing illness and death among patients receiving hemodialysis (HD). Monitoring trends in antibiotic use in dialysis units is important for improving patient safety and quality of care. This study aimed to facilitate the guidelines toward effective antibiotic therapy to the patients on HD with BSIs.

**Materials and Methods:** A total of 100 patients who undergone HD were enrolled in the study. Their blood cultures were performed according to automated robotic (BacT/Alert Three-dimensional, BioMérieux Inc.) blood culture system, to identify the organism cause BSIs.

**Results:** A total of 27 patients were confirmed to have HD BSIs based on our study criteria. 19 patients had Gram-positive (*Staphylococcus aureus*: 14, *Staphylococcus epidermidis*: 5) and 8 had Gram-negative infections (*Escherichia coli*: 4, *Pseudomonas aeruginosa*: 4). The most common Gram-positive organisms were sensitive to vancomycin and clindamycin. The *E. coli* has been sensitive to pазufloxacin and meropenem. The *P. aeruginosa* has been sensitive to imipenem with cilastatin.

**Conclusion:** Gram-positive organism *S. aureus* and *S. epidermidis* were highly sensitive to vancomycin and clindamycin once in week and 3 times per day through intravenous (IV), respectively, *E. coli* was sensitive to pазufloxacin and meropenem twice daily through IV for 2 weeks. *P. aeruginosa* was sensitive to imipenem with cilastatin once in 48 h for 2 weeks.

**Key words:** Antibiotic therapy, Blood stream infections, Gram-positive, Gram-negative, Hemodialysis

## INTRODUCTION

Chronic kidney disease is a noteworthy public health burden.<sup>1</sup> End-stage renal disease is increasing exponentially across the world.<sup>2</sup> Comprehensively, dialysis is the foremost methodology for renal replacement therapy. Among dialysis patients, infection related results have an effect on hemodialysis (HD) patients lopsidedly as they have greater chances of blood stream infection (BSI) when put next with peritoneal dialysis patients.<sup>3</sup> HD catheter assumes a relevant phase within the treatment of patients

requiring HD. It is moderately simple to be offered and may also be utilized immediately as a part of vast type of kidney failure patients. Unfortunately, HD catheter is just not without issues. Apart from thrombosis, infection is a standout among probably the most dreaded complexities. Disease of the HD catheter used to be suggestion to bring about an increase of >50% mortality in HD patients contrasted with patients on native fistulas in addition cause noteworthy morbidity in dialysis population.<sup>4</sup> The reason for HD BSIs is multifactorial starting from patient's elements (i.e., comorbidities and cleanliness) to catheter's variables (i.e., style of catheter and site of insertion).<sup>5</sup> Presently, the administration of HD BSIs depends on the kind of catheter integrated, variety of microorganism and the seriousness of the diseases. Antibiotics are the spine for the healing of HD BSIs. Occasionally, the HD catheters will have to be replaced in problematic instances. Cure have to be customized equipped as per the microbiology results.<sup>6</sup> The period of treatment is

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dependent on the organism cultured, as well as, whether or no longer the catheter was removed.<sup>7</sup> Nonetheless, there is a shortage of local data on this issue. This study meant to explore the viability of antibiotics for the treatment of BSI in patients receiving HD.

## MATERIALS AND METHODS

A total of 100 patients who underwent HD were enrolled within this study. The selection of patients based on the following: mild fever, chills and/or hypotension, and semi quantitative laboratory confirmation, when blood from the catheter displays microbial progress not <2 h than progress is distinguished in blood culture while from a peripheral vein.<sup>8</sup> HD patients who presented other routes of infections had been rejected from the study. Consents were taken from the patients. Two arrangements of blood cultures have been taken from every patient. One set of blood culture (anaerobic and oxygen consuming) was taken from a peripheral vein and a different set from the catheter. The peripheral blood culture was taken from a vein in the middle cubital fossa or the flexor part of the lower arm. A sterile zone was then separated using hanging the territory with a sterile sheet. The sterile zone was once made by means of cleansing the zone with 70% alcohol took after by way of 10% povidone-iodine in a roundabout movement establishing from the within and moving outward, and the site was once left to dry. Blood was taken from the catheter in a comparative design. The catheter center was once then cleaned with 10% povidone-iodine and left to dry. An identical measure of blood was once drawn for catheter and peripheral cultures. All administrators wore plastic outfits, face covers, and sterile gloves to counteract infection of the blood culture.

The blood has been cultured utilizing a robotic blood culture (BacT/Alert three-dimensional, BioMérieux Inc.) approach. The blood inoculated immediately into BacT/Alert FA plus aerobic blood culture bottles with 0.025% of sodium polyanethol sulfonate as anticoagulant. After assortment, these bottles had been right away incubated in BacT/Alert 3D (manufactured by means of BioMérieux) an absolutely automatic blood culture approach for identification of growth in culture. The negative results have been followed as much as 7 days and final report was issued. At the same time, in case of a positive progress, the BacT/Alert robotically offers an alert. The positive bottles had been then subcultured on MacConkey agar for identification of microorganisms with the aid of common microbiological ways.<sup>9</sup> The antibiotics have been given as per the international guidelines, sensitivity tests and observed the efficacy of the antibiotics. This study protocol has been approved via hospital ethics committee

and we bought written and informed consent from the study patients before the study.

## RESULTS

Out of 100 blood samples subjected for culture, 27% showed culture positive result. No anaerobic bacteria identified in this study. Among these positive cases, 19 patients had Gram-positive (*Staphylococcus aureus*: 14, *Staphylococcus epidermidis*: 5) and 8 had Gram-negative infections (*Escherichia coli*: 4, *Pseudomonas aeruginosa*: 4).

Among the Gram-positive infectious patients, the predominant causative organism was *S. aureus*. Out of 14 patients, 13 were susceptible for vancomycin 1 g once in a week by intravenous (IV) route for 2 weeks. Another 1 patient was susceptible for clindamycin 600 mg 3 times per day by IV route for 2 weeks. Similarly, out of five patients with *S. epidermidis*, four patients showed susceptible for vancomycin 1 g once in a week by IV route for 2 weeks and one patient was susceptible for clindamycin 600 mg 3 times per day by IV route for 2 weeks (Table 1).

Two Gram-negative organisms were observed with equal numbers in this study. *E. coli* showed susceptible for pazufloxacin (500 mg twice a day by IV for 2 weeks) in 2 patients and another two patients were susceptible for meropenem (500 mg twice a day by IV for 2 weeks). *P. aeruginosa* has showed susceptible for imipenem with cilastatin as a combinational therapy with 0.5 g once in 48 h through IV for maximum 14 days (Table 1).

In view of this significance, vancomycin showed 89% efficacy against *S. aureus* and *S. epidermidis*. 100% efficacy has been observed in pazufloxacin and meropenem against *E. coli* and *P. aeruginosa* was susceptible 100% with imipenem with cilastatin.

## DISCUSSION

In this study, 27% samples processed have been culture positive cases. No organism was detected from 74% blood samples processed until 1 week of incubation and these instances had been viewed as culture negative. Blood culture positivity was visible in 27 of 100 (27%) cases which is fairly scale down to different experiences of previous authors.<sup>8,10,11</sup> This may be when you consider that of majority of the patients suggested to us are referred with the aid of other experts or hospitals, and these patients have been given antibiotics somewhere else earlier than they reached our medical institution. Many patients developed infections after hospitalization or after surgical procedure

**Table 1: Antibiotic profile for microorganisms caused BSIs**

Microorganisms	Antibiotic	Dose	Route of administration	Response (how many days)
<i>Staphylococcus aureus</i>	1. Vancomycin	1 g	IV once in a week	2 weeks
	2. Clindamycin	600 mg 3 times a day	IV daily	1-2 weeks
<i>Staphylococcus epidermidis</i>	1. Vancomycin	1 g	IV once in a week	2 weeks
	2. Clindamycin	600 mg 3 times a day	IV daily	1-2 weeks
<i>Escherichia coli</i>	1. Pazufloxacin	500 mg twice daily	IV daily	1-2 weeks
	2. Meropenem	500 mg twice daily	IV daily	1-2 weeks
<i>Pseudomonas aeruginosa</i>	Imipenem with cilastatin	0.5 g	IV once in 48 h	7-14 days

BSIs: Blood stream infections

during which they already had been given antibiotics before sampling of blood for culture.

Vancomycin acts on Gram-positive bacteria by inhibiting its cellular wall synthesis. It must be given intravenously since it has high molecular weight and not easily absorbed from the intestine. Vancomycin dose has half-life approximately 6 h in subjects with normal kidney function.<sup>12</sup> The half-life is greatly increased in kidney failure (half-existence is up to 7.5 days in anephric patients, indicating minimal nonrenal clearance), and dosage regimen is carried according to the need of these patients.<sup>13,14</sup> Bisiwe *et al.*, (2015)<sup>15</sup> revealed that a vancomycin-resistant Gram-positive organism used to be not recognized of their study and their discovering helps the advice of utilizing vancomycin empirically to duvet Gram-positive organisms in these patients while waiting for blood culture outcome. The identical results were observed in our study additionally. Published vancomycin protocols<sup>13,14</sup> are also adopted to inspire nontoxic and effective administration. This study had been followed the same protocol.

Clindamycin is an antibiotic which stops the growth of microorganisms especially bacteria. It binds on 50 s ribosomal unit to inhibit protein synthesis. Its activity against to respiratory infection caused by *S. pneumoniae*, *S. pyogenes*, and MSSA, also an extensive variety of Gram-positive and Gram-negative anaerobes.<sup>16</sup> Clindamycin is basically bacteriostatic agent shows time-dependent endeavor at >4 times concentration than the MIC, and has a moderate *in vitro* postantibiotic influence against *S. aureus*.<sup>17</sup> As a result, this study has been used clindamycin for Gram-positive organisms which used to be now not respond with vancomycin.

Pazufloxacin is a potent large spectrum antibiotic against both Gram-positive and negative microorganisms including multidrug resistant strains.<sup>18,19</sup> It also showed that it has DNA antagonist efficiency.<sup>20</sup> The present has been utilized the pazufloxacin against *E. coli* and results have been incredibly commendable.

Meropenem is a carbapenem antibiotic. It kills bacteria by inhibiting cell wall synthesis. It has efficiency to kill most

Gram-positive and negative microorganisms. Mostly, it is used to treat intra-abdominal infections for 7-14 days. In this study also followed the identical protocol.

Imipenem is a carbapenem antibiotic and cilastatin facilitates the imipenem works efficiently by inhibiting the breakdown in the kidney. Imipenem/cilastatin combination is an antibiotic useful for the treatment of a number of bacterial infections. It is a broad-spectrum beta-lactam containing equal quantities of imipenem and cilastatin. It is related to the penicillin/cephalosporin family of antibiotics, but is classified as belonging to the carbapenem class. It has activity against many aerobic and anaerobic Gram-positive and Gram-negative organisms, including *P. aeruginosa*. Based on the above fact, in this study, we used combinational therapy for *P. aeruginosa*.

In conclusion, Gram-positive organism was predominant to cause BSI. Vancomycin can be appropriate treatment option for Gram-positive organisms. If vancomycin fails, can use clindamycin as an alternate to vancomycin. In Gram-negative organisms especially *E. coli*, pazufloxacin and meropenem can be used based on the clinical condition and sensitivity patterns of patients. Imipenem with cilastatin may be served as a better combination for treating *P. aeruginosa* infections.

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# Role of Optical Coherence Tomography and Scanning Laser Polarimetry (GDx Variable Corneal Compensation) in the Assessment of Retinal Nerve Fiber Layer in Primary Acute Angle Closure Glaucoma

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## Abstract

**Introduction:** Primary acute angle closure glaucoma (PAACG) is an ophthalmic emergency and potentially blinding diseases (the distribution of ACG has shown striking differences by racial groups in individual over 40 years of age with optic nerve damage which occurs after a sudden rise of intraocular pressure associated with a PAACG episodes).

**Materials and Methods:** The study enrolled 30 patients with unilateral PAACG attack in the first 4 months after remission and 30 normal persons for control. Using the stratus optical coherence tomography (OCT) (Version 4.0.2) and GDx variable corneal compensation (VCC), the retinal nerve fiber layer (RNFL) thickness was assessed in both eyes within 2 weeks after PAACG and again after 4 months. As assessed by OCT and GDx VCC, RNFL thickness in subjects became thicker at 2 weeks and thinner by 4 months of acute attack compared with the fellow unaffected and normal eyes.

**Results:** RNFL of PAACG eyes became thicker by an average of  $143.87 \pm 15.23 \mu$  compared to  $108.53 \pm 7.44 \mu$  in the fellow eye and  $108.90 \pm 7.93 \mu$  in the normal eye ( $P < 0.001$ ) within 2 weeks. It became thinner by an average of  $88.73 \pm 10.27 \mu$  in the affected eyes compared to  $107.87 \pm 7.20 \mu$  in the fellow eyes and  $107.17 \pm 7.29 \mu$  in the normal eye ( $P < 0.001$ ) at 4 months. Significant differences were demonstrated comparing the average and four quadrant RNFL thickness for attacked eyes and those of normal control ( $P < 0.001$ ) and fellow eyes ( $P < 0.001-0.002$ ) using analysis of variance both within 2 weeks and at 4 months after remission.

**Conclusion:** Using OCT and GDx VCC, RNFL thickness was found increased in eyes immediately after an episode of PAACG followed by a decrease in RNFL thickness over time (up to 4 months). This detection can aid in better understanding of the pathological changes in the retina in PAACG and thus help in the assessment and management of these patients.

**Key words:** Goldmann applanation tonometry, GDx variable corneal compensation, Optical coherence tomography, Primary acute angle closure glaucoma, Retinal nerve fiber layer

## INTRODUCTION

Primary acute angle closure glaucoma (PAACG) is an ophthalmic emergency and potentially blinding diseases (the

distribution of ACG has shown striking differences by racial groups in individual over 40 years of age, with optic nerve damage which occurs after a sudden rise of intraocular pressure [IOP] associated with a PAACG episodes). The optic disc appears edematous during this episode and pallor with or without cupping may develop after remission. When treatment is delayed vision may reduce markedly to hand movement or light perception.<sup>1</sup> Pathologically, the ganglion cells die by apoptosis and their axons disappear over and above the normal apoptotic loss that occurs naturally with age. Perimetric examination during acute episodes is difficult and usually

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unreliable. After remission, visual field defect varies greatly in severity and type.<sup>2</sup> Measurement of retinal nerve fiber layer (RNFL) thickness loss after PAACG is very important as it is both objective and sensitive in terms of detection of optic disc damage with either normal or unreliable fields.

In recent years various glaucoma imaging modalities - optical coherence tomography (OCT), scanning laser polarimetry (SLP), confocal scanning laser ophthalmoscopy, SLP + variable corneal compensation (VCC) (GDx VCC, Carl Zeiss Meditech, Inc., Dublin, CA) in the management of glaucoma. OCT is a high-resolution glaucoma imaging device capable of obtaining reproducible RNFL thickness measurement.<sup>3-5</sup> This device has been shown in cross-sectional studies to allow differentiation between normal and glaucoma patient.<sup>6-9</sup> Studies have shown that SLP with VCC significantly improves the structure - function relationship<sup>10,11</sup> agreement with other imaging technologies<sup>10,12</sup> and discriminating power for detection for glaucoma.<sup>13-16</sup>

## MATERIALS AND METHODS

This was a prospective observational study undertaken in a tertiary health-care center in West Bengal from March 2014 to February 2015 which was approved by institution ethics committee. A prior written consent from the participants was taken. The study population included 30 eyes of the patient with unilateral attack of PAACG, 30 fellow eyes and 30 eyes of control, patient attending ophthalmology outpatient department of same age and sex without symptoms and sign suggestive of ACG over a time period of 1 year. To be eligible patients required to have at least two of the following symptoms - ocular pain, blurred vision, headache, vomiting and presence of any of the signs like conjunctival congestion, mid dilated nonreactive pupil, corneal edema, IOP >45 mmHg, closed angle on gonioscopy, duration of PAACG attack ≤120 h and complete resolution of attack with medical therapy and surgery and IOP below 21 mm Hg after treatment. Patients were excluded if the attack was bilateral, secondary angle closure, PAACG of the fellow eye in the past, refractive error of ≥5.00 D spherical and or 3.0 D cylindrical, persistent corneal edema or opacity after PAACG attack, previous intraocular surgery or intraocular disease that may result in abnormal RNFL thickness. OCT and GDx VCC were done once at 2 weeks and an interval of 4 months. The parameters studied were the global RNFL thickness and four quadrant RNFL thickness. Each subject underwent a comprehensive ophthalmological examination including best corrected visual acuity, IOP by Goldmann applanation tonometry, Slitlamp Biomicroscopy, Gonioscopy, Fundus evaluation on slit lamp with +90 D lens, standard achromatic perimetry on Humphrey Field Analyzer using 30-2 testing protocol by Swedish interactive threshold algorithm standard protocol.  $P < 0.05$  was considered as significant.

## RESULTS

A total of 30 patients and 30 controls with the same sex ratio with age group between 25 and 65 years were studied (Table 1). The mean duration of the PAACG attack was  $72 \pm 48$  h. The global and four quadrant RNFL thickness as measured by OCT and GDx VCC showed a statistically significant difference between the eyes with acute attack and fellow or normal eye ( $P < 0.001$ ) at 2 weeks - Table 2. These parameters also changed significantly within 4 months in eyes suffering from the acute attack. The statistical analysis was done by one-way analysis of variance. The average and (four quadrants) RNFL thickness in the eyes suffering from PAACG attack increased to  $143.87 \pm 15.23 \mu$  compared to  $108.53 \pm 7.44 \mu$  of the unaffected fellow eyes at 2 weeks ( $P < 0.001$ ). The four quadrants RNFL also increased in the affected eyes at 2 weeks but not in the fellow eyes. At 4 months of follow-up also the four quadrant RNFL thickness decreased in the affected eye compared to the fellow eyes or normal eyes ( $P < 0.001$ ).

**Table 1: Characteristics of study population**

Characteristics	n=30		
	Affected eyes	Unaffected eyes	Controls
Age	45±20	46±18	46±13
IOP	42±3.6	13±3.9	12±2.8
Visual field			
MD	-6.4±3.2	-1.87±0.88	-1.56±0.56
PSD	3.87±2.22	2.22±1.08	1.67±0.89

IOP: Intraocular pressure, MD: Mean deviation, PSD: Pattern standard deviation

**Table 2: The global and four quadrant RNFL thickness as measured by OCT and GDx VCC**

Parameters	Affected eyes±SD	Fellow eyes±SD	Control eyes±SD	P value
Average thickness				
Within 2 weeks	143.87±15.23	108.53±7.44	108.90±7.93	<0.001
At 4 months	88.73±10.27	107.87±7.20	107.17±7.29	<0.001
Superior quadrant				
Within 2 weeks	173.00±23.51	131.97±12.77	132.57±12.54	<0.001
At 4 months	101.43±21.29	131.17±12.74	129.93±12.35	<0.001
Nasal quadrant				
Within 2 weeks	112.77±21.83	83.87±13.44	83.27±12.92	<0.001
At 4 months	68.40±15.98	82.83±14.05	84.50±13.68	<0.001
Inferior quadrant				
Within 2 weeks	196.13±25.17	149.77±12.60	146.90±14.39	<0.001
At 4 months	110.03±26.96	150.00±12.90	147.77±13.71	<0.001
Temporal quadrant				
Within 2 weeks	96.03±25.83	71.70±9.65	73.10±10.64	<0.001
At 4 months	64.00±10.31	74.43±10.83	75.40±11.75	<0.001

RNFL: Retinal nerve fiber layer, OCT: Optical coherence tomography, SD: Standard deviation, VCC: Variable corneal compensation

vide Table 2. Therefore, we conclude that there is an initial increased in global RNFL thickness after an acute attack followed by a decrease around 4 months.

The average, temporal, superior, nasal and inferior peripapillary RNFL thickness as measured by OCT and GDx showed a statistically significant difference between the eyes with acute attack and fellow or normal eyes, respectively ( $P < 0.001$ ).

## DISCUSSION

In our study, the possible explanation for the increased global average and four quadrant RNFL thicknesses at 2 weeks is the apparent edema of the Optic Nerve Head (ONH) after a PAACG attack persisting up to 2 weeks after onset in spite of remission. Tso and Fine<sup>18</sup> also found from histopathology that the peripapillary RNFL thickness increased in patient with optic disc edema. Yoles and Schwartz<sup>19</sup> have suggested a mechanism whereby glaucomatous neuropathy continues to progress even after alleviation of the high IOP.

In this study, we find that the RNFL thickness in the affected eyes correlates with the interval of follow-up of PAACG. We find that there is a rapid thinning of RNFL and gradual stabilization thereafter. This suggests that a longitudinal follow-up to detect changes in RNFL thickness is not only necessary to assess the actual loss and damage but also provides more information. The average and four quadrant RNFL thicknesses after the acute attack decreased in the affected eyes but not in the fellow eyes during the 4-month follow-up and an average and four quadrants RNFL thickness for the affected eyes correlated strongly with interval of follow-up, according to inverse regression analysis in this study.

The main limitation of the study was a relatively small sample size and limited number of the patient with less severe PAACG episodes (<48 h).

## CONCLUSION

Results of this intereye and intertest comparison of RNFL thickness after a single unilateral PAACG attack using Stratus OCT and GDx VCC demonstrated an initial increase in diffuse RNFL thickness followed by a decrease. The interval between the episodes and measurement influences the result of RNFL thickness assessment. It thus appears reasonable to suggest that longitudinal follow-up

must be considered in any comprehensive study of the long-term effect of PAACG.

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# Comparative Assessment of Diffusion of Calcium and Hydroxyl Ions from Calcium Hydroxide Formulations used for Obturation in Primary Teeth

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## Abstract

**Introduction:** Calcium hydroxide ( $\text{Ca}(\text{OH})_2$ ) has been extensively used in pediatric endodontics and its properties depend on two ions, calcium and hydroxyl. The aim of the study was to assess the diffusion of calcium and hydroxyl ions from three  $\text{Ca}(\text{OH})_2$  based materials through roots of primary teeth using atomic absorption spectrometer and pH meter, respectively.

**Materials and Methods:** A total of 40 extracted human deciduous teeth roots were used for the study. The specimens were divided into 4 groups, with 10 roots in three experimental groups and 10 in control group. The root canals in the experimental group were filled with  $\text{Ca}(\text{OH})_2$  mixed with propylene glycol (CaPE), Ultracal paste and Metapex, respectively, whereas root canals in the control group were left empty. pH analysis and calcium ion diffusion from the specimens were done using digital pH meter and atomic absorption spectrophotometer, respectively at baseline, 24 h, 7, 15, and 30 days. Statistical analysis was performed using analysis of variance.

**Results:** Calcium and hydroxyl ion diffusion was maximum from CaPE group at all test periods except at 24 h, where ultracal group showed maximum diffusion of both the ions. Metapex group showed intermediate diffusion of ions.

**Conclusion:** Clinical situations that require a rapid ionic liberation, aqueous  $\text{Ca}(\text{OH})_2$  pastes (Ultracal) should be used and in situations that require a gradual ionic liberation; a viscous vehicle containing paste should be used such as CaPE paste. Situations where very slow ionic dissociation is required, pastes containing oily vehicles (Metapex) should be used.

**Key words:** CaPE, Metapex, Primary teeth, Ultracal

## INTRODUCTION

The main objective of pulp therapy in primary teeth is to maintain health of the teeth and supporting structures stabilize the affected primary tooth, but also create a favorable environment for normal exfoliation of the primary tooth, without harm to the developing enamel or interference with the normal eruption of its permanent successor.<sup>1</sup>

Since the introduction of calcium hydroxide ( $\text{Ca}(\text{OH})_2$ ) to dentistry, it has been included within several materials and antimicrobial formulations which are used in a number of treatment modalities in endodontics. The use of  $\text{Ca}(\text{OH})_2$  in endodontic treatment of necrotic; infected teeth is now well documented.<sup>2</sup>  $\text{Ca}(\text{OH})_2$  is also useful in the treatment of root resorptions, perforations, root fractures, apexification, and pulp capping.<sup>3,4</sup> The material is chemically classified as a strong base. The ionic dissociation of  $\text{Ca}^{2+}$  and  $\text{OH}^-$  ions and their effect on vital tissues is responsible for its antimicrobial activity and the property of hard tissue deposition.<sup>5</sup>

Studies conducted on permanent teeth proved that  $\text{Ca}(\text{OH})_2$  has the capacity to release calcium and hydroxyl ions which diffuse through exposed dentinal tubules and raise the pH of roots' surface and periapical environment.<sup>6,7</sup> However,

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only a few studies have been conducted on primary teeth to assess the diffusion of calcium and hydroxyl ions from  $\text{Ca}(\text{OH})_2$  based pastes through root dentin.<sup>8,9</sup> The vehicles mixed with  $\text{Ca}(\text{OH})_2$  powder play an important role in the overall dissociation process because they determine the velocity of ionic dissociation causing the paste to be solubilized and resorbed at various rates by the periapical tissues and from within the root canal.<sup>10</sup> Vehicles used to mix  $\text{Ca}(\text{OH})_2$  can be classified into aqueous, viscous, and oily.<sup>11</sup>

The three materials used in the study represented all the three vehicles used to mix  $\text{Ca}(\text{OH})_2$ . Considering these points, the purpose of this research was to evaluate the diffusion of  $\text{Ca}^{2+}$  and  $\text{OH}^-$  ions from three  $\text{Ca}(\text{OH})_2$  based materials, through the intact roots of primary teeth using atomic absorption spectrometer and pH meter, respectively.

## MATERIALS AND METHODS

The study was conducted on 40 extracted primary human teeth roots, with single and straight canals. Institutional Ethical Committee clearance was obtained for the study. Initially, the teeth were stored in a 10% formaldehyde solution until ready for use. The soft tissues and dental calculus adhered to the roots were removed with an ultrasonic dental scaler. Transverse sectioning of roots 2 mm coronal to cemento-enamel junction using double faced diamond disk was done to obtain the specimens. All the roots were then analyzed macroscopically using stereoscopic magnifying glass ( $\times 4$ ). Only intact roots with no perforating resorption were included in the study. However, since the teeth used in the study were deciduous, they were in initial stages of physiologic resorption. Thus, they presented with apices showing different degrees of resorption. Therefore, to standardize root lengths, the apices were cut at 7 mm from cemento-enamel junction using double faced diamond disk. Instrumentation was done for all the roots by a single operator. The canals were enlarged till 40 no. K file and 1% sodium hypochlorite was used for irrigation between change of files. The specimens were randomly divided into Four groups, with 10 roots in each experimental group (Groups 1-3) and 10 in the control group (Group 4). Simple randomization using random table was used.

Group 1: Thickened  $\text{Ca}(\text{OH})_2$  powder with a viscous vehicle propylene glycol (CaPE) was mixed in a ratio of 2:1 by weight and canals were obturated using reamers and cotton pellet. Group 2: Aqueous vehicle based  $\text{Ca}(\text{OH})_2$  paste-Ultracal (Ultradent) was used to fill the canals using a disposable plastic tip connected to a syringe. Group 3: Premixed metapex (Meta Biomed) consisting of an oil

based vehicle was used to fill the canals using a syringe with disposable plastic tip. Group 4 (control group): BMP was performed and irrigation was done as in experimental group, but the canals were kept empty without any medication. The canals were considered full when the paste flowed from the pulp chamber at the root canal opening for all the samples in the experimental group. Following this, vertical pressure was applied with cotton pellets. Individual radiographs using pedo films were taken in buccolingual direction to check whether the canals were completely filled. After confirming that the canals of all the roots were totally filled, the access cavities were restored with glass ionomer cement. The teeth from the control group were also restored using the same technique. Roots were then cleaned to remove debris of the filling material from the external surface. Araldite (Brascola Ltd.), mixed in equal parts of base paste and catalyst, according to the manufacturer's instructions, was used to make the foramen and apical third impermeable. After a hardening time of 30 min, a layer of nail varnish was applied over the Araldite. This was done to make the teeth more impermeable so that the diffusion of ions occurred only through the roots of teeth.

The teeth were stored in individual plastic flasks, each containing 30 ml of saline solution. They were kept at a constant temperature of  $37^\circ\text{C}$  and at 100% relative air humidity during the entire test period of 1-month. The flasks had a modeling wax lid where the tooth's crowns were fixed, allowing only the root to be in contact with the saline solution.

Measurements were taken at regular intervals for each group at baseline, 24 h, 7, 15, and 30 days. The pH was measured using a digital pH meter. The pH readings were taken for the test and control groups after 2 min of electrode immersion in the solutions that contained each specimen. After measurement, each tooth was returned to the same flask. Between readings, the electrode was washed with deionized water and dried with absorbent paper. The values obtained were then recorded. An atomic absorption spectrophotometer was used to determine the concentration of calcium ions. For determination of calcium ions released in the saline solution, 0.5 ml liquid was removed with a pipette from each flask and transferred to a sterile test tube pertaining to each group. Since there were 10 samples in each group, 5 ml liquid was collected which was then transferred to a test tube.

A small quantity from these 5 ml of solution from the test tube of each group (never  $<0.1$  ml) was removed with a pipette for analysis. This was then diluted according to the saturation of the solution. The solutions were kept at room temperature at the time of readings. Calcium ion diffusion was measured at baseline, 24 h, 7, 15, and 30 days.



The collected data were tabulated, and statistical analysis was performed using analysis of variance to compare groups. The decision criterion was to reject the null hypothesis if the  $P$  value was  $<0.05$ . Otherwise, null hypothesis was accepted. If there was a significant difference between the groups, multiple comparisons (*post-hoc* test) using Bonferroni test was carried out.

## RESULTS

All the study groups as well as the control group showed diffusion of calcium and hydroxyl ions at various test periods. The diffusion of calcium ions was very less for the first 24 h for all the groups after which it increased significantly. However, for the control group, it remained low over the entire test period. Overall, the mean calcium ion diffusion was maximum from Group 1, i.e.,  $\text{Ca}(\text{OH})_2$  mixed with propylene glycol. In first 24 h, Group 2, i.e., Ultracal showed maximum diffusion. Highest diffusion of calcium ions from all the groups was seen at 7 days after which it declined. At 24 h, maximum diffusion was seen from Ultracal group followed by  $\text{Ca}(\text{OH})_2$  mixed with propylene glycol, Metapex and control group. At 7, 15, and 30 days; maximum diffusion was seen from  $\text{Ca}(\text{OH})_2$  mixed with propylene glycol followed by Metapex, Ultracal and control group (Table 1 and Figure 1).

The pH was close to 6 for all the groups at the baseline. It was acidic for all the groups because the media in which the teeth were placed was saline. pH increased for all the study groups after 24 h when the diffusion of hydroxyl ions started. At 24 h pH of Group 1, i.e., Ultracal was seen to be highest. At 7, 15, and 30 days pH of Group 2, i.e.,  $\text{Ca}(\text{OH})_2$  mixed with propylene glycol was highest. For all the groups except Group 2, i.e., Ultracal, highest pH was recorded at 15 days. For Group 2, it was recorded at 24 h. pH decreased significantly for all the groups at 30 days (Table 2 and Figure 2).

## DISCUSSION

In primary dentition, infection of the root canal system quickly extends to involve the periradicular tissues. Early loss of primary teeth causes a number of adverse effects, including space loss for successor permanent teeth.<sup>12</sup> Thus, it is best that primary teeth are saved, provided they can remain free of disease and can be restored. A tooth successfully disinfected and restored is a superior space maintainer than any appliance.<sup>13</sup>

Primary teeth show various anatomical and histological complexities in their root canal systems. Their proximity to the developing permanent tooth germs, coupled with

**Table 1: Calcium ion diffusion**

Time	Mean $\pm$ SD				
	Baseline	24 h	7 days	15 days	30 days
Group 1	0.38 $\pm$ 0.49	8.24 $\pm$ 0.46	15.45 $\pm$ 0.50	12.72 $\pm$ 0.33	11.22 $\pm$ 0.59
Group 2	0.43 $\pm$ 0.41	10.63 $\pm$ 0.62	8.59 $\pm$ 0.53	7.73 $\pm$ 0.41	6.25 $\pm$ 0.33
Group 3	0.37 $\pm$ 0.49	7.52 $\pm$ 0.51	13.40 $\pm$ 0.88	10.41 $\pm$ 0.51	6.91 $\pm$ 0.28
Group 4	0.30 $\pm$ 0.35	1.79 $\pm$ 0.59	3.21 $\pm$ 0.38	2.42 $\pm$ 0.73	2.05 $\pm$ 0.31

SD: Standard deviation

**Table 2: Hydroxyl ions diffusion (pH)**

Time	Mean $\pm$ SD				
	Baseline	24 h	7 days	15 days	30 days
Group 1	5.85 $\pm$ 0.24	7.20 $\pm$ 0.12	7.40 $\pm$ 0.12	8.05 $\pm$ 0.20	7.40 $\pm$ 0.12
Group 2	5.95 $\pm$ 0.37	7.57 $\pm$ 0.18	7.50 $\pm$ 0.18	7.20 $\pm$ 0.16	7.10 $\pm$ 0.18
Group 3	5.95 $\pm$ 0.28	7.50 $\pm$ 0.24	7.30 $\pm$ 0.18	7.73 $\pm$ 0.24	7.42 $\pm$ 0.23
Group 4	5.90 $\pm$ 0.46	6.08 $\pm$ 0.08	7.08 $\pm$ 0.15	7.14 $\pm$ 0.13	7.12 $\pm$ 0.08

SD: Standard deviation

the difficulty in behavior management in children, make the endodontic treatment in deciduous teeth more difficult.

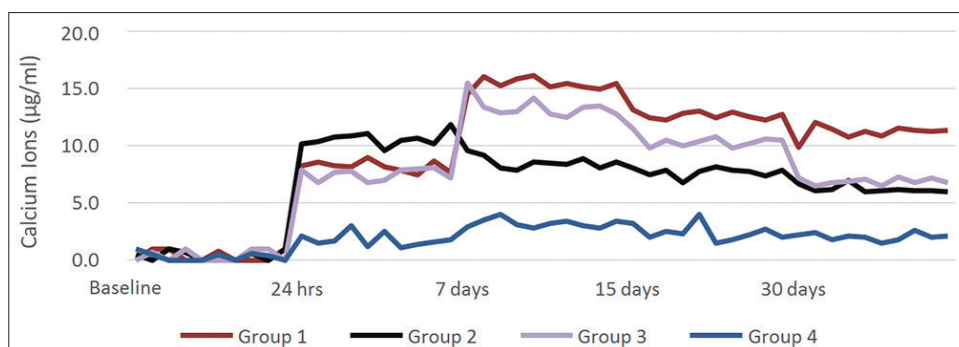
$\text{Ca}(\text{OH})_2$ , in various combinations, has been used as successful root canal filling material in primary teeth. It is also well documented that all biological actions are due to the ionic dissociation of  $\text{Ca}(\text{OH})_2$  into calcium and hydroxyl ions.<sup>14</sup> Vehicle plays the most important role in the overall process. It determines the velocity of ionic dissociation, which in turn determines the rate of resorption of these pastes from the periapical tissues and from within the root canal.<sup>11</sup>

Studies conducted on permanent teeth proved that  $\text{Ca}(\text{OH})_2$  has the capacity to release calcium and hydroxyl ions which diffuse through exposed dentinal tubules and raise the pH of roots' surface and periapical environment.

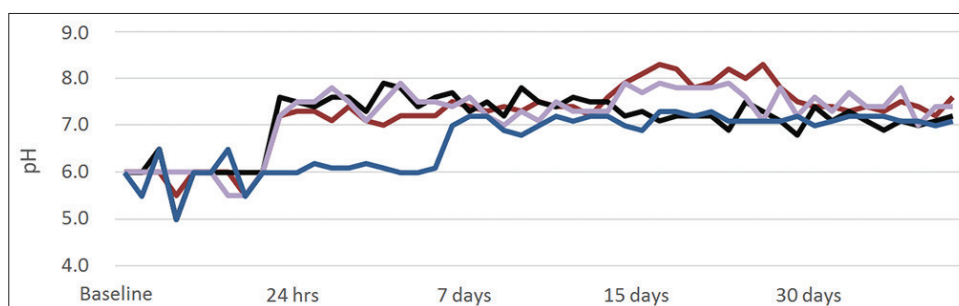
In general, three types of vehicles are used to mix  $\text{Ca}(\text{OH})_2$ : Aqueous, viscous or oily.<sup>11</sup> None of the previous studies conducted to assess the diffusion of calcium and hydroxyl ions tested all these three media. However, in this study, all the three vehicles were tested. Ultracal paste represented the aqueous vehicle,  $\text{Ca}(\text{OH})_2$  mixed with propylene glycol was the viscous vehicle, and Metapex represented the oily vehicle.

This study demonstrated the diffusion of calcium and hydroxyl ions through root dentin and cementum of primary teeth. It can be confirmed that the release of the ions had occurred only thorough the roots of the specimen since the crown and apical portion of the roots were sealed, with the only possible passage of ions through root dentin and cementum of the teeth. Diffusion of calcium and hydroxyl ions from deciduous teeth roots have been demonstrated previously.<sup>8,9</sup>





**Figure 1: Calcium Ions released at different time intervals in each group (in each sample)**



**Figure 2: pH recorded at different time intervals**

Biomechanical preparation consisted of instrumentation with K files and intermediate irrigation with 1% sodium hypochlorite solution. This was followed by root canal filling. The same methodology was used in a few previous studies.<sup>8</sup> It has been shown that 1% NaOCl solution has good antimicrobial action and promotes pulp tissue dissolution. This capacity of NaOCl is increased when used with root canal dressings containing  $\text{Ca}(\text{OH})_2$ .<sup>15</sup>

Selection of the materials tested in this study was based on the fact that the three materials contained three different vehicles, i.e., aqueous, viscous and oily. Some *in vitro* studies have shown that the type of vehicle has a direct relationship with the diffusion and the velocity of ionic liberation as well as with the antibacterial action of the paste in a contaminated area.<sup>16</sup>

This study showed that ultracal group showed maximum diffusion of calcium ions at 24 h, i.e., 10.63 mg/L. Furthermore, this group showed maximum diffusion of hydroxyl ions at 24 h represented by pH, i.e., 7.57. At 7, 15, and 30 days test periods, the calcium ion and hydroxyl ion diffusion from this group declined. This was because when  $\text{Ca}(\text{OH})_2$  is mixed with a water-soluble substance or an aqueous media, calcium and hydroxyl ions are rapidly released. Aqueous vehicles promote higher solubility when the paste is in direct contact with the tissue and tissue fluids. This also causes it to be rapidly solubilized and resorbed by macrophages. This implies that the root canal may become empty in a short period, delaying the

healing process.<sup>17</sup> However, the root canal may have to be redressed several times until the desired effect is achieved, thus increasing the number of appointments.

In a recent study, it was reported that maximum diffusion of calcium and hydroxyl ions occurred from CaPE group.<sup>9</sup> Even in this study, the maximum diffusion of calcium ions was seen from Group 1, i.e.,  $\text{Ca}(\text{OH})_2$  mixed with propylene glycol (CaPE) which is a viscous vehicle. This was seen at 7, 15, and 30 days.

Viscous vehicles are also water-soluble substances. However, they have higher molecular weights which lower their solubility when compared with aqueous vehicles. This slower diffusion maintains the paste in the desired area for longer intervals, prolonging the action of the paste.<sup>14</sup> As a viscous vehicle containing paste may remain in the root canal for a 2-4 months interval, the number of appointments and redressing of the root canal is reduced.<sup>11</sup> It has been asserted that an infected deciduous tooth should not be obturated in 1 week. It is best to wait at least 1 month to allow a residual action of the  $\text{Ca}(\text{OH})_2$  dressing, thus allowing better wound healing.<sup>8</sup> For these clinical situations, viscous vehicles are the best choice. Some examples of viscous vehicles are glycerine, polyethyleneglycol, and propylene glycol.

The mean calcium ion and hydroxyl ion diffusion from Metapex was found to be more than Ultracal group but less than CaPE group. This was in accordance with a previous

study where the authors had found that Vitapex released lesser calcium and hydroxyl ions than CaPE.<sup>8</sup> Metapex contains silicon oil, i.e., an oily vehicle. Pastes containing this kind of vehicle may remain within the root canal for longer than the pastes containing aqueous vehicles. Some examples of oily vehicles are olive oil, silicone oil, camphor (the essential oil of camphorated parachlorophenol), metacresylacetate and some fatty acids such as oleic, linoleic, and isostearic acid.

The control group, although did not contain any intracanal medication, showed a slight increase in the pH and calcium ion diffusion. Similar findings were also reported in some previous studies.<sup>8,9</sup> This was because the roots of primary teeth had inherent hydroxyapatite crystals. However, this was in contrast to a study where the authors did not find any increase in calcium ion or pH in control group.<sup>18</sup> This may be due to different methodology used by these authors, i.e., the use of glass tubes instead of extracted human primary roots in their studies. The relevance of this study is based on the results that indicate importance of each material for different clinical situations.

## CONCLUSION

Based on the results of this study, it is recommended that that  $\text{Ca}(\text{OH})_2$  mixed with aqueous vehicle can be used in clinical situations that require a fast release of ions at the beginning of treatment, such as in an infected tooth with periapical lesion or in an acute exacerbation of a chronic lesion.

$\text{Ca}(\text{OH})_2$  mixed with a viscous vehicle such as propylene glycol can be used in clinical situations that require a gradual and uniform ionic liberation such as in chronic lesions.

$\text{Ca}(\text{OH})_2$  mixed with an oily vehicle can be used in those clinical situations that require a very slow ionic dissociation over time. These pastes are recommended to be used for obturation of primary teeth depending on the clinical situation.

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# Incidence and Clinical Spectrum of Opportunistic Infections among Human Immunodeficiency Virus-infected Children Aged 18 Months to 14 Years in North East India – A Hospital-based Study

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## Abstract

**Background:** Human immunodeficiency virus (HIV) infection in children is a major public health problem. Opportunistic infections (OIs) are generally seen in children due to pre-existing immunocompromised state. OIs are an important cause of morbidity and mortality in children infected with HIV.

**Objective:** The objective of this study was to evaluate the incidence of OIs and clinical spectrum in HIV-infected children among the age group 18 months to 14 years.

**Materials and Methods:** This is a cross-sectional study conducted in a tertiary care hospital between September 2012 and August 2014. All the enrolled children infected with HIV were examined for the development of OIs after getting written informed consent from parents. Demographic details, clinical examination, and relevant investigations were done for all the children. Clinical spectrum of OIs and HIV categorization as per WHO and NACO guidelines was recorded. Data were analyzed using SPSS version 22.

**Results:** Out of 100 children infected with HIV, the incidence of OIs is 38%. The mean age of children was  $5.4 \pm 2.02$  years at enrollment with female to male ratio of 1:1.2. 48.5% of children having OI was in the age group between 10 and 14 years. Tuberculosis (TB) (73.69%) was the most common OI identified followed by *Candida* (10.53%). All the OIs were treated as and when indicated. 92 children were receiving OI preventing prophylaxis as per NACO guidelines. 77% of children were underweight and 10 children need hospitalization.

**Conclusion:** OI in HIV-infected children is a serious health concern. There is a need for continued surveillance to assess the effort of antiretroviral therapy in the occurrence of OIs. Early identification of OI and its appropriate measures should be taken up as it can help in reducing the morbidity and mortality of HIV-infected children.

**Key words:** Children, Human immunodeficiency virus, Incidence, Opportunistic infections, Tuberculosis

## INTRODUCTION

Human immunodeficiency virus (HIV) infection is a growing concern in the pediatric population.

Approximately, 2.5 million children globally are infected with HIV at the end of the 2009.<sup>1</sup> Infection with HIV reduces the immune system's ability to fight infections. An opportunistic infection (OI) is an infection caused by pathogens that take various illnesses in children infected with HIV. OIs are usually responsible for causing death among the HIV infected children. Children living with HIV infection are prone to OIs due to various microbial agents. They are at risk of developing OI with fall in their CD4 counts and persistence of OI cause further fall in CD4 counts.<sup>2,3</sup>

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The OIs are an important factor for morbidity and mortality in children living with HIV infection. The understanding of the pathogenesis of HIV and many of the opportunistic pathogen has led to the development of variety of efficacious therapies for the infections.<sup>4</sup> The spectrum of OI of a particular locality should be known to prevent these infections by giving adequate prophylaxis. Prophylactic therapies are not hundred percent protective and despite improved treatment, few OIs are cured. Most of the children infected with HIV and coinfection of OIs require lifelong maintenance therapy in the absence of immune reconstitution. OI in HIV-infected children can occur in children on antiretroviral therapy (ART) as well as not on ART. Considering the importance of identifying the pathogen responsible for OI in HIV-infected children, we take up this study with the aim of knowing incidence of OI and clinical spectrum in HIV-infected children.

## MATERIALS AND METHODS

An observational cross-sectional study was conducted between September 2012 and August 2014 in the Pediatrics Department of a tertiary care hospital in North East India. Children infected with HIV in the age group between 18 months and 14 years attending pediatric orthodontics pediatric dentistry and admitted in the pediatric ward were enrolled after getting approval from the Institutional Ethical Committee. A written informed consent was obtained from the parents or caregivers of each child before enrolment in the study. Children with congenital disease and malignancy were excluded from the study. A sample size of 100 was calculated presuming 50% prevalence rate of OIs in HIV-infected children with 10% margin of error on either side. Children of those parents who are willing to participate are enrolled by the sequential sampling. Strict confidentiality was maintained throughout the study period to protect the identity and record of study subjects.

The diagnosis of HIV was confirmed by Elisa using two different antigens. Parents or caregivers of the enrolled children were explained regarding the development of signs and symptoms of the OIs. Demographic profile, anthropometric measurement, clinical signs, and symptoms of OIs were recorded in a predesigned proforma. Detailed history including mode of transmission and medication were recorded. The clinical and immunological status of the disease were determined according to the WHO guidelines 2006. Laboratory examination of blood, stool, urine, chest X-ray, and sputum/gastric aspirate for acid-fast bacilli (AFB) was done for each participant. The baseline value of the liver function, kidney function, and blood sugar were obtained from all the participants. The examination of skin and oral mucosa with scraping for potassium

hydroxide mount preparation were done when indicated. Blood cultures and other specific investigations including imaging study were done as and when indicated depending on the clinical condition of the child. CD4 T-cell count was quantitated by standard flow cytometry technique with fluorescent activated cell sorter method.

All the OIs were treated for the specific organisms isolated. Children with tuberculosis (TB) were diagnosed and treated with antitubercular drugs 2-8 weeks before start of the ART. Children who need ART were started as per NACO guidelines. Children with severe diseases were admitted in the pediatric ward and given appropriate management. Preventive measures for children with OIs were given with prophylactic drugs as and when necessary according to NACO guidelines. Data collected were entered into the computer software, and statistical analysis was performed using SPSS version 22. Descriptive statistics were reported as means, standard deviations and percentage for categorical variables. To determine the difference between the groups ANOVA test was used. Criterion for statistical significance was set at  $P \leq 0.05$ .

## RESULTS

A total of 100 children infected with HIV in the age group between 18 months and 14 years were enrolled for the study. There were 45 females and 55 male with a ratio of 1:1.2. The mean age of HIV-infected children at the time of diagnosis was  $5.4 \pm 2.02$  years. The majority (84%) of HIV-infected children were in the age group 10 years and above. Mode of HIV transmission was vertical in all the cases. At the time of enrollment, 37 % children with HIV infection were in WHO clinical Stage III and only 4% children were in WHO clinical Stage IV. 73 % children were anemic with hemoglobin level below 11 g/dl. Undernourished cases as per WHO growth reference chart was present in 77 % of the enrolled children infected with HIV. The majority (70%) of children did not have immune suppression while 15% of the cases had mild immune suppression with CD4 T-cell count below 500 cells/mm<sup>3</sup> and 10% cases had severe immune suppression (Table 1).

In this study, the overall incidences of OIs among the children infected with HIV were 38%. Out of 38 children with OIs 52.6% was male and 47.4 were female. The different presentations of OIs are represented in Table 2. Among the OIs, TB (73.69%) was found to be the most common infection followed by *Candida albicans* (10.53%). Out of 28 cases of TB, 85.2% were pulmonary TB and only 14.8% were extrapulmonary including one case of TB sinovitis (Table 3). AFB was isolated from sputum of a child with HIV infection not on ART which is shown in Figure 1.



**Table 1: Baseline parameters of HIV infected children in the study population**

Parameters	Number (n=100) (%)
Gender	
Female	45 (45.0)
Male	55 (55.0)
Age at enrollment (years)	
<10	16 (16.00)
≥10	84 (84.0)
Nutritional status	
Normal	23 (23.0)
Underweight	77 (77.0)
Children with anemia	
Hb<11 (g/dl)	73 (73.0)
Baseline WHO clinical staging	
Stage I	38 (38.0)
Stage II	21 (21.0)
Stage III	37 (37.0)
Stage IV	4 (4.0)
Baseline immunological staging	
No immune suppression	70 (70.0)
Mild immune suppression	15 (15.0)
Advance immune suppression	5 (5.0)
Severe immune suppression	10 (10.0)
Mode of transmission	
Vertical	100 (100.0)
Others	Nil
Number of hospitalization required	10 (10.0)

HIV: Human immunodeficiency virus, Hb: Hemoglobin

**Table 2: Different infections among HIV infected children with presentation of OI**

Infection	Number of children (n=38) (%)
<i>Mycobacterium tuberculosis</i>	28 (73.69)
<i>Candidiasis</i>	4 (10.53)
<i>Cryptosporidium</i>	1 (2.63)
<i>Streptococcus pyogenes</i>	1 (2.63)
<i>Salmonella typhi</i>	1 (2.63)
<i>Escherichia coli</i>	1 (2.63)
Herpes zoster	1 (2.63)
<i>Scabies</i>	1 (2.63)

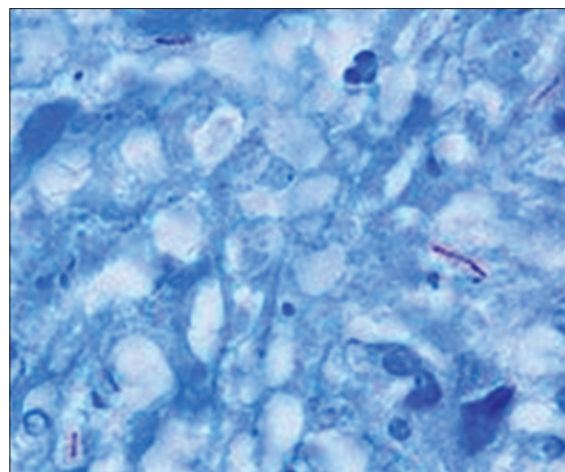
HIV: Human immunodeficiency virus, OI: Opportunistic infection

**Table 3: Spectrum of TB in HIV infected children at presentation**

Site involve	Number of children (n=28) (%)
Pulmonary TB	23 (82.15)
TB lymphnode (peripheral)	2 (7.14)
TB meningitis	1 (3.57)
Milliary TB	1 (3.57)
Osteoarticular (synovial)	1 (3.57)

HIV: Human immunodeficiency virus, TB: Tuberculosis

All the TB cases were treated with antitubercular drugs as per recommended treatment regimes for HIV-infected children (WHO 2010). For children receiving treatment for TB, initiation of ART is defer for 2-8 weeks. Among the study population, one child presented as cryptosporidial diarrhea (Figure 2). OIs with one case of scabies and one



**Figure 1: Acid-fast bacilli isolated from sputum of 8-year-old male child not on antiretroviral therapy**



**Figure 2: Female, 2-year-old undernourished child not on antiretroviral therapy presenting as *Cryptosporidium* diarrhea**

case of herpes zoster (Figure 3) were diagnosed based on clinical examination. All the OIs were treated with appropriate medications as and when indicated. 10 children needed hospitalization and 3 children expired. 85% of the children infected with HIV were receiving ART as per NACO guidelines.

## DISCUSSION

The introduction of highly active ART (HAART) in HIV-infected children has led to their better survival, but with increasing spectrum of OIs. There is a lack of data on OIs developing among HIV-infected children in our region. The identification of pathogens responsible for OI is very important in managing the HIV-infected children. The results of this study show that the overall incidence of OIs is 38% which demonstrates increase of OIs in HIV-infected children since the introduction of ART. In a study done by Gona *et al.* about the incidence of opportunistic and





**Figure 3: Female, 12-year-old child not on antiretroviral therapy with Herpes labialis**

other infections in HIV-infected children in the HAART Era, the OI rates is 14% only and found to be lower than those reported in the HAART Era.<sup>5</sup>

In 2000, the pediatric AIDS clinical trials group (PACTG) repeated a meta-analysis of 3331 HIV-positive infants and children who were enrolled in 13 PACTG studies conducted before treatment with HAART had become available to determine the rates of various HIV-associated infectious complications.<sup>6</sup> In their study, pneumonia and bacteremia were the most common bacterial infections reported. In this study, TB infection were found to be the most common OI (73.69%) followed by *Candidiasis*. Sterling *et al.* noted that TB is the most common OI in children infected with HIV and most HIV-infected patient with TB have relatively advanced HIV disease.<sup>7</sup> According to pediatric ART guidelines 2013, there is involvement of extra pulmonary sites in 14% of TB infection in children with HIV and this finding is near to the finding of this study (17.85%). Increase incidence of extrapulmonary TB has been also observed recently, constituting approximately 20% of the TB cases among children with HIV infection.<sup>8</sup> In another study done at Gautemale Sub-Saharan Africa, TB infection is found to be the most common OI among HIV-infected individual.<sup>9</sup> Increasing levels of co-infection with TB and HIV in children have been reported from countries with epidemics. Infection with HIV is a strong risk factor for progression from latent to active TB. HIV-infected children with TB represent a deadly co-morbidity. Another study done by Biswas *et al.* found that the incidence of pulmonary TB in HIV-infected children was 42.85% which is very high.<sup>10</sup> As immune competence decreases in HIV-infected patients, the incidence of atypical presentations increases, including high proportions of patients with extrapulmonary disease and disseminated TB.<sup>11</sup>

In this study, one case of TB sinovitis was found among the extrapulmonary TB. TB sinovitis is a repeatedly missed diagnosis when diagnosis is delayed. Knee joint involvement is a relatively rare manifestation of extrapulmonary TB, but the number of patients is increasing among the TB infection. Although osteoarticular TB is reported in 1-3% of patients with TB, the knee joint involvement of TB is not common in children.<sup>12,13</sup> Wanjari *et al.* reported a case of TB sinovitis in seropositive adult with HIV.<sup>14</sup>

Among this study group, the overall prevalence of underweight were 77%. Padmapriyadarsini *et al.* have observed 63% prevalence of underweight among children infected with HIV in South India.<sup>15</sup> The relative frequencies of specific OIs may vary in different countries and even in different areas within the same country.<sup>16</sup> 20% of AIDS defining illnesses in children are recurrent bacterial infections caused primarily by encapsulated organisms such as *Streptococcus pneumoniae* and *Salmonella*.<sup>17</sup> Repeated common infection occurs in 10 cases of this study population. Before combination ART era, serious bacterial infection was the most commonly diagnosed OIs in HIV-infected children with an event rate of 15 per 100 child-year.<sup>18</sup>

All study children on screening for hepatitis found a case of viral hepatitis B infection. Hepatitis B virus and C virus infection are common in HIV-infected patient due to their overlapping mode of transmission. In this study, the second most common OI was due to *C. albicans* (10.53%) affecting oral cavity extending to pharynx. A study from North India done by Misra *et al.* reported that TB as the most common OI (71%) followed by *Candidiasis* (39%).<sup>19</sup> Infection with *Cryptosporidium* was significantly associated with HIV infection.<sup>20</sup> 32% cases of diarrheal illnesses were revealed in this study children and *Cryptosporidium* infection was found in one children. In a study done by Asnake *et al.* shows that the prevalence of diarrhea in HIV-infected children were approximately 55%.<sup>21</sup> Although protozoal infection like *Toxoplasma* can be associated with HIV infection, no such case was found among the enrolled children infected with HIV.

In a study done by Sharon *et al.*, severe bacterial infection was observed among children infected with HIV.<sup>22</sup> In this study, out of 6 cases of bacterial infections, one case of *Salmonella typhi* and another case of *E. coli* infection were found. There was one event of Herpes zoster infection in our study. In a study done by Moore and Chaisson, the incidence of Herpes zoster in HIV-infected person was decrease compare to other OIs.<sup>23</sup> Less serious bacterial infections such as otitis media and sinusitis were particularly common in untreated HIV-infected children.<sup>24</sup>

In this study, out of 85 cases of children with HIV on ART OI were found in 30.6% whereas among the children with HIV not on ART 73.33% were having OIs. These findings suggest that ART if started early after the diagnosis of HIV can prevent the development of OIs, thus reduces the morbidity and mortality. The risk of developing an OI for a person receiving potent ART is highest during the initial months of therapy, and this patient should be follow-up closely during this critical period.<sup>25</sup> However new HAARTs are boosting the blood absolute CD4 T cell counts of many patients with AIDS and are decreasing the prevalence of AIDS-related OIs.

In this study, the CD4 cell count was lowest among the age group 10-14 years and the OIs were most commonly present between these age groups (52.63%). A study done by Nathalie *et al.* shows that more number of children with OIs than children without OIs had a CD4 percentage of less than 15% at the time of HAART initiative at enrollment.<sup>26</sup> This study shows that lower the immunological status higher is the incidence of OI in HIV-infected individual. In a study done by Gomber *et al.* observed that OIs were more common in children with higher degrees of immunosuppression.<sup>27</sup> The immunologic stage is a stronger independent predictor of short-term risk than long-term risk suggests that CD4 cell level reflects current disease stage more than it predicts future disease.

In this study, 92 cases of the study population are receiving OI preventive prophylaxis. Although current practice for determining the timing and initiation of prophylactic therapies relies chiefly on CD4 count, the occurrence of specific AIDS defining OIs in patients with HIV infection should also be taken into account in making-decision regarding prophylaxis strategies.<sup>28</sup> The introduction of ART in children has dramatically improved survival and quality of life in children living with HIV infection by reducing OIs.<sup>29</sup> The incidence of many OIs is decreasing primarily because of advances in HIV-related therapy. However, OIs are still occurring, especially when patients access care late during the course of disease. Even after accessing care, children with HIV infection may develop OIs because of lack of prescription for prophylaxis, AR drug resistance or poor adherence to therapy. Early diagnosis and prompt treatment of OIs definitely contributes to increased life expectancy among infected patients, delaying the progression to AIDS.<sup>30</sup> The understanding of the pathogenesis of HIV and many of the opportunistic pathogens has led to the development of a variety of efficacious therapies for these infections. In this study, we did not analyze the potential impact of the use of vaccines to prevent OIs and follow-up studies were not included.

## CONCLUSION

The OIs are an important cause of morbidity and mortality in children infected with HIV. However, few data are available regarding the overall prevalence, incidence and clinical correlates associated with OIs in the pediatric HIV population. Knowledge of the most common OI of those geographical areas will help in implementing the preventive measures against that pathogen. Our findings demonstrate that HIV-infected children continue to develop OI in spite of ART and preventive OI prophylaxis. Further studies are necessary to isolate OIs and other related infections with improvement in resources for OI investigations. Measures should be taken up to closely monitor the children infected with HIV to find out the development of OIs.

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# Evaluation of Adnexal Masses - Correlation of Clinical, Sonological and Histopathological Findings in Adnexal Masses

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## Abstract

**Introduction:** Adnexal mass is a common clinical presentation in gynecologic practice and can be of gynecologic or non-gynecologic origin. The term adnexal mass is most often used for masses involving the ovary because of the high propensity of the ovary for neoplasia. Fewer neoplasms occur in the fallopian tube, which are generally involved in inflammatory process.

**Materials and Methods:** This study covers all patients admitted to Department of Obstetrics and Gynecology, Cheluvamba Hospital, Mysore Medical College and Research Institute, Mysore from December 2013 to May 2015 with the clinical diagnosis of adnexal masses. Selective cases underwent an ultrasound examination with color Doppler. Ca-125 was measured, and risk of malignancy index (RMI) for each tumor was calculated. Following surgery, specimens were sent for histopathological examination, and the reports were correlated with pre-operative clinical and imaging findings.

**Results:** The incidence of ovarian masses was 93% with the majority (84%) being neoplastic. When both clinical and sonological diagnosis were combined, the overall sensitivity, specificity, positive and negative predictive value for diagnosis and discriminating benign and malignant ovarian neoplasms were 87.5%, 96.7%, 70%, and 98.88%, respectively. Their combined accuracy was 96%. Ca-125 as a laboratory test showed a sensitivity of 62.5% and specificity of 84.25%. RMI <200 showed a sensitivity of 62.5% and specificity of 95.65%.

**Conclusion:** Clinical findings, sonography, and RMI levels correlate positively with histopathology in early detection of malignancy and its appropriate management.

**Key words:** Adnexal mass, Clinical, Histopathology, Ultrasound

## INTRODUCTION

Adnexal mass is a common clinical presentation in gynecologic practice and can be of gynecologic or non-gynecologic origin. The term adnexal mass is most often used for masses involving the ovary because of the high propensity of the ovary for neoplasia. Fewer neoplasms occur in the fallopian tube, which are generally involved in the inflammatory process. Differential diagnosis of adnexal

mass is complex and includes functional cysts, benign and malignant ovarian tumors, paraovarian cysts, tubo-ovarian abscesses, hydrosalpinx, ectopic pregnancies, tubal malignancy, broad ligament fibroid, fimbrial cysts, sigmoid colon or colon distended with gasses or feces, pelvic kidney, and pregnancy in bicornuate uterus. These masses pose both a diagnostic and management dilemma. Ultrasonography is the primary modality used for detection and characterization of the mass. Many screening tests are being actively investigated at present, but there is no sufficient evidence to support the routine use of pelvic ultrasound and Ca-125 to screen for ovarian cancer in the general population. Histopathology is still taken as gold standard for the evaluation of benign and malignant adnexal masses.

This study will be done to find out the diagnostic value of clinical examination, ultrasonography and its

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correlation with histopathological diagnosis in adnexal masses.

## MATERIALS AND METHODS

This prospective study was undertaken in the Department of Obstetrics and Gynecology, Cheluvamba Hospital, Mysore Medical College and Research Institute, Mysore from December 2013 to May 2015 (18 months). All patients with clinical diagnosis of adnexal masses during the study period were included. Age <15 years, pregnancy with adnexal masses, mass arising from an abdominal organ on laparotomy (non-gynecologic causes) and patients who do not get operated were excluded from the study.

### Method of Collection of Data

Detailed history about demographic factors, presenting complaints and menstrual histories were obtained. Complete general physical examination and bimanual examination was performed, and provisional diagnosis was made. To evaluate the adnexal mass, an ultrasound examination consisting of either transvaginal or transabdominal sonography with color Doppler for suspicious cases of malignancy were done. Sonographic findings regarding size of adnexal mass, laterality, locularity, solid elements, hemorrhage, presence of ascites, evidence of metastasis and Doppler studies with pulsatility index (PI) and resistance index (RI) were assessed. An ultrasound diagnosis was made. Standard laboratory tests consisting of complete hemogram, fasting and postprandial blood sugars, liver and renal function tests, beta-human chorionic gonadotropin (in suspicion of pregnancy) and Ca-125 with a cutoff value of 35 U/ml were taken before surgery. Risk of malignancy index (RMI) for each tumor was calculated. Laparotomy was performed. Following surgery, specimens were sent for histopathological examination, and the reports were correlated with pre-operative clinical and imaging findings. The accuracy of clinical and ultrasound diagnosis was assessed. Sensitivity, specificity, negative and positive predictive value of clinical findings, sonography, Ca-125 and RMI in predicting malignancy for each adnexal mass were noted and tabulated using SPSS for windows (v16). Data was analyzed using Epi Info software. Frequencies and percentages were calculated for categorical data. Association between groups for categorical data was calculated using Chi-square/Fischer exact test. Validity and predictive values and accuracy for the test were calculated. Interobserver variability was assessed by kappa statistics.  $P < 0.05$  at 95% confidence interval was considered statistically significant.

Ethical committee clearance and patient consent were obtained for all cases in the study.

## RESULTS

The total admissions to the gynecology ward were 1899 in the study. A number of cases of adnexal masses with surgical interventions were 100 with an incidence of 5.26%. The incidence of ovarian masses was 93% of which 84% were neoplastic, and 16% were non-neoplastic. The incidence of malignancy was 9.5%. The patient ages ranged from 17 to 80 with a mean age of presentation of adnexal masses being 38.11 years. There were no significant differences among tumor types regarding the age ( $\chi^2 = 7.13$ ;  $F = 5$ ;  $P = 0.211$ ). There were highly significant differences among tumor types regarding the menstrual status of examined women ( $\chi^2 = 5.6$ ;  $P$  [Fisher's exact test] = 0.021) with most belonging to postmenopausal group. The majority of patients had multiple symptoms. The most common complaint was pain abdomen in 83% of cases followed by mass abdomen in 14% of cases. Constitutional symptoms were more seen in malignant patients. 75 cases were clinically diagnosed to be benign tumors, malignancy being diagnosed in 13 cases.

Sonographically, 89 cases were diagnosed to be benign and eleven malignant with 87.5% sensitivity, 95.65% specificity, false-positive rate of 36.36% and false-negative rate of 1.12%. On color Doppler sonography, all the malignant tumors showed neovascularization. Some ( $n = 4$ , 5.26%) of the benign tumors also showed color signals. This difference was statistically significant by test of proportion ( $P < 0.001$ ). The RI in malignant tumors was  $<0.4$  in 87.5% of cases and  $>0.4$  in 12.5% of malignant tumors. This difference was statistically significant ( $P < 0.001$ ) by test of proportion. Thus, the general trend of lower RI and PI in malignant ovarian masses was confirmed in the present study. There is an excellent agreement between clinical and ultrasound diagnosis in diagnosing adnexal masses with kappa value 0.742. The combined use of clinical and ultrasonography for diagnosis of malignancy had a  $P < 0.001$  (significant), 87.5% sensitivity, 96.7% specificity, 30% false-positive rate, 1.11% false-negative rate, 70% positive predictive value, 98.88% negative predictive value and an accuracy of 96%. Serum Ca-125 showed a sensitivity of 62.5%, specificity of 84.25% and an accuracy of 82.14% in discriminating between benign and malignant ovarian neoplasms. RMI showed a sensitivity of 62.5%, specificity of 95.65% and an accuracy of 93% in diagnosing benign and malignant tumors. RMI values more than 200 were statistically significant in diagnosing malignancy ( $P < 0.001$ ).

On laparotomy, 78 cases were found to be benign tumors out of which 76 cases were of ovarian origin, the other 2 being broad ligament fibroid. 8 cases were found to be malignant ovarian tumors all subjected to staging. Histopathology being the gold standard, in our study



showed benign pathology in the majority of cases (76%). Malignant changes were seen in 8 cases. Endometriosis was seen in 6 cases. The rest showing changes suggestive of hemorrhage, torsion, hydrosalpinx, and tubo-ovarian mass, respectively. There is an excellent agreement between ultrasound and histopathology diagnosis in diagnosing adnexal masses with kappa value 0.897. In our study, most common histopathological type was serous type (36%) followed by mucinous cystadenoma in 18% cases and dermoid cysts in 9 cases.

## DISCUSSION

Ovarian cancer carries the worst prognosis among all gynecological cancers mainly due to the lack of effective screening methods for early detection of the disease.<sup>1</sup> Accurate pre-operative prediction of the benign or malignant nature of an adnexal mass is essential for proper management.<sup>1</sup> In the present study, out of 1899 admissions in the gynecology ward, the incidence of adnexal masses undergoing surgical intervention was 5.26% of which 93% were ovarian in origin. Among the ovarian neoplasms, 90.46% were benign, and 9.54 % were malignant. These findings are comparable with Sharadha *et al.*,<sup>2</sup> Narula *et al*<sup>3</sup> and Jha and Karki<sup>4</sup> study.

Mean age of malignant tumors was 45 years in our study which is similar to other studies done by Mondal *et al.*<sup>5</sup> and Wasim *et al.*,<sup>6</sup> The above age of incidence is lesser than that seen in literature. The higher percentage of malignant ovarian tumors in postmenopausal women in the present study is similar to that in other studies.<sup>1,7</sup> This confirms the characteristic of malignant ovarian tumors being more common in postmenopausal women. On the other hand, patients in the reproductive period more often have benign lesions. Several studies have shown that women with ovarian cancer experience gastrointestinal and constitutional symptoms more as compared to those with benign tumors.<sup>6</sup> Our study has similar results, but was not statistically different, whereas other studies have reported more association with malignant disease. None of our cancer patients were asymptomatic while few other studies have reported 7-15% of ovarian cancer patients to be asymptomatic.<sup>6</sup> Targeting women with specific symptoms and possibility of development of a symptom index has been recommended by a study from the USA.<sup>6</sup>

Although sensitivity of clinical examination for distinguishing a malignant mass from a benign one is somewhat better, these results need to be interpreted with caution. Based on the available literature,<sup>8,9</sup> bimanual examination does not appear to be a sensitive test for detecting the presence of adnexal masses and appears to have limited ability to

discriminate benign from malignant masses. Although specificity was somewhat better, positive predictive values will still be quite low in low prevalence settings (Tables 1-3).

Sonography (transvaginal and transabdominal) is a sensitive method for detecting ovarian cancer. Our study showed that abdominal sonography had a sensitivity of 87.5% and a specificity of 95.65% with an accuracy of 95% for predicting ovarian cancer which is similar to studies by Wasim *et al.*,<sup>6</sup> Topuz *et al.*<sup>10</sup> and Pourissa *et al.*<sup>11</sup> Color Doppler study increases the diagnostic accuracy of plain sonography with good accuracy in identifying malignancy with cut off values of 0.4 and 1 for RI and PI<sup>12</sup> respectively. Although ultrasound is considered the primary diagnostic modality for ovarian imaging, there are numerous false-positive and false negative findings (Tables 2, 4, 5).<sup>1</sup>

Serum Ca-125 level is a valuable parameter for both diagnosis and monitoring of epithelial carcinoma. The overall sensitivity of Ca-125 screening in distinguishing

**Table 1: Clinical and using diagnosis discrepancies in diagnosis of adnexal masses**

Clinical diagnosis	Using diagnosis				
	Acute abdomen	Endometriosis	Benign	Malignant	Total
Acute abdomen	8	1	0	0	9
Endometriosis	0	3	0	0	3
Benign	3	1	69	2	75
Malignant	0	0	4	9	13
Total	11	5	73	11	100

**Table 2: Ultrasound and histopathology diagnosis discrepancies in diagnosis of adnexal masses**

Using diagnosis	HP report				
	Acute abdomen	Endometriosis	Benign	Malignant	Total
Acute abdomen	9	0	2	0	11
Endometriosis	0	5	0	0	5
Benign	1	1	70	1	73
Malignant	0	0	4	7	11
Total	10	6	76	8	100

**Table 3: Clinical diagnosis versus histopathology report for malignant tumors**

Clinical diagnosis	Histopathology report		Total
	Malignancy present	Malignancy absent	
Malignancy present	7	6	13
Malignancy absent	1	86	87
Total	8	92	100

benign from malignant adnexal masses reportedly ranges from 61% to 90%, specificity ranges from 71% to 93%, positive predictive value ranges from 35% to 91% and negative predictive value ranges from 67% to 90%<sup>13</sup> which is similar to our study with a sensitivity of 62.5% (Table 6), specificity of 84.25%. Wide variations in these figures reflect differences in cancer prevalence in the study population, the proportion of patients who are postmenopausal and the threshold of Ca-125 levels considered abnormal. Since most of the clinical conditions with elevated Ca-125 occur in premenopausal women and most epithelial ovarian cancers occur in postmenopausal women, the sensitivity

**Table 4: Ultrasound diagnosis versus histopathology report for malignant tumors**

Ultrasound diagnosis	Histopathology report		Total
	Malignancy present	Malignancy absent	
Malignancy present	7	4	11
Malignancy absent	1	88	89
Total	8	92	100

**Table 5: Combined (clinical and ultrasound) diagnosis versus histopathology report for malignant tumors**

Combined (clinical and ultrasound)	Histopathology report		Total
	Malignancy present	Malignancy absent	
Malignancy present	7	3	10
Malignancy absent	1	89	90
Total	8	92	100

**Table 6: Ca-125 values in diagnosis of benign and malignant tumors**

Ca-125	Malignant (%)	Benign (%)	Total (%)
>35 IU/ml	5 (6.0)	12 (14.3)	17 (20.2)
<35 IU/ml	3 (3.6)	64 (76.2)	67 (79.8)
Total	8 (9.5)	76 (90.5)	84 (100)

**Table 7: RMI values versus histopathology report for malignant tumors**

RMI (IU)	Histopathology report		Total
	Malignancy present	Malignancy absent	
<200			
Malignancy present	5	4	9
<200			
Malignancy absent	3	88	91
Total	8	92	100

RMI: Risk of malignancy index

and specificity of an elevated Ca-125 level in concert with a pelvic mass is highest after menopause. Sensitivity in our study is lesser when compared to other studies<sup>14,15</sup> compared to the high level of specificity of 84.25% in our study. RMI, based on menopausal status, ultrasound findings and serum Ca-125 is an easily applicable method in the primary evaluation of patients with adnexal masses, resulting in timely referral to gynecological oncology centers for suitable surgical operations.<sup>1</sup> In previous studies using RMI 2, sensitivity and specificity were 74% and 89%,<sup>16</sup> 71% and 89%,<sup>17</sup> and 76% and 82%.<sup>18</sup> Our values for RMI 2 had a sensitivity of 62.5% and a specificity of 95.65% which is similar to a study by Hemeda *et al.*<sup>19</sup> with a sensitivity of 70.5%, specificity of 93.5% but lesser when compared to other studies. However, it was found to be statistically significant with a  $P < 0.001$  and an accuracy of 93%. Thus, according to our results, calculation of RMI in pre-operative triage of patients with adnexal tumors is strongly recommended (Table 7).

Among the major histological classes, the most common type of ovarian neoplasm seen in our study was surface epithelial tumors (62%) similar to other studies with 64% and 70%<sup>20,21</sup>, respectively. The most frequent subtype being serous cystadenocarcinoma followed by mucinous cystadenocarcinoma similar to other studies.<sup>22</sup> Germ cell tumors (GCTs) comprise the second largest group in our study in which benign tumors dominated the malignant ones. Among the benign GCTs, our study showed the highest incidence of dermoid cysts which are similar to studies by Ahmad *et al.*<sup>20</sup>

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# *In Vitro* Assay to Determine the Minimal Inhibitory Concentration<sub>90</sub> of $\beta$ -lactam and $\beta$ -lactam – $\beta$ -lactamase Inhibitor against Community Acquired Respiratory Pathogens

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## Abstract

**Background:** Respiratory tract infections (RTIs) accounts for two-third of all community-acquired bacterial infection. Antibiotic resistance in the form of penicillin-resistant *Streptococcus pneumoniae* or  $\beta$ -lactamase producing *Hemophilus influenzae*, *Moraxella catarrhalis*, *S. pneumoniae* forms the basis for overwhelming preference of  $\beta$ -lactam or  $\beta$ -lactam –  $\beta$ -lactamase inhibitor. However, with the increasing use of these drugs as empirical therapy, the prevalence of antibiotic resistance is on rise.

**Objective:** To determine minimal inhibitory concentration<sub>90</sub> (MIC<sub>90</sub>) of  $\beta$ -lactam and  $\beta$ -lactam –  $\beta$ -lactamase inhibitor against community-acquired respiratory pathogens.

**Materials and Methods:** *In vitro* study was conducted to determine MIC<sub>90</sub> value of three commonly used antibiotics against three community respiratory pathogen. Isolates from patient's sputum, nasal swab, and throat swab were collected from 12 community centers across India, and the MIC<sub>90</sub> value for each antibiotic was determined using Broth dilution method.

**Results:** Totally 106 isolates were collected from 12 community center's across India. For isolates tested for *H. influenzae*, the mean MIC<sub>90</sub> of cefpodoxime-clavulanic acid was 0.26  $\mu$ g/ml, cefpodoxime was 0.72  $\mu$ g/ml and amoxicillin-clavulanic acid 0.84  $\mu$ g/ml. For isolates tested for *S. pneumoniae* MIC<sub>90</sub> for cefpodoxime-clavulanic acid was 0.09  $\mu$ g/ml; cefpodoxime was 0.69  $\mu$ g/ml, and amoxicillin-clavulanic acid was 0.27  $\mu$ g/ml. For isolate tested for *M. catarrhalis*, MIC<sub>90</sub> for cefpodoxime-clavulanic acid was 0.18  $\mu$ g/ml, cefpodoxime was 1.01  $\mu$ g/ml, and amoxicillin-clavulanic acid was 0.62  $\mu$ g/ml. For all the isolate tested cefpodoxime-clavulanic acid demonstrated lower MIC<sub>90</sub> than cefpodoxime and amoxicillin-clavulanic acid for all the three pathogens. Cefpodoxime when used in combination with clavulanic acid there was a significant decrease in the MIC<sub>90</sub> against all the three pathogen which shows the synergistic action of the combination.

**Conclusion:** The fixed dose combination of cefpodoxime-clavulanic acid showed lower MIC<sub>90</sub> for the community respiratory pathogen and hence can be considered as a preferred therapy of choice for the treatment of RTI.

**Key words:** Amoxicillin-clavulanic acid, Cefpodoxime, Cefpodoxime-clavulanic acid, Minimal inhibitory concentration<sub>90</sub>, Respiratory infection

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## INTRODUCTION

Acute respiratory tract infections (RTIs) are common and persistent causes of morbidity, disability, and mortality. RTIs represent 60% of all community-acquired bacterial infections<sup>1,2</sup> and account for two-thirds of all antibiotic prescriptions written for the treatment of community-

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acquired infections.<sup>3</sup> It is the third commonest cause of mortality and morbidity worldwide.<sup>4</sup> Although most RTIs are caused by viruses, various bacteria, particularly *Streptococcus pneumoniae*, *Hemophilus influenzae* and *Moraxella catarrhalis*, are common causes of community-acquired pneumonia, acute exacerbations of chronic bronchitis, otitis media and sinusitis.<sup>4</sup>

Epidemiologically *S. pneumonia* accounts for 42% of acute sinusitis, 15% of acute exacerbation of chronic bronchitis and 20-75% of community-acquired pneumonia; *H. influenzae* accounts for 29% of acute sinusitis, 32% of acute exacerbation of chronic bronchitis and 3-10% of community-acquired pneumonia whereas *M. catarrhalis* accounts for 22% of acute sinusitis, 13% of acute exacerbation of chronic bronchitis and very less for community-acquired pneumonia.<sup>3</sup>

Antimicrobial therapy forms a mainstay in the treatment of all infectious disease. Ideally before starting an antimicrobial therapy an infectious disease diagnosis is reached by determining the site of infection, defining the host (e.g, Immunocompromised, diabetic, of advanced age), and establishing, when possible, a microbiological diagnosis. To optimize an accurate microbiological diagnosis, clinicians should ensure that diagnostic specimens are properly obtained and promptly submitted to the microbiology laboratory, preferably before the institution of antimicrobial therapy. Because microbiological results do not become available for 24-72 h, initial therapy for infection is often empiric and guided by the clinical presentation.<sup>5</sup>

Antimicrobial activity of drugs is usually assessed by determination of the minimal inhibitory concentration<sub>90</sub> (MIC<sub>90</sub>) and the minimal bactericidal concentration of the drug *in vitro* after overnight aerobic incubation in a protein-free liquid medium at pH 7.2. The MIC<sub>90</sub> is defined as the minimal concentration of antibiotic that prevents the clear suspension of 105 CFU/mL from becoming turbid after overnight incubation; turbidity usually connotes at least a 10 fold increase in bacterial density. It is the lowest concentration of antimicrobial agent required to inhibit the microorganism. The MIC<sub>90</sub> is a measure of the potency of an antimicrobial drug. Sensitive strains have relatively low MIC<sub>90</sub>s, and resistant strains have relatively high MICs.<sup>6</sup> The MIC<sub>90</sub> can guide the choice of antimicrobial used in treatment by predicting efficacy. If pharmacokinetic and pharmacodynamics principles are met by careful selection of a specific anti-MIC<sub>90</sub> microbial given at an appropriate dosage, it will lead to a clinical cure, eradication of carrier status of a specific organism, and prevention of selection of resistance.

The present study was conducted to determine the MIC<sub>90</sub> of the three most commonly used antibiotic: Cefpodoxime,

cefpodoxime-clavulanic acid and amoxicillin-clavulanic acid in the treatment of RTI against three most common organisms responsible for RTI: *S. pneumonia*, *H. influenzae* and *M. catarrhalis*.

## MATERIALS AND METHODS

The present *in vitro* study was conducted for 4 months (June 2015 to September 2015) to determine MIC<sub>90</sub> of three commonly used antibiotic, that is, cefpodoxime, cefpodoxime-clavulanic acid and amoxicillin-clavulanic acid against three community respiratory pathogen, that is, *S. pneumonia*, *H. influenzae* and *M. catarrhalis*. Isolates from patient's sputum, nasal swab and throat swab were collected from 12 different community centers across India, and the MIC<sub>90</sub> for each antibiotic was determined using Broth dilution method. 10 isolates per center were subjected for evaluation. Susceptibility of antibiotics or combination was evaluated as per the Clinical and Laboratory Standards Institute (CLSI) breakpoint criteria.<sup>7</sup> The data obtained was kept confidential and was used for the purpose of study. Data were compiled, analyzed and expressed in terms of arithmetic mean and percentage. The difference was statistically determined using GraphPad Prism software version 7.

## RESULTS

The present *in vitro* study was conducted to analyze the MIC<sub>90</sub> of three commonly used antibiotics in the treatment of RTI against three common organisms. 106 isolated were collected of which, 36 were for *H. influenzae*, 42 for *S. pneumoniae* and 28 for *M. catarrhalis*. Samples from patient's sputum, nasal swab and throat swab were analyzed for MIC<sub>90</sub> of three antibiotics (i.e., cefpodoxime-clavulanic acid; cefpodoxime and amoxicillin-clavulanic acid) against *H. influenzae*. The mean MIC<sub>90</sub> of cefpodoxime-clavulanic acid was  $0.26 \pm 0.41$   $\mu\text{g/ml}$  (0.01-1) in comparison to cefpodoxime ( $0.72 \pm 1.21$   $\mu\text{g/ml}$ ) and amoxicillin-clavulanic acid ( $0.84 \pm 0.79$   $\mu\text{g/ml}$ ) (Figure 1). Statistically significant result ( $P = 0.0002$ ) was seen between the MIC<sub>90</sub> of cefpodoxime-clavulanic acid with cefpodoxime monotherapy ( $P = 0.03$ ) (Table 1). Among the isolate tested 5 (13.8%), resistance strain was seen. Cefpodoxime-clavulanic acid retained sensitivity for 3 out of 5 resistant strains (60%), but the strains remained resistant to amoxicillin-clavulanic acid.

For all the isolates tested for *S. pneumonia*, cefpodoxime-clavulanic acid demonstrated lower MIC<sub>90</sub> ( $0.09 \pm 0.12$   $\mu\text{g/ml}$ ) (0.01-0.1); than cefpodoxime ( $0.69 \pm 0.35$   $\mu\text{g/ml}$ ) and amoxicillin-clavulanic acid ( $0.27 \pm 0.39$   $\mu\text{g/ml}$ ) (Figure 2). Statistically significant result ( $P = 0.0054$ ) was seen between

the MIC<sub>90</sub> vales of cefpodoxime-clavulanic acid with cefpodoxime monotherapy ( $P = 0.0001$ ) (Table 2). Among the isolate tested 2 (4.7%), resistant strain were seen. Cefpodoxime-clavulanic acid and amoxicillin-clavulanic acid retained sensitivity for all the resistant strains.

28 isolates from patient's sputum, nasal swab and throat swab were analyzed for *M. catarrhalis*. For all the isolates tested cefpodoxime-clavulanic acid demonstrated lower MIC<sub>90</sub>  $0.18 \pm 0.31$  µg/ml (0.01-0.1) than cefpodoxime ( $1.01 \pm 1.16$  µg/ml) and amoxicillin-clavulanic acid ( $0.62 \pm 0.62$  µg/ml) (Figure 3). Statistically significant result ( $P = 0.0014$ ) was seen between the MIC<sub>90</sub> vales of cefpodoxime-clavulanic acid cefpodoxime monotherapy ( $P = 0.0001$ ) (Table 3). Among the isolate tested 2 (7.1%), resistant strain were seen. Cefpodoxime-clavulanic acid and amoxicillin-clavulanic acid retained sensitivity for all the resistant strains.

## DISCUSSION

The increasing prevalence of antibiotic-resistant bacterial pathogen commonly associated with RTI and the variation in the rate of resistance to a range of antibiotic is now acknowledged to be a global problem. The antibiotic susceptibility (or resistance) of a strain cannot be measured directly but must be deduced from the *in vitro* activity of the antibiotic. Among the various methods available, MIC<sub>90</sub> determination is the most widely used to assess *in vitro* activity for clinical categorization of clinical isolates.<sup>8</sup>

**Table 1: Comparison of MIC<sub>90</sub> of combination versus monotherapy for *H. influenzae***

Anti- microbial agents	P value
Amoxicillin-clavulanic acid versus cefpodoxime	0.61
Cefpodoxime-clavulanic acid versus cefpodoxime	0.03

MIC: Minimal inhibitory concentration, *H. influenzae*: *Hemophilus influenzae*

**Table 2: Comparison of MIC<sub>90</sub> of combination versus monotherapy for *S. pneumoniae***

Anti- microbial agents	P value
Amoxicillin-clavulanic acid versus cefpodoxime	0.001
Cefpodoxime-clavulanic acid versus cefpodoxime	0.0001

MIC: Minimal inhibitory concentration, *S. pneumoniae*: *Streptococcus pneumoniae*

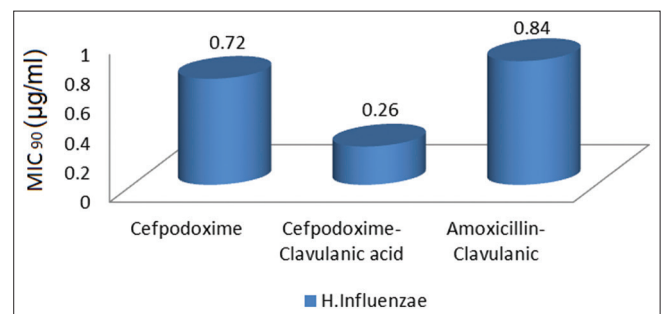
**Table 3: Comparison of MIC<sub>90</sub> of combination versus monotherapy for *M. catarrhalis***

Anti- microbial agents	P value
Amoxicillin-clavulanic acid versus cefpodoxime	0.12
Cefpodoxime-clavulanic acid versus cefpodoxime	0.0006

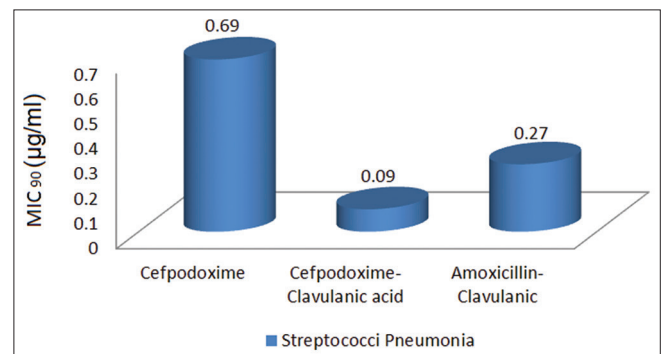
MIC: Minimal inhibitory concentration, *M. catarrhalis*: *Moraxella catarrhalis*

The present study was conducted to determine the MIC<sub>90</sub> of the three common antibiotic used in the treatment of RTI against common community respiratory pathogen, that is, *S. pneumoniae*, *H. influenzae* and *M. catarrhalis*. For all the isolate tested cefpodoxime-clavulanic acid demonstrated lower MIC<sub>90</sub> than cefpodoxime and amoxicillin-clavulanic acid for all the three pathogens. A significant difference was seen in the MIC<sub>90</sub> value of cefpodoxime-clavulanic acid and cefpodoxime for all pathogens.

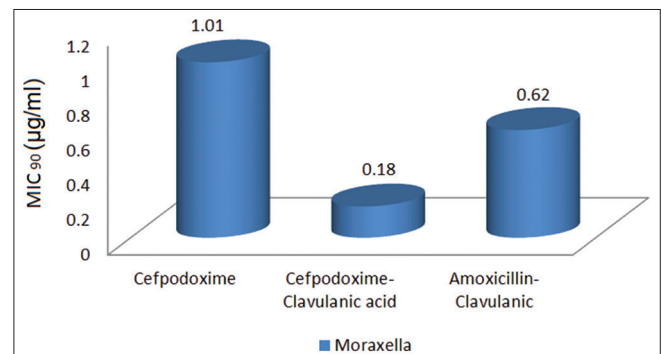
The present study showed the MIC<sub>90</sub> of amoxicillin-clavulanic acid to be 0.84 µg/ml for *H. influenzae* with 94.44% susceptibility, 0.27 µg/ml for *S. pneumoniae* with 100% susceptibility and 0.62 µg/ml with 100%



**Figure 1: Comparison of minimal inhibitory concentration<sub>90</sub> values of three antibiotics against *Hemophilus influenzae***



**Figure 2: Comparison of minimal inhibitory concentration<sub>90</sub> values of three antibiotics against *Streptococcal pneumonia***



**Figure 3: Comparison of minimal inhibitory concentration<sub>90</sub> values of three antibiotics against *Moraxella catarrhalis***

susceptibility for *M. catarrhalis*. The results of our study can be compared to MIC<sub>90</sub> of amoxicillin-clavulanic acid conducted Koeth and team where the MIC<sub>90</sub> was 1 µg/ml for *H. influenzae* with 98.7% susceptibility, 0.25 µg/ml with 100% susceptibility for *M. catarrhalis* and 1 µg/ml with 93.5% susceptibility for *S. pneumoniae*.<sup>9</sup> Jacob and team in their susceptibility study for 10 oral antibiotics reported, MIC<sub>90</sub> of amoxicillin-clavulanic acid to be 1 µg/ml for *H. influenzae* with 97.5% susceptibility, 2 µg/ml for *S. pneumoniae* with 93.9% susceptibility.<sup>10</sup>

According to the CLSI susceptibility criteria,<sup>7</sup> for amoxicillin-clavulanic acid MIC<sub>90</sub> of  $\leq 2$  µg/dl in a susceptible range and  $\geq 8$  µg/dl is in resistance range for *S. pneumoniae*. For *H. influenzae* MIC<sub>90</sub> of 2 µg/ml in a susceptible range and 16 µg/ml is in resistance range. For cefpodoxime MIC<sub>90</sub> of 0.25 µg/ml is in a susceptible range and 1 µg/dl is in resistance range for *H. influenzae* whereas for *S. pneumoniae* MIC<sub>90</sub> of  $\leq 0.5$  µg/ml is in a susceptible range and for  $\geq 2$  µg/ml is in resistance range.

*In vitro* studies have shown the peak plasma concentration of cefpodoxime 200 mg single dose to be 2.18 mcg/ml<sup>11</sup> and that of clavulanic acid 125 mg single dose to be 2.2 mcg/ml.<sup>12</sup> Microbiological studies have shown that antibiotic: Clavulanate ratio ranging from 1:1 to 16:1 improves sensitivity of antibiotic.<sup>13</sup> The peak plasma concentration of cefpodoxime-clavulanic acid lies within the ratio of 1:1 to 2:1.

The present study has also highlighted, when cefpodoxime was used in combination with clavulanic acid, there was a significant decrease in the MIC<sub>90</sub> against all the three pathogens which shows the synergistic action of the combination. MIC<sub>90</sub> of both the combination, that is, cefpodoxime-clavulanic acid and amoxicillin-clavulanic acid were within the susceptibility range according to the CLSI susceptibility criteria.

## CONCLUSION

The recent increase in the resistance of the major respiratory pathogens to oral antimicrobial agents has produced a need to re-evaluate treatment options for RTIs. The fixed dose combination of cefpodoxime-clavulanic

acid showed lowest MIC<sub>90</sub> for the community respiratory pathogen and hence can be considered as a preferred therapy of choice for the treatment of RTI. The results of this study should be applied to clinical practice based on the clinical presentation of the patient so a randomized blinded clinical trial should be conducted to confirm the benefit obtained from our study.

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# Evaluation of Pattern of HER2 neu Overexpression in Primary Gastric Carcinoma by Immunohistochemistry

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## Abstract

**Introduction:** Gastric carcinoma is the fourth most frequent cancer worldwide, representing the second most common cause of death from cancer cases. Despite a steady decline in the incidence rate over the last few decades, the absolute incidence has risen due to the aging of the worldwide population. According to Lauren classification, it is divided into two major histological types, intestinal and diffuse. Very less is known about the molecular pathways induced by the HER2/neu receptor in gastric cancer compared to breast cancer. A descriptive study investigating the HER2/neu protein overexpression in gastric carcinoma was undertaken.

**Materials and Methods:** Our study was a descriptive study conducted for 2 years. Data for the study are obtained using patient diagnosis, case details, and examination of tissue sections. The sample size was calculated using odds ratio which comes out as 31. Cases were selected based on the inclusion and exclusion criteria. Permission was obtained from importer-exporter code before starting the study. Tissue samples of gastric carcinoma were obtained from gastrectomy and biopsy specimens which were analyzed using immunohistochemical staining. Statistical analysis is performed using SPSS 23 version.

**Results:** In our study, HER2/neu status was positive in 22.6% of all tested gastric cancer samples. Out of 31 cases, 7 cases show HER2/neu positivity of 3+, while 24 cases were HER2/neu negative or HER2/neu positive 1+ and none case showed HER2/neu positivity 2+ score. HER2/neu expression was a more common in intestinal type gastric cancer than the diffuse type (31.6% vs. 10%, respectively). HER2/neu positive 3+ cases are more common in those carcinoma located near gastroesophageal junction (57.1%) in comparison to carcinoma located in the body of the stomach (28.6%) and antral tumors (14.3%).

**Conclusion:** Gastric carcinoma occurring in this study population does not appear to differ considerably from that of their Western counterparts in terms of age of onset and sexual predilection. Further studies are required to prove more significant association with large sample size.

**Key words:** Gastric carcinoma, HER2/neu, Immunohistochemistry

## INTRODUCTION

Gastric carcinoma accounts for 10% of cancers worldwide.<sup>1</sup> Despite a steady decline in the incidence rate over the last few decades, the absolute incidence has risen due to the aging of the worldwide population.<sup>2</sup> Cancers of the antropyloric region are more common in high-risk

regions (Asia, Eastern Europe), whereas tumors of the cardia occur more commonly in low-risk regions (North America, Northern Europe).<sup>3,4</sup> Gastric carcinoma is the fourth most frequent cancer worldwide, representing the second most common cause of death from cancer cases (approximately 700,000/year).<sup>5,6</sup> Lauren divided gastric carcinoma into two major histological types, intestinal and diffuse types. Tumors that contain equal intestinal and diffuse components are defined as mixed tumors. Various etiological factors were associated with an increased risk of gastric cancer which includes chronic inflammation of gastric mucosa, exposure to diverse carcinogens, and genetic susceptibility, *Helicobacter pylori* infection, smoking and dietary habits (high intake of salt-preserved and/or smoked foods).

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HER2/neu (c-erbB2) is a proto-oncogene located on chromosome 17q21.<sup>7</sup> HER2/neu encodes a 185-kDa transmembrane tyrosine kinase receptor, a member of the epidermal growth factor receptor family (EGFRs), comprises four members: HER1 (EGFR), HER2, HER3, and HER4. They are involved in various aspects of tumor cell biology: Cell proliferation, apoptosis, adhesion, migration, and differentiation.<sup>8</sup> HER2/neu overexpression or amplification has been best studied in breast carcinoma but also reported in other solid tumors such as ovarian, endometrial, salivary gland, lung, esophageal, and gastric carcinomas.<sup>9,10</sup>

Various stromal-derived ligands, including EGF, EGF-like ligands, and neuregulins bind HER1, HER3, and HER4, inducing homodimerization and heterodimerization, phosphorylation of cytoplasmic tyrosine kinase moieties, and activation of complex signaling pathways essential for cell survival, differentiation, and proliferation.<sup>11-14</sup> HER2, however, is an orphan receptor with no known high-affinity ligand. HER2 becomes activated by heterodimerization after direct ligand binding by HER1, HER3, or HER4. Thus, the role of HER2 in the network of membrane receptor kinases seems to be as an amplifying coreceptor for HER1, HER3, and HER4.<sup>12,13</sup> A specific erbB-2 interacting protein (ERBIN) restricts the spatial distribution of the HER2 molecule to the basolateral membrane of epithelial cells.<sup>15</sup> ERBIN binds HER2, but not HER1, HER3, or HER4, and may be involved in connecting HER2 to cytosolic and cytoskeletal-associated components. Although much less is known about the molecular pathways induced by the HER2/neu receptor in gastric cancer compared to breast cancer, the current publication status suggests that the HER2/neu receptor plays a similar role in gastric cancer. There is evidence that HER2/neu is a prognostic factor for gastric cancer. Similar to breast cancer, HER2/neu over-expression correlates with a shorter overall survival.<sup>13,16-18</sup> For clinical HER2 determination, tissue-based methods, such as immunohistochemical (IHC) analysis and fluorescence *in situ* hybridization (FISH), have replaced whole-tissue extraction methods, such as Southern blot analysis, enzyme-linked immunosorbent assay, and polymerase chain reaction, which may require fresh tissue or suffer dilution owing to admixing of tumor and normal cells.<sup>19</sup> Frozen section IHC analysis, the “gold-standard” method for HER2 over-expression, is impractical in the current era of early cancer detection, in which tumor size often precludes ancillary testing of fresh tissue. IHC analysis is an attractive method for clinical HER2 determination owing to its retrospective potential and specific targeting of tumor cells. The plethora of available antibodies, methods, and grading schemes, however, has made standardization impossible.<sup>20,21</sup>

Up to now, fluoropyrimidine and platinum compound based therapies have been the standard of care. However, the prognosis of advanced gastric or gastro-esophageal cancer is poor with a 5-year survival rate of about 5-20%. HER2/neu overexpression was first described in 1986 using IHC.<sup>13</sup> Since then research is on, and it is turning out to be a useful molecule for which targeted therapy in the form of trastuzumab is available. This study is being undertaken to evaluate the pattern of HER2/neu protein overexpression in gastric carcinoma.

## Aim and Objectives

### Aim

To evaluate the pattern of HER2/neu expression in the primary gastric carcinoma cases by IHC techniques.

### Objectives

1. To assess the pattern of HER2/neu positivity in cases of gastric carcinoma.
2. To determine the relationship between HER2/neu expression with clinicopathological parameters such as age, sex, grade, stage, and types of gastric carcinoma.
3. To observe any variation in HER2/neu overexpression in small biopsy and resected specimen obtained after NACT.

## MATERIALS AND METHODS

This was a descriptive study conducted in a tertiary care hospital of an urban city between January 2013 and January 2015. Cases were selected from surgical pathology records in a retrospective as well as prospective way. The cases that had sufficient remaining tissue in the paraffin blocks (focus of interest for IHC stains) were identified and invited to participate in the study. A total of 31 cases were selected including small as well as total gastrectomy cases. The Institutional Ethics Committee approval was taken, and informed consent was received before beginning the study. Selected gastric carcinoma samples (paraffin blocks containing sufficient tissue left), hematoxylin and eosin (H and E) stained slides, and relevant data (age, treatment history available with requisition forms) have been collected. Standard IHC staining method using super sensitive polymer-horseradish peroxidase detection system (biotin-free) was used in the study. The additional benefit of using this method are:

1. Clean stain without endogenous biotin background
2. High signal to noise ratio for intense stain
3. Excellent sensitivity for weakly expressed antigens
4. Higher dilution of antibodies.

For each run of staining, a positive and negative control slide was also prepared. Prostatic carcinoma and benign prostatic tissue serve as positive and negative controls



that show the predicted staining patterns or the antigen under study. IHC analysis was performed as specified by the manufacturer using the Hercep Test kit. Briefly, 3 µm paraffin sections were placed in an oven overnight at 37°C. The slides were dewaxed in xylene, rehydrated in graded alcohol, incubated in citrate buffer at 95°C (pressure cooker). The slides then were placed on an immunostainer (DAKO) using the primary polyclonal antibody and polymer detection system supplied by DAKO. Following IHC analysis staining, the slides were placed in H for 1 min, dehydrated in graded alcohol, cleared in xylene, and coverslipped. Two pathologists independently scored slides as 0, 1+, 2+, or 3+ according to DAKO guidelines. Cytoplasmic staining was ignored. Only invasive tumor was scored. Scores of 0 or 1+ were regarded as immunohistochemically negative and 3+ as immunohistochemically positive. Discrepant IHC scores were resolved at the 2-headed microscope (Table 1).

## RESULTS

The study included a total 31 cases. Further results are shown in Tables 2-4, Figures 1 and 2.

## DISCUSSION

Gastric carcinoma remains an important problem among the Indian population. The male predominance observed in intestinal type of gastric carcinoma does not differ from what has also been previously noted by Lauren in a study in a large Finnish population. Currently, several molecular factors are studied as prognostic and predictive for gastric cancer. They include oncogenes and tumor suppressor genes, growth factors and receptors, cell adhesion molecules, proteolytic molecules and angiogenic factors (HER2, EGFR, p53, Cadherin, catenin, cyclooxygenase-2 [COX-2], matrix metalloproteinases, and vascular endothelial growth factor [VEGFR]).<sup>22</sup> Some of those prognostic factors can also be considered predictive for response to therapy as

a molecular target to chemotherapeutics or a new class of antineoplastic molecules (HER2/neu targeted by Trastuzumab, COX-2 by nonsteroidal anti-inflammatory drugs, matrix metalloproteinases, EGFR and VEGFR by specific inhibitors).

A number of studies have analyzed HER2/neu overexpression in gastric cancer, and the rate of HER2 positivity is variable, ranging from 6% to 35%. Two major explanations for this discrepancy in HER2 expression are as follows: First, in the earlier studies polyclonal antibodies were used in contrast to more recent studies where monoclonal antibodies were used, and second, the more recent studies restricted their evaluation to membrane staining, excluding the cytoplasmic staining that was in the earlier studies considered in evaluation.<sup>23</sup> After the scoring system for gastric cancer was standardized by a panel of international oncology and pathology experts in 2007, the discrepancy in HER2 expression has become smaller.<sup>24</sup> The largest ongoing international trial which enrolled 2992 gastric or gastroesophageal junction carcinomas, defined 21.7% of evaluable tumor samples as HER2 positive.<sup>25</sup> In our study, HER2/neu status was determined by IHC, and all IHC 3+ score tumors are accepted as HER2/neu positive cases. In our study, out of 31 cases, 7 cases show HER2/neu positive 3+score, 24 cases were HER2/neu negative or HER2/neu positive 1+ score and no cases showed HER2/neu positive 2+ score. In this study, HER2/neu status was positive in 22.6% of all tested gastric cancer samples.

A high correlation between HER2 overexpression and intestinal type was reported by several authors in 1990s and confirmed in more recent studies. In the ToGA trial, HER2 positivity differed significantly by histological subtype (intestinal 34%, diffuse 6%, and other 20%). In this study, results are HER2/neu expression was more common in intestinal type gastric cancer than the diffuse type (31.6% vs. 10%, respectively). Adenosquamous type tumors showed no HER2/neu expression, probably due to small sample

**Table 1: Reporting system of IHC**

Staining intensity score	Surgical-staining pattern	Biopsies-staining pattern	HER2 Over-expression
0	No reactivity or membranous reactivity in<10% of tumor cells	No reactivity or membranous reactivity in any (or<5%) of tumor cells	Negative
1+(40×)	Faint/barely perceptible membranous reactivity in>10% of tumor cells; cells are reactivity only in part of their membrane	Tumor cell clusters with a faint/barely perceptible membranous reactivity irrespective of percentage of tumor cells stained (at least 5 tumor cells)	Negative
2+(10-20×)	Weak to moderate complete, basolateral or lateral membranous reactivity in>10% of tumor cells	Tumor cell clusters with a weak to moderate complete, basolateral or lateral membranous reactivity irrespective of percentage of tumor cells stained (>5 tumor cells)	Equivocal (FISH Confirmation)
3+(2.5-5×)	Strong complete, basolateral or lateral membranous reactivity in>10% of the tumor cells	Tumor cell clusters with a strong complete, basolateral or lateral membranous reactivity irrespective of percentage of tumor cells stained (>5 tumor cells)	Positive

IHC: Immunohistochemistry, FISH: Fluorescence *in situ* hybridization

**Table 2: Age distribution of gastric carcinoma cases (n=31)**

Type of gastric carcinoma	Age			
	Mean±SD	Median	Minimum	Maximum
Intestinal	61.42±14.366	65.00	27	79
Diffuse	55.90±12.635	57.00	39	77
Adenosquamous	65.00±0.000	65.00	65	65
Total	59.87±13.426	64.00	27	79

SD: Standard deviation

**Table 3: Age distribution of gastric carcinoma cases according to site of carcinoma (n=31)**

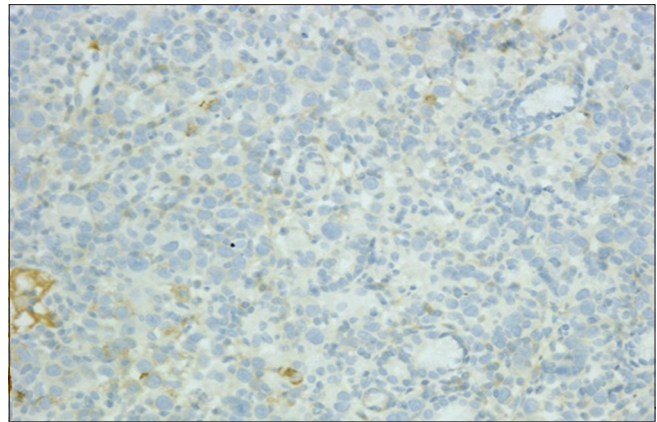
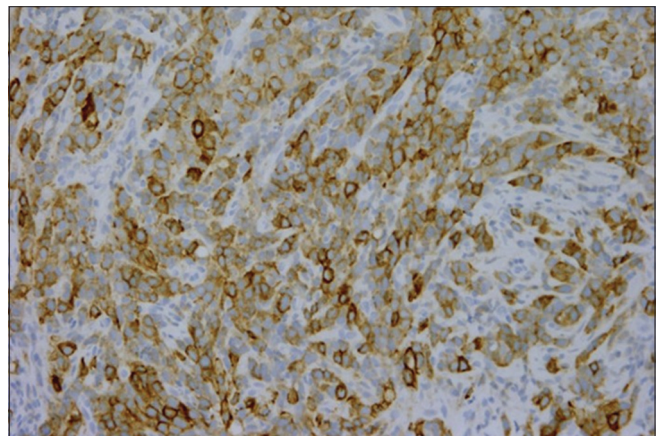
Location	Age			
	Mean±SD	Median	Minimum	Maximum
Antrum	57.79±17.777	65.00	27	79
Body	60.86±5.551	60.00	54	70
Fundus	62.10±10.525	64.00	44	75
Total	59.87±13.426	64.00	27	79
P value	0.735			

SD: Standard deviation

number. Different studies say the distribution of gastric carcinoma is increasing in the cardiac region,<sup>26-29</sup> but others have noted relatively stable time trends.<sup>30-33</sup>

In this study, it was found gastric carcinoma is more common in the antral region (45.2%) in respect to the body (22.6%) and fundus (32.3%). Irrespective of sex, the antral region is the most common site of gastric carcinoma (male - 45.5% and female - 44.4%). Mean age for gastric carcinoma located in the antral region is 57.79 years with a standard deviation (SD) of 17.77. The mean age for gastric carcinoma located in body is 60.86 years with an SD of 5.55 and for carcinoma located in the fundal region is 62.10 years with an SD of 10.52. HER2/neu positive cases with 3+ score are more common in those carcinoma located near gastroesophageal junction (57.1% in respect to carcinoma located in body of the stomach 28.6%, and antral tumors 14.3%). Different studies show that gastric carcinoma shows male predominance (8:1).<sup>34</sup> In this study, the incidence of gastric carcinoma is more common in male gender (male - 71%, female - 29%). As per Table 5 we have seen HER2 neu positivity ranging from 19.0% to 22.6% in different trials using different techniques like FISH or IHC

Maximum age of intestinal type of gastric carcinoma reported in our study is 79 years and minimum age is 27 years. The median age of intestinal type of gastric carcinoma is 65 years with a mean of 61.42 years and an SD of 14.366. Maximum age reported in diffuse type of gastric carcinoma is 77 years and minimum age is 39 years. The median age of diffuse type of gastric carcinoma is 57 years with a mean of 55.9 years and an SD of 12.63. Maximum

**Figure 1: Immunohistochemistry slide showing HER2 neu positive staining score 1****Figure 2: Immunohistochemistry slide showing HER2 neu positive staining score**

age reported in the adenosquamous type of gastric carcinoma is 65 years and minimum age is 65 years. The median age of adenosquamous type of gastric carcinoma is 65 years with a mean of 65 years and a SD of 0.00.

## CONCLUSION AND RECOMMENDATION

1. Before evaluation of the IHC slide, all morphologically atypical glands must be identified by H and E.
2. It is important to recognize that sensitivity of immunostaining may vary from laboratory to laboratory. Therefore, appropriate external and internal positive and negative controls must be used while interpreting the stain.
3. HER2/neu positivity must be evaluated with caution. A focal, weak, and noncircumferential staining patterns in benign-appearing glands should not be interpreted as indicative of a malignant diagnosis.
4. Finally, an internal ring study should be used as a good training method among pathologists who analyze HER2 expression in gastric cancer, especially because

**Table 4: IHC of gastric carcinoma cases (n=31)**

Variable	Type of gastric carcinoma			Total	P value	Significance
	Intestinal	Diffuse	Adenosquamous			
Gender						
Female	8 (42.1)	1 (10)	0 (0)	9 (29)	0.125	Not significant
Male	11 (57.9)	9 (90)	2 (100)	22 (71)		
Total	19 (100)	10 (100)	2 (100)	31 (100)		
HER2/neu1						
Positivity						
Absent	6 (31.6)	1 (10)	0 (0)	7 (22.6)	0.306	Not significant
Present	13 (68.4)	9 (90)	2 (100)	24 (77.4)		
Total	19 (100)	10 (100)	2 (100)	31 (100)		
HER2/neu2						
Positivity						
Absent	19 (100)	10 (100)	2 (100)	31 (100)	NA	NA
Present	0 (0)	0 (0)	0 (0)	0 (0)		
Total	19 (100)	10 (100)	2 (100)	31 (100)		
HER2/neu3						
Positivity						
Absent	13 (68.4)	9 (90)	2 (100)	24 (77.4)	0.306	Not significant
Present	6 (31.6)	1 (10)	0 (0)	7 (22.6)		
Total	19 (100)	10 (100)	2 (100)	31 (100)		

IHC: Immunohistochemistry

**Table 5: HER2 positivity rate in gastric cancer**

Reference	Type of assay	n	HER2-positive rate (%)
ToGA trial	IHC/FISH	3667	22.1
Jørgensen <sup>35</sup>	IHC	6542	19.0
Jørgensen <sup>35</sup>	FISH/CISH	869	19.4
Present study	IHC	31	22.6

FISH: Fluorescence *in situ* hybridization, IHC: Immunohistochemistry

the scoring system for HER2/neu expression in gastric cancer differs from the one for the breast cancer. Due to the biological origin of gastric tissue, basolateral (not luminal) membranes are stained, resulting in incomplete immunoreaction of membranes of the tumor cells (typically “U” shaped). An identical scoring should be applied to samples with complete membranous reactivity, as well as those, where reactivity was restricted to the basolateral membrane if it was noted in 10%.

### Limitations of the Study

1. The study is limited by its small sample size.
2. Follow-up of the cases was not feasible due to the wide residential spread of patients and lack of direct contact with laboratory post-surgery and hence was not included study design.
3. Unfortunately, the gold standard test (FISH) was not available for confirmation of HER2/neu overexpression.
4. Manual antigen retrieval technique, used in the present study, has its limitations compared to automated one.
5. In cases of very small endoscopic biopsy tissue, during antigen retrieval or subsequent treatment, loss of foci of interest was also faced frequently.

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# Clinical Profile of Multiple Sclerosis in Kashmir (India): A Tertiary Care Hospital Based Study

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## Abstract

**Background:** Multiple sclerosis is chronic inflammatory demyelinating disorder of central nervous system occurring worldwide. It is believed to be an autoimmune disorder with variability in frequency, severity and chronicity.

**Materials and Methods:** Demographic and clinical records of 25 multiple sclerosis patients were reviewed which included; age, sex, marital and occupation states, presenting symptoms, time of on set, type of MS, family history and history of autoimmune or other disease.

**Results:** In total, 25 patients of multiple sclerosis (MS) diagnosed on the basis of Poser's criteria from Kashmir (India) were studied. The mean age of onset was 33.5 in males and 26.40 years in females. Male to female ratio was 1:1.57. Most of the patients were between second and third decade. Definite MS comprised of 64%, while remaining 36% were clinically probable. Visual involvement was seen in 40%, weakness of limbs (35%), sphincter involvement (20%), sensory symptoms (10%) and trigeminal neuralgia (10%) were the most common presenting symptoms. Pyramidal tract involvement (70%), spinothalamic and posterior column involvement (50%), cerebellar (25%), optic nerve (20%), internuclear ophthalmoplegia (8%), and optospinal involvement (12%) were common signs. Relapsing and remitting MS was found (72%), secondary progressive MS (20%) and primary progressive MS (8%) cases. Magnetic resonance imaging brain showed positive results in 60% cases. Cerebrospinal fluid was positive for oligoclonal bands in 8% of cases. Visual evoked potentials and brainstem auditory evoked response were positive in 20% and 16% of cases respectively.

**Conclusion:** Findings in this study revealed that the clinical profile of MS in Kashmir (India) was similar to that in other parts of the India and Asia.

**Key words:** Internuclear ophthalmoplegia, Multiple sclerosis, Oligoclonal bands

## INTRODUCTION

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disorder of the central nervous system occurring worldwide resulting from immune response to myelin and to some extent to axons also. It is well recognized since the early description of Charcot. It is believed to be an autoimmune disorder with variability in frequency, severity and chronicity. MS was considered to be non-existent in Kashmir (India) till 1994.<sup>2</sup> There has been an increase in the number of diagnosed

cases in recent times with the growth of neurology as a sub-speciality in Kashmir (India) and availability of modern diagnostic tools like magnetic resonance imaging (MRI). Optic nerve and spinal cord involvement are more common in the Asian variety of MS.<sup>3</sup> In present study we studied clinical pattern of MS in Kashmir (India).

## MATERIALS AND METHODS

This study was conducted in Inpatient and Outpatient Departments of Neurology, Government Medical College and associated Hospitals Srinagar Kashmir (India). Totally 25 patients with varying clinical presentation were analyzed. Relevant investigations were done to diagnose MS and to exclude other MS mimicking conditions.

Complete hemogram, X-ray chest, erythrocyte sedimentation rate, blood chemistry comprising of kidney

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function test, blood sugars, collagen vascular profile, venereal disease research laboratory, and sarcoidosis profile were studied. Cerebrospinal fluid (CSF) for oligoclonal bands (OCBs), visual evoked potentials and brainstem auditory evoked response were done in some cases. MRI brain was done in all cases and MRI spinal cord in most of the cases. The cases were diagnosed according to Poser's diagnostic criteria (Table 1). No case of Devic's disease was included in the study.

## RESULTS

The patients enrolled in the study were categorized as definite or probable MS. The mean age of onset was 33.5 years in males and 26.40 years in females. The youngest patient was 18 years and the oldest 55 years of age. Maximum number of cases were found in the second and fourth decade. Male: female ratio was 1:1.57. The proportion of definite and probable cases was 64% and 36%, respectively.

### Demographic characteristics

Mean age at onset (males)	33.50 years
Mean age at onset (females)	26.40 years
Youngest patients age	18 years
Oldest patients age	55 years
Female to male ratio	1:1.57
Definite MS cases	64%
Probable MS cases	36%

MS: Multiple sclerosis

As far as clinical course of MS is concerned relapsing-remitting MS was seen in 72% cases, followed by secondary progressive MS in 20% and primary progressive MS in 8% and none of progressive relapsing MS was seen (Figure 1).

The most common presentation of MS was pyramidal tract involvement in 70% of cases, followed by sensory symptoms in 50%, visual symptoms in 40% of cases, bladder involvement in 20%, cerebellar in 25% and trigeminal neuralgia in 10% of cases (Figure 2).

Investigations including haemogram, biochemistry, and other relevant investigations were normal. CSF examination revealed OCB positivity in 8% of cases only. MRI was compatible with MS in 60% of cases. MRI cervical and dorsal spine were compatible with MS in 16% of cases (Figure 3).

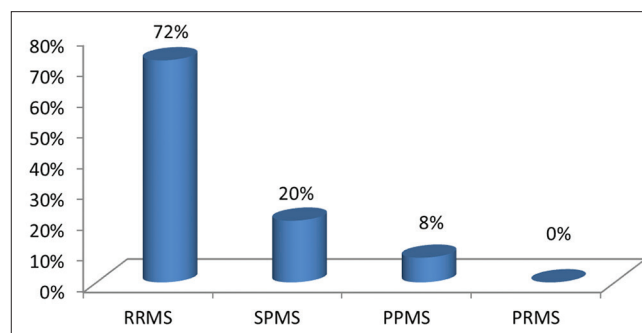
## DISCUSSION

MS is less common in tropical countries.<sup>2-5</sup> Epidemiological data are unavailable. Existing data have been obtained from small often retrospective studies from different parts of the country. Consideration of illness as insignificant by

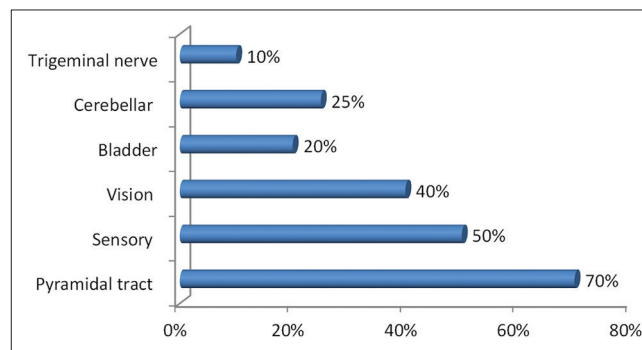
**Table 1: Poser criteria**

Diagnostic category	Number of lesions		Paraclinical	CSF
	Relapses	Clinical		
Clinical definite				
CDMS A1	2	2	NA	NA
CDMS A2	2	1	1	NA
Laboratory-supported definite				
LSDMS B1	2	1	1	(+)
LSDMS B2	1	2	NA	(+)
LSDMS B3	1	1	1	(+)
Clinical probable				
CPMS C1	2	1	(-)	(-)
CPMS C2	1	2	(-)	(-)
CPMS C3	1	1	1	(-)
Laboratory-supported probable				
LSPMS D1	2	(-)	(-)	(+)

MS: Multiple sclerosis, CSF: Cerebrospinal fluid



**Figure 1: Topography of multiple sclerosis**

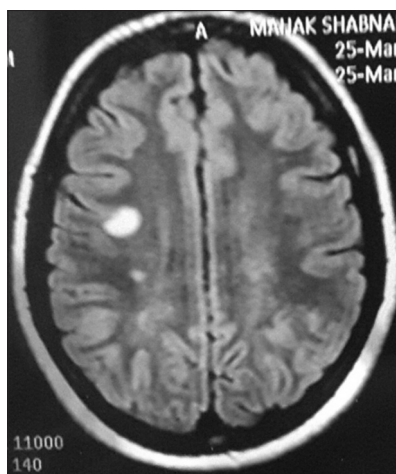


**Figure 2: Distribution by signs/symptoms**

the patients or reluctance on the part of treating doctor to consider the diagnosis of MS because of low frequency may be contributory for reported lower incidence.<sup>1</sup>

The present study has documented female to male ratio of 1:1.5. Five studies<sup>6-10</sup> have shown male preponderance (range 1.25-2), and one study<sup>11</sup> has shown female preponderance.

Kurtzke *et al.*<sup>12</sup> have shown female predominance (female: male - 1.8:1) among US veterans.



**Figure 3: Magnetic resonance imaging showing fresh hyperintense lesions**

Sahraian *et al.*<sup>13</sup> reported in Iran that mean age of onset was similar to other studies but the calculated prevalence of early onset MS was increased. The cumulative data indicate that the female to male ratio is increasing annually.

Börü *et al.*<sup>14</sup> reported that clinical features and course of MS patients in Turkey were typical of European MS. Turkey is a high-risk MS area. The present study has shown similar clinical features and course.<sup>15</sup>

Deleu *et al.*<sup>15</sup> reported that Qatar is a medium to high-risk area for MS in some different clinical characteristics as compared to other countries. Present Etemadifer *et al.*<sup>16</sup> reported that MS rate in Isfahan Iran is highest in the middle east. A possible explanation could be enhanced diagnosis of MS with MRI, revised MacDonald criteria, increasing number of neurologists and increasing younger population, etc.

Same criteria are responsible for diagnosing and identifying MS patients in our study as previously before MRI era and scarcity of neurologists MS was considered almost non-existent in Kashmir (India).

Browne *et al.*<sup>17</sup> reported that number of MS cases increased 2.1 million in 2008 to 2.3 million in 2013 reasons being improved health care, support services, inequity in the availability of services, number of MS groups and organizations worldwide have increased.

Orton *et al.*<sup>18</sup> reported that substantial increase in the female to male sex ratio in Canada seems to result from a disproportional increase in the incidence of MS in women.

Koch-Henriksen and Sørensen<sup>19</sup> reported that in even distribution of MS across populations can be attributed to differences in genes and the environment and their inter-relationship.

Cerreta<sup>20</sup> reported that MRI findings have proved to be useful diagnostic test in the initial evaluation and monitoring of patients with MS. It provides quantitative assessment of the disease and progression during clinical trials. The present study also revealed MRI positivity in significant number of patients and this diagnostic entity has revolutionized the diagnosis of MS.

Pugliatti *et al.*<sup>21</sup> reported prevalence rates are higher for women for all countries considered. Highest prevalence rates have been estimated from the age group 35-64 years for both sexes and all countries.

Singhal and Wadia<sup>6</sup> in their study of 30 patients from the Bombay region observed that MS patients were mostly from higher socio-economic status. The present study revealed patients belonging to different social strata.

Heydarpour *et al.*<sup>22</sup> reported that recent advances in MS registries will allow nationwide studies and temporal comparisons between countries provided that age and sex standardized estimates are available.

## CONCLUSION

We conclude that MS is not uncommon in Kashmir (India). There was a greater preponderance of women as seen worldwide. However clinical pattern conforms more to the "Asian variety" of MS. MRI positivity was lesser as compared to western series. The OCBs in CSF were less seen than in other Asian and western countries.

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# Clinical Profile, Subtypes, and Risk Factors among Glaucoma Patients in a Tertiary Hospital in Central India

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## Abstract

**Background:** Glaucoma is a leading cause of irreversible blindness and prevalence of glaucoma varies from region to region. There are many risk factors associated with glaucoma which encompasses the need for comprehensive evaluation of all glaucoma patients.

**Material and Methods:** Our study was a prospective, observational, hospital-based study conducted in the Eye Department of R.D. Gardi Medical College, Ujjain, India. 200 Glaucoma patients were enrolled for the study. All the patients underwent a detailed and comprehensive glaucoma workup. The associated risk factors were also noted. The results were recorded and analyzed in detail.

**Results:** In our study, 200 patients were enrolled. There were 88 (44%) males and 112 (56%) females. 67 (33.5%) patients were found to be suffering from primary open angle glaucoma while 105 (52.5%) patients had primary angle closure glaucoma (PACG). 13 (6.5%) patients were found to be having secondary glaucoma. 218 (54.5%) eyes had visual acuity <6/60. 33 (16.5%) patients were found to be suffering from hypertension while 28 (14%) patients were detected to be diabetic. 16 (8%) patients were myopic while 5 (2.5%) patients had a genetic predisposition for glaucoma. Smoking was also found in 12 (6%) patients to be associated risk factor in glaucoma patients.

**Conclusion:** Chronic PACG was the most common subtype of glaucoma found in our study. Timely detection and proper management of glaucoma patients is recommended to reduce the burden of glaucoma blindness.

**Key words:** Blindness, Glaucoma, Primary angle closure glaucoma, Primary open angle glaucoma, Secondary glaucoma

## INTRODUCTION

Glaucoma is a leading cause of irreversible blindness and managing glaucoma patients is a real challenge for ophthalmologists worldwide. This is more so in developing countries due to lack of patient awareness, frequent late presentation, and noncompliance with treatment. Glaucoma can be defined as a multifactorial optic neuropathy with a characteristic accelerated degeneration of retinal ganglion

cells, presenting with classical optic nerve head features and correlating visual field changes, which may or may not be associated with angle abnormality in the presence or absence of any cause for the disease.<sup>1</sup>

Glaucoma, the second leading cause of world blindness accounts for 15% of global blindness.<sup>2,3</sup> The prevalence and subtypes of glaucomas vary with age, sex, geographical location, and race.<sup>4</sup>

Many studies have shown a higher prevalence of angle closure glaucoma in Asian individuals, as compared to Caucasians or black people, in whom open angle glaucoma is found to be more prevalent.<sup>5,6</sup> Male preponderance has been seen in primary open angle glaucoma (POAG), normal tension glaucoma (NTG) and secondary glaucoma whereas ocular hypertension (OHT), primary angle closure

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glaucoma (PACG) and developmental glaucoma have shown a higher prevalence in the female sex.<sup>7</sup> Diabetes, hypertension, cardiovascular diseases, myopia, and smoking are some risk-factors which have been found to be associated with glaucoma. This study was conducted in our institute, which is a tertiary hospital located in Central India, to study the clinical profile, distribution of subtypes of glaucoma and the associated risk factors among the patients coming to the Eye Outpatient Department.

## MATERIALS AND METHODS

Our study is a prospective, observational, hospital-based study conducted in the Department of Ophthalmology, R. D. Gardi Medical College, Ujjain, Madhya Pradesh, India, over a period of 1-year from January 2015 to December 2015. Prior approval was obtained from the institutional Ethics Committee. 200 consecutive patients found to be suffering from glaucoma or with a suspicion of glaucoma were enrolled in the study.

A written informed consent was obtained from each patient. A detailed history was taken, with regard to the chief complaint, any family history of glaucoma, history of prolonged steroid medication as well as a history of any prior ocular trauma or ocular surgery. History of any systemic illness like diabetes mellitus, hypertension was also sought.

Each patient was subjected to a comprehensive ophthalmic examination which included a record of the unaided visual acuity as well as the best corrected visual acuity. Slit-lamp examination which included Von Herick's grading of the peripheral anterior chamber depth was performed. Pseudoexfoliation and rubeosis were looked for. Refraction was also done. Gonioscopy was done using the Goldmann single-mirror gonioscopy. Intra-ocular pressure (IOP) was measured using the Goldmann applanation tonometer. An IOP of  $>21$  mm of Hg was considered abnormal. Central corneal thickness was recorded to obtain the corrected value of IOP. This was especially helpful in case of glaucoma suspects, patients of NTG and OHT. Fundus examination with special emphasis on the optic disc was done by direct ophthalmoscopy as well as slit-lamp biomicroscopy using the 90 D lens. Automated visual field analysis was done.

Diurnal variation of IOP was done in patients who had borderline pressures on 2 or more separate occasions and/or disc changes suggestive of glaucoma, with open angles. A difference of  $>8$  mm of Hg between maximum and minimum values or a rise in IOP to  $>30$  mm Hg was considered to be significant.

Anterior chamber was classified according to Shaeffer's grading.<sup>8</sup> Grades 3 and 4 angles were considered open, while angles of Grade 2 and less were considered occludable. Disc changes suggestive of glaucoma included asymmetrical cupping, vertical elongation of the cup, focal notching, and thinning of the neuro-retinal rim. Anderson's criteria were followed to define glaucomatous visual field defect on visual field analysis.<sup>9</sup> This was co-related with the disc changes and retinal nerve fiber layer defects.

## Exclusion Criterion

Patients who were previously diagnosed cases of glaucoma and already on anti-glaucoma medications, or had undergone any laser procedure or filtration surgery for glaucoma were excluded from the study. Patients suffering from ocular surface disorders were also excluded from the study.

After comprehensive ocular work-up, the patients were grouped under different glaucoma sub-types based on a standard criterion. These glaucoma subtypes are congenital glaucoma, POAG, juvenile open angle glaucoma: Patients of age  $<40$  years with clinical features of POAG, PACG, NTG, secondary glaucoma and glaucoma suspects.

Glaucoma suspects: Included patients with: (1) OHT (2) occludable angles on gonioscopy, but no other symptoms/signs of glaucoma (3) strong family history of glaucoma (4) optic nerve head change suggestive of glaucoma, with normal IOP, open angles, and no glaucomatous visual field changes.

## RESULTS

Our study was a hospital-based study in which 400 eyes of 200 patients were studied. Our study included 88 (44%) male patients and 112 (56%) female patients. 164 (82%) of the patients in our study were  $>50$  years of age, and only 5 (2.5%) patients were  $<40$  years of age (Figure 1). This finding suggests that glaucoma usually affects individuals in later decades of life. 137 (68.5%) patients belonged to rural area, whereas 63 (31.5%) patients were from urban area. 117 (58.5%) patients in our study group presented with diminution of vision as main presenting complaint. 31 (15.5%) patients presented with ocular pain, while only 13 (6.5%) patients presented with a headache. 6 (3%) patients presented with colored haloes as their chief complaint (Figure 2). In our study, 67 (33.5%) patients were diagnosed as having POAG while 105 (52.5%) patients were diagnosed to be suffering from PACG. In our study, we had 13 (6.5%) patients of secondary glaucoma, and 9 (4.5%) patients were found to be glaucoma suspects

(Table 1). In our study, there were 42 (62.68%) males out of 67 patients in the POAG group. We also found that 60 (57.14%) out of 105 patients in the PACG group were females. This finding suggests female disposition for the development of PACG (Figure 3). 89 (84.76%) out of 105 patients ( $P < 0.05$ ) of PACG presented with chronic angle closure glaucoma (Table 2). Among the 13 patients of secondary glaucomas, we found a predominance of lens-induced glaucoma (30.76%) and pseudophakic glaucoma (23.07%) (Figure 4).

Hypertension and diabetes have been found to be prominent risk factors associated with glaucoma in various studies. We found 33 (16.5%) patients in our study to be hypertensive. 19 (57.57%) out of these 33 hypertensive patients had PACG while 14 (42.43%) patients had POAG. 28 (14%) patients were found to be suffering from diabetes. 21 (75%) out of 28 diabetics were having POAG whereas 7 (25%) diabetic patients were found to be suffering from PACG. Myopia as an associated risk factor was seen in 16 (8%) patients. 12 (6%) patients were found to be smokers while a history of glaucoma among parents and siblings was found in 5 (2.5%) patients (Figure 5).

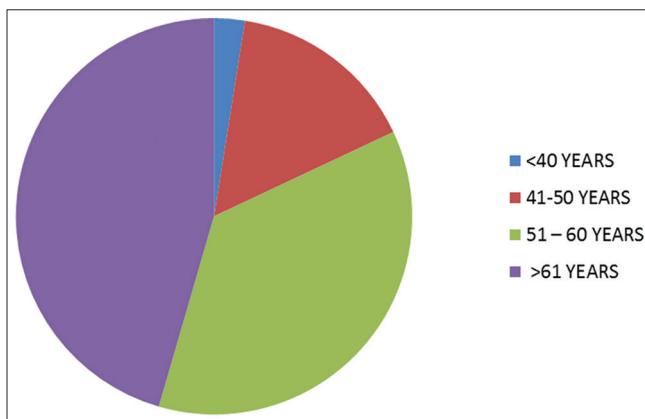


Figure 1: Age distribution in the study group ( $n = 200$  patients)

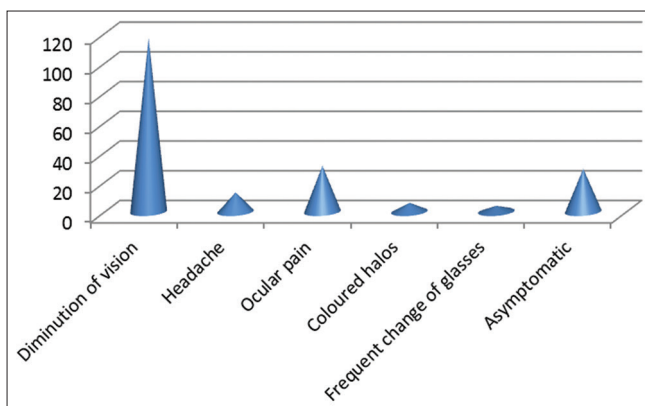


Figure 2: Distribution of the main presenting complaint in the study group ( $n = 200$  patients)

Glaucoma profoundly affects the optic nerve and eventually leads to blindness, if not detected on time and managed properly. In our study, we found that 218 (54.5%) eyes had visual acuity less than 6/60, 141 (35.25%) eyes had visual acuity between 6/60 and 6/18 whereas only 41 eyes (10.25%) had visual acuity of more than 6/18. Major factors which led to a delay in seeking treatment were financial constraints, lack of escort, lack of health care infrastructure in rural areas and belief in local village practices for treating diseases. We found that hypertension, diabetes, smoking, and myopia were important risk factors associated with various types of glaucoma and these risk factors should also be evaluated while managing patients suffering from glaucoma.

## DISCUSSION

Glaucoma with its various subtypes has remained a challenge to ophthalmologists world over. Even today, glaucoma remains a leading cause of irreversible blindness despite tremendous progress in the investigative modalities which help in early detection of glaucoma, of availability of newer and extremely effective anti-glaucoma medications as well as new and innovative modifications in the surgical and laser treatment of glaucoma. Glaucoma

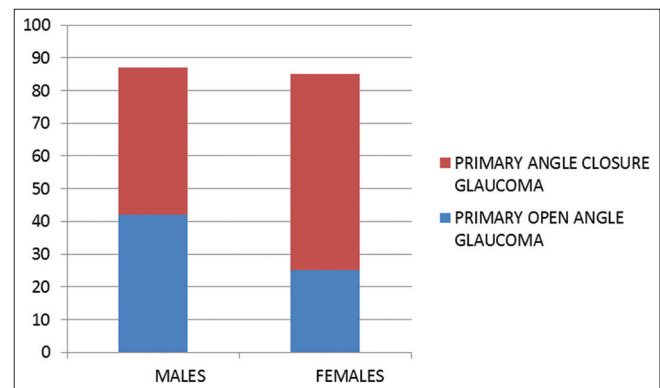


Figure 3: Gender-wise distribution of primary glaucomas in study group ( $n = 172$  patients)

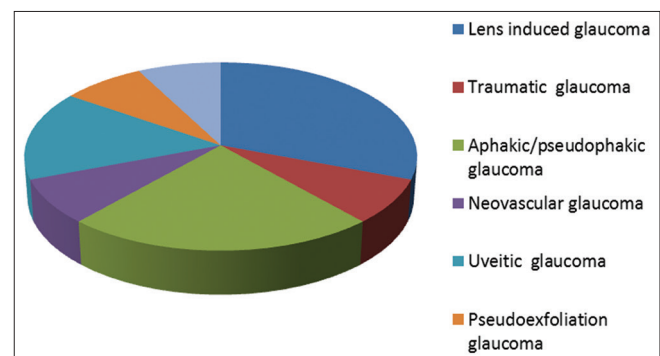


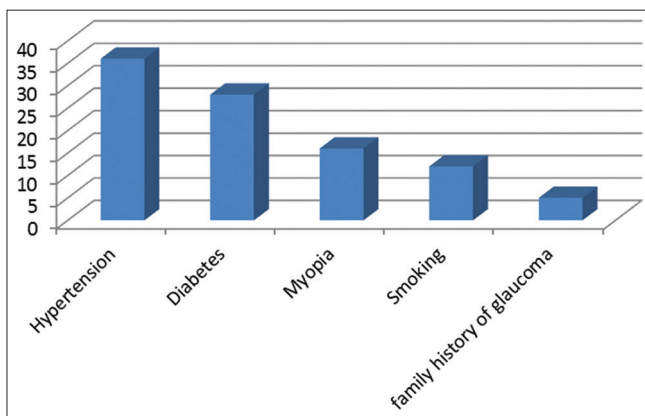
Figure 4: Distribution of secondary glaucoma in the study group ( $n = 13$  patients)

**Table 1: Distribution of glaucoma sub-types in the study group (n=200 patients)**

Type of glaucoma	Number of patients (%)
Congenital glaucoma	2 (1)
Juvenile open angle glaucoma	3 (1.5)
Primary open angle glaucoma	67 (33.5)
Primary angle closure glaucoma	105 (52.5)
Normal tension glaucoma	1 (0.5)
Glaucoma suspect	9 (4.5)
Secondary glaucoma	13 (6.5)
Total	200 (100)

**Table 2: Distribution of primary angle closure glaucoma in the study group (n=105)**

Type of angle closure glaucoma	Number of patients (%)
Acute angle closure glaucoma	13 (12.38)
Intermittent angle closure glaucoma	3 (2.86)
Chronic angle closure glaucoma	89 (84.76)
Total	105 (100)

**Figure 5: Distribution of risk factors associated with glaucoma in study group (n = 200 patients)**

is characterized by myriad clinical manifestations and a large subgroup of patients may be asymptomatic, who are detected during the course of a routine ophthalmological examination. Thus, a clinician needs to have a high index of suspicion for timely detection of glaucoma. Many factors such as the patient's accessibility to medical facilities and compliance to treatment directly affect the overall disease outcome.

Our study included 200 patients, newly diagnosed to be suffering from glaucoma during the study period, or those meeting the criteria for glaucoma suspects. All patients were subjected to a comprehensive glaucoma work-up. 137 (68.5%) patients belonged to rural area whereas 63 (31.5%) patients were residing in urban area. The predominance of rural patients in our study group is probably due to the fact that our institute caters to a large extent to the rural populace in and around Ujjain district as

well as other villages in Malwa region of Madhya Pradesh. Our study included 88 (44%) male patients and 112 (56%) female patients. Results of our study are comparable to the study of Sihota *et al.* who in their study also found a female preponderance amongst glaucoma patients.<sup>10</sup> However, another study by Das *et al.* found a male:female ratio of 1.35:1.<sup>7</sup> This difference in gender distribution can be attributed to regional and ethnic diversity in various study groups. 164 (82%) of the 200 patients in our study were >50 years of age and only 5 (2.5%) patients were <40 years of age. Sharma *et al.* in their study also had the majority of patients >50 years of age.<sup>11</sup> This strongly suggests that glaucoma is primarily a disease of the elderly population. Therefore, it is recommended that all individuals above 40 years of age should undergo ocular screening for glaucoma. This should go a long way in reducing the global burden of glaucoma blindness.

Glaucoma has many presenting features, which vary with the type of glaucoma. In our study, we found that 117 (58.5%) patients presented with diminution of vision as main presenting complaint. 31 (15.5%) patients presented with ocular pain. The result of our study is comparable with the study of Sharma *et al.* who also found that 35.6% patients in their study had decreased vision as the main presenting complaint.<sup>11</sup> Results of both the studies suggest that glaucoma is a leading cause of loss of vision and blindness.

Glaucoma has a wide racial variation. In the Caucasian race, POAG accounts for 75-95% of primary glaucoma.<sup>12</sup> Sihota *et al.* reported that angle-closure glaucoma constituted 45.9% of all adult glaucomas.<sup>10</sup> A study in the Asian population by Martinez *et al.* found PACG in 24.78% patients, while POAG was found in 22.80% patients.<sup>13</sup> In our study, we found that 67 (33.5%) patients were suffering from POAG while 105 (52.5%) patients were diagnosed to be having from PACG. The result of our study correlates with the study of Das *et al.* who in their study found POAG:PACG as 37:63, suggesting PACG to be the most common glaucoma subtype.<sup>7</sup> Results of our study also correlates with study of Al Obeidan *et al.* who in their study found that PACG (46.6%), was most common glaucoma subtype followed by POAG (12.8%) and secondary glaucoma (13%).<sup>14</sup>

In our study, 89 (84.76%) out of 105 patients of PACG presented with chronic angle closure glaucoma (CACG). Das *et al.* found that chronic ACG constituted 64.86% of PACG cases.<sup>7</sup> Sharma *et al.* also found chronic ACG (44%) to be the most common sub-type of PACG.<sup>11</sup> Results of all these studies as well as our study show chronic angle-closure glaucoma to be the most common subtype of angle closure glaucoma.



A number of ocular diseases as well as trauma can lead to secondary glaucoma. In our study, among the 13 patients of secondary glaucoma, we found a predominance of lens-induced glaucoma (30.76%). This was mainly due to a lack of awareness, hesitancy in seeking medical help leading to a cataract backlog among the rural populace of our study group. Congenital glaucoma remains an important cause of blindness in children <5 years. We found 2 (1%) patients to be suffering from congenital glaucoma. Rashid *et al.* also quoted a 1.5% incidence of congenital glaucoma in their study.<sup>15</sup>

Whether diabetes is a significant risk factor for glaucoma is mired in controversy. Two large studies, the Beaver Dam study and Rotterdam study, demonstrated an increased prevalence of POAG among diabetic subjects.<sup>16,17</sup> Another study by Ellis *et al.* failed to conclusively link diabetes mellitus with POAG and OHT.<sup>18</sup> In our study, 28 (14%) patients were found to be suffering from diabetes. 21 (75%) out of 28 diabetics were diagnosed as having POAG whereas 7 diabetic patients were found to be cases of PACG. The higher incidence of glaucoma in diabetic patients could be attributed to the fact that diabetics tend to undergo regular eye check-up and thus have higher chances of detection of asymptomatic glaucoma.

The relationship of systemic blood pressure with glaucoma onset and progression is complex. The Blue Mountain Eye Study, the Erga-Neumarkt Study and the Baltimore Study showed a positive association between systemic hypertension and POAG prevalence.<sup>19-21</sup> On the other hand, the Barbados Eye Study showed that the relative risk of POAG was halved at 4 years in patients of systemic hypertension.<sup>22</sup> We found that 33 (16.5%) patients in our study group were suffering from hypertension. 19 (57.57%) out of 33 hypertensive patients were cases of PACG, while 14 (42.43%) patients were having POAG. It has been postulated that glaucoma occurs, at least to some extent, due to decreased optic nerve head perfusion. Systemic hypertension causes increased blood flow to optic nerve head before small vessel damage occurs.<sup>23</sup> But later on, prolonged systemic hypertension causes microvascular damage and thereby impaired blood flow and subsequent neuronal damage resulting in glaucoma. The result of our study shows that hypertension and diabetes are significant risk factors associated with glaucoma.

Myopia, as an associated risk factor, was seen in 16 (8%) patients in our study. The Blue Mountain Eye Study found that myopic subjects had an increased risk of glaucoma, which was independent of other glaucoma risk factors and IOP.<sup>24</sup> The role of cigarette smoking as a risk factor for POAG remains controversial. Klein *et al.* in their study found that there was no difference in the frequency of

glaucoma by cigarette smoking status.<sup>25</sup> However, the meta-analysis results of a study by Bonovas *et al.* suggested that current smokers are at a significantly increased risk of developing POAG.<sup>26</sup> 12 (6%) patients were found to be smokers in our study suggesting smoking to be one of the risk factors associated with glaucoma. Glaucoma is known to have a genetic predisposition. This was also seen in our study as a positive history of glaucoma among parents and siblings was found in 5 (2.5%) patients. However, a study with a larger sample size needs to be undertaken to further evaluate the relative influence of each of these factors on glaucoma causation and progression.

Glaucoma, if not timely detected and treated, leads to profound and permanent loss of vision. Grant *et al.* in their study suggested that there are three potential reasons for glaucoma blindness: One-third patients remain undiagnosed, one-third patients are improperly treated, and remaining one-third of patients show non-compliance to therapy.<sup>26</sup> In our study, we found that 218 (54.5%) eyes had visual acuity <6/60. This high incidence of poor vision at the time of presentation in our study group was mainly due to lack of awareness and lack of medical facilities in far-flung rural areas.

## CONCLUSION

Glaucoma is primarily a disease of the elderly, as most patients in our study belonged to the age group of >50 years. Primary angle-closure glaucoma is the most common subtype of glaucoma detected in our study. Glaucoma, if left untreated, leads to irreversible blindness. This finding was corroborated by our study. Hypertension, diabetes, myopia, and smoking were the associated risk factors of glaucoma in our study. Our study recommends timely diagnosis and appropriate management of glaucoma to decrease the burden of glaucoma blindness.

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# Anatomical Variation of Tentorial Hiatus in Indian Population

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## Abstract

**Introduction:** Tentorial hiatus anatomy is varied from individual to individual. Its anatomical variation influences the degree of brainstem distortion in head injury.

**Materials and Methods:** Anatomical variation of tentorial hiatus is a cadaveric study. Cases excluded from the study are head injury, intracranial pathology, and accidental distortion during dissection. In this study, human cadavers are opened in a standard manner within 12-48 h after death.

**Results:** In this study, the relationships among the tentorial notch, mesencephalon, and oculomotor nerves were examined in 100 autopsy cases. 100 statistical data were obtained for all variables. The notch length is grouped into short, medium, long; maximum notch width is grouped into narrow, medium, wide by quartile distribution technique. These data are interpolated into a matrix. The tentorial notch is classified from the matrix.

**Conclusion:** Cephalic index is included in this study and no variable correlated with the cephalic index. Age and sex have no influence over the tentorial hiatus. Anatomical variation is implicated in, a variation of clinical presentation in tentorial herniation.

**Key words:** Anatomical Variation, Tentorial Herniation, Tentorial Hiatus, Tentorium Classification, Trans Tentorial Approach

## INTRODUCTION

Tentorial hiatus anatomy is varied from individual to individual its anatomical variation influences the degree of brainstem distortion in head injury.<sup>1-4</sup>

The aim of this study is to analyze the variation in the anatomy of tentorium in our population, this study helps to obtain baseline measurements of notch length (NL), and notch width in Indian population and analyze the correlation of NL to the size of the skull. This knowledge will help us in various neurosurgical procedures in the skull base. Tentorial hiatus can be easily measured by magnetic resonance imaging (MRI) and pre-operative analysis of the hiatus is useful in the skull base neurosurgical procedures.<sup>5-10</sup>

## MATERIALS AND METHODS

Anatomical variation of tentorial hiatus is a cadaveric study. Cases excluded from the study are head injury, intracranial pathology, and accidental distortion during dissection.

In this study, human cadavers are opened in a standard manner within 12-48 h after death. Skullcap is opened in a circular manner. The dura mater over the vertex and the posterior falx are kept intact. The frontal lobes are lifted and the anterior falx is cut. The diencephalon is cut axially above the level of the optic chiasm, through the third ventricle to the apex of the tentorial notch. The cerebral hemispheres are removed, leaving intact a small portion of the diencephalon, the posterior portion of the falx, and the tentorium. The optic nerves are cut proximal to the sella turcica. The optic chiasm is lifted and the mesencephalon cut at the level of the interpeduncular fossa in the axial plane, extending posteriorly. The vein of Galen is cut, the pineal gland removed, and the arachnoid dissected, allowing for a clear view of cerebellar anatomy within the tentorial notch. The field is irrigated to remove fresh blood. Measurements are taken with the help of vernier caliper.

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The following measurements are taken to analyze the morphometric variation of tentorial hiatus in Indian population.

1. Anterior Notch width, the width of the tentorial hiatus in the axial plane through the posterior aspect of the dorsum sellae.
2. Maximum notch width (MNW), the maximum width of the notch in the axial plane.
3. NL, the distance between the superoposterior edge of the dorsum sellae in the median plane and the apex of the notch.
4. Posterior tentorial length, the shortest distance between the apex of the notch and the most anterior part of the confluence of sinuses.
5. Apicotectal distance, the distance from the tectum in the median plane to a perpendicular line dropped from the notch apex to the cerebellum.
6. Interpedunculoclival distance, the distance from the interpeduncular fossa to the superoposterior edge of the dorsum sellae.
7. Cephalic index.

The data obtained from the above measurements are analyzed to classify the tentorial hiatus.

## RESULTS AND DISCUSSION

Statistical analysis is performed using SPSS software release 16. Quartile distribution is used to analyze the data. Frequency distribution and parametric and non-parametric correlation among data are analyzed. The correlation which is significant at the level of is worth to mention. The correlation among variables is considered to be significant when the  $P < 0.01$  and if it is  $<0.05$ , more significant.

In this study, the relationships among the tentorial notch, mesencephalon, and oculomotor nerves were examined in 100 autopsy cases. 100 statistical data were obtained for all variables.

The NL is grouped into short, medium, long; MNW is grouped into narrow, medium, wide by quartile distribution technique. These data are interpolated into a matrix. The tentorial notch is classified from the matrix.

### NL

NL less than 48.6 is classified as short.

NL more than 55.9 mm is classified as long.

### MNW

MNW less than 27.4 mm is classified as narrow.

MNW more than 31 mm is classified as wide.

The tentorial notch is categorized into six major groups by applying quartile analysis to the NL and MNW over a continuum of values. These groups were classified as long (27% of specimens), short (26% of specimens), and midrange (47% of specimens) for the NL, and wide (26% of specimens), narrow (27% of specimens), and midrange (47% of specimens) for the MNW.

### Types of Tentorial Incisura

These groups are combined into matrix. This matrix allowed us, to classify the tentorial notch into nine types. Using NL and MNW as variables tentorial notch is categorized as:

Short and wide	6%
Short and medium	10%
Short and narrow	10%
Medium wide	10%
Classical	25%
Medium narrow	12%
Long wide	10%
Long medium	12%
Long and narrow	5%

### Pearson Correlations between the Variables are Analyzed

In this study, MNW positively correlates with the NL. Anterior notch width positively correlates with the MNW. The cephalic index does not correlate with any of the variable studied. There is no significant correlation between the NL and the posterior tentorial length. Apicotectal distance, NL, and the interpedunculoclival distance are positively correlated. There is no significant correlation between the apicotectal distance, interpedunculoclival distance and posterior tentorial length (Tables 1 and 2, Figure 1).

Mean age is 38.7 with standard deviation of 17.13 range from 1 to 77.

Mean anterior notch width is 16.8 mm with standard deviation of 3.51 ranges from 10 to 30.

Mean max notch width is 29 mm with standard deviation of 3.18 ranges from 21.1 to 38 mm.

Mean NL is 52.2 mm with standard deviation of 5.2 range from 36.7 to 66 mm.

Mean post tentorial length is 53.7 mm with standard deviation of 6.88 ranges from 25.8 to 70.3 mm.

Mean Apicotectal distance is 17.9 mm with standard deviation of 4.78 ranges from 4.2 to 30.6 mm.

Mean Interpedunculoclival distance is 16.2 mm with standard deviation of 3.37 range from 7.1 to 24.2 mm.

Mean cephalic index is 81.8 with standard deviation of 8.10 ranges from 67.7 to 133.4.

**Table 1: Statistical Analysis of various distances and cephalic Index**

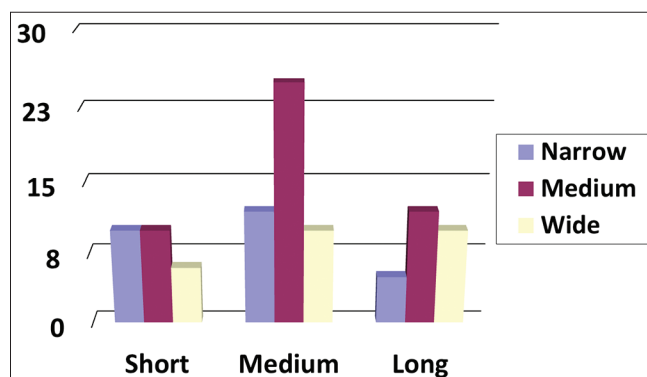
Statistics	Age	Anterior notch width	Max notch width	Notch length	Post tentorial length	AT	ICD	Cephalic index
Mean	38.77	16.8840	29.0320	52.2490	53.7580	17.94	16.26	81.8856
Standard error of mean	1.722	0.35189	0.31895	0.52779	0.68848	0.4783	0.3379	0.81056
Standard deviation	1.713	3.51894	3.18950	5.27788	6.88484	4.783	3.379	8.10564
Minimum	1.00	10.90	21.10	36.70	25.80	4.20	7.10	67.74
Maximum	77.00	30.00	38.00	66.00	70.30	30.60	24.20	133.45
Percentiles								
25	25.00	14.4500	27.4000	48.6000	50.3750	15.50	13.90	77.8492
50	38.00	16.1500	29.2500	52.2000	53.8500	17.80	15.95	81.0692
75	52.00	18.2000	30.9750	55.9750	58.5000	21.17	18.60	84.1806

AT: Apicotectal distance, ICD: Interpedunculo clival distance

**Table 2: Correlations**

Parameters	Age	Anterior notch width	Max notch width	Notch length	Post tentorial length	AT	ICD	Cephalic index
Age								
Pearson correlate	1	-0.032	0.299**	0.061	0.225*	0.047	0.019	-0.173
Sig. (2-tailed)		0.750	0.003	0.550	0.025	0.643	0.855	0.087
Anterior notch width								
Pearson correlate	-0.032	1	0.282**	0.028	0.071	-0.107	-0.057	0.035
Sig. (2-tailed)	0.750		0.004	0.782	0.480	0.289	0.571	0.726
Max notch width								
Pearson correlate	0.299**	0.282**	1	0.248*	0.263**	0.143	0.194	-0.023
Sig. (2-tailed)	0.003	0.004		0.013	0.008	0.156	0.053	0.821
Notch length								
Pearson correlate	0.061	0.028	0.248*	1	0.122	0.712**	0.388**	0.134
Sig. (2-tailed)	0.550	0.782	0.013		0.228	0.000	0.000	0.185
Post tentorial length								
Pearson correlate	0.225*	0.071	0.263**	0.122	1	0.048	0.074	-0.100
Sig. (2-tailed)	0.025	0.480	0.008	0.228		0.637	0.463	0.321
AT								
Pearson correlate	0.047	-0.107	0.143	0.712**	0.048	1	0.204*	0.079
ICD								
Pearson correlate	0.019	-0.057	0.194	0.388**	0.074	0.204*	1	0.052
Sig. (2-tailed)	0.855	0.571	0.053	0.000	0.463	0.041		0.607
Cephalic index								
Pearson correlate	-0.173	0.035	-0.023	0.134	-0.100	0.079	0.052	1
Sig. (2-tailed)	0.087	0.726	0.821	0.185	0.321	0.436	0.607	

AT: Apicotectal distance, ICD: Interpedunculo clival distance

**Figure 1: Classification of tentorial hiatus**

## CONCLUSION

NL, MNW, interpeduncular, apico tectal, and posterior tentorial distances have been measured in Indian population.

Mean anterior notch width is 16.8 mm ranges from 10.9 to 30 mm.

Mean max notch width is 29 mm ranges from 21.1 to 38 mm.

Mean NL is 52.2 mm range from 36.7 to 66 mm.

Mean post tentorial length is 53.7 mm ranges from 25.8 to 70.3 mm.

Mean apico tectal length is 17.9 mm ranges from 4.2 to 30.6 mm.

Mean interpedunculo clival distance is 16.2 mm range from 7.10 to 24.20 mm.

Mean cephalic index is 81.8 ranges from 67.7 to 133.4.

Cephalic index is included in this study and no variable correlated with the cephalic index.



Age and sex have no influence over the tentorial hiatus.

Anatomical variation is implicated in, variation of clinical presentation in tentorial herniation.

Anatomical variation in pre-operative live patients measured by MRI is useful in neurosurgical decision-making.

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# Clinico-epidemiological Study of Patients with Melasma in a Tertiary Care Hospital - A Prospective Study

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## Abstract

**Background:** Melasma is a common pigmented disorder with symmetrically occurring brownish patches, most commonly in sun-exposed skin.

**Aims:** This study aimed to establish the epidemiological pattern of melasma in patients attending our hospital and to study the variation in demographics, etiological factors, and clinical features in melasma occurring in males and females.

**Materials and Methods:** This study was conducted over a period of 1 year and a total of 100 patients were enrolled.

**Results:** The mean age of 100 patients with melasma was 40.53 years, with a female-to-male ratio of 4:1. Melasma had a peak incidence of onset in the third decade with mean age of onset at 31.22 years. Nearly 35% of the study population gave a definite exacerbation due to sun exposure. Among the 80 female patients, 23 reported onset of melasma during pregnancy and 11 reported exacerbation with oral contraceptive. There appears to be a strong genetic predisposition evident by the increased incidence of familial cases of melasma in about 38% of patients. Malar area involvement was the most common pattern seen in 61% of patients. In Wood's lamp examination, the epidermal type was common, as seen in 47% of patients.

**Conclusion:** Melasma is a very common dermatological condition with unknown etiology. There is a wide variation in demography, clinical picture, and etiological factors. Both environmental and genetic factors play a role in the precipitation and exacerbation of melasma.

**Key words:** Epidemiology, Melasma, Sun exposure

## INTRODUCTION

Melasma is an acquired hyperpigmentation disorder, attributed as a cause of facial melanosis. It is characterized by hyperpigmented or brownish macules distributed bilaterally symmetrically mainly in sun-exposed areas. It usually affects people with Fitzpatrick skin Types III and IV. It is associated with exposure to sunlight, pregnancy,

and exogenous hormones.<sup>1</sup> Women are most commonly affected. It is derived from the greek word "melas" meaning black. It occurs mostly on the face, occasionally on the neck, and rarely on the forearms. The term, "chloasma," is derived from greek term "chloazein" meaning "to be green" which describes melasma developing in pregnancy. Melasma has been described in olden literatures like reports of Hippocrates (470-360 BC) where they documented hyperpigmented facial lesions exacerbated by heat, sunlight. Doctrine of Morbis Cutaneis written by Joseph Plenck described melasma under the term Ephelis.<sup>2</sup> Prevalence of melasma is different from region to region since it varies with skin type, intensity of sun exposure, and also ethnicity. It is one of the most common causes of facial melanosis in Indian population.<sup>3</sup> According to the distribution of lesions, three clinical patterns of melasma are recognized.

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The centro-facial pattern involves the forehead, nose, upper lip, and chin. The malar pattern involves cheeks and nose. The mandibular pattern is melasma occurring along the ramus of mandible. With the help of Wood's light examination, melasma is classified into four major types - epidermal, dermal, mixed, and indeterminate.<sup>4</sup> Dermoscopy will show diffuse reticular pigmentation with sparing of follicular openings. Melasma adversely affects the quality of life of patients as most melasma lesions occur on the face. Melasma Quality of Life scale is used to assess the impact of melasma upon the emotional state of patient, how melasma affects the social relationship and daily activities.<sup>5,6</sup> Melasma Area Severity Index score was proposed by Kimbrough-Green *et al.*, in 1994, to quantify severity of melasma occurring on the face.<sup>7</sup> It takes into account the hyperpigmentation, area affected, and homogeneity of pigmentation. Forehead, right cheek, left cheek, and chin are separately calculated.<sup>8</sup>

### Aim

This study aimed to establish the epidemiological pattern of melasma in patients attending our hospital and to study the variation in demographics, etiological factors, and clinical features in melasma occurring in males and females.

## MATERIALS AND METHODS

This prospective observational study was conducted in the Dermatology Department at Madras Medical College. 100 patients with a clinical diagnosis of melasma were enrolled in the study after obtaining informed consent. Ethical Committee's approval was obtained. Pregnant patients and patients on treatment were excluded from the present study. Data regarding various demographic features such as present age, age of onset of melasma, gender, total duration of disease as well as socio economic status, occupational history and family history were noted. Data on various predisposing and precipitating factors such as sun exposure, cosmetics, pregnancy, endocrine disorders, ovarian tumor, and sunscreen usage were enquired. After clinical examination of patients, they were categorized into centrofacial, malar, or mandibular depending on the distributions of lesions. Wood's lamp examination was carried out to identify the histological pattern.

## RESULTS

The study population comprised 100 patients diagnosed as a case of melasma. There were 80 females and 20 males (age range of 12-65 years), with a mean age of 40.53 years. Bulk of our study population comprised females, with a female-to-male ratio of 4:1. The mean age of onset was

31.22 years, presenting mostly after the third decade of life. Most of them sought medical treatment only 6.43 years after the appearance of their melasma. Most of the patients were from lower socioeconomic status accounting for 59% of the study population.

A definite family history was present in 33% of the patients. Out of the total 100 patients, exacerbation after sun exposure was evident in 22 patients, but the remaining 78 patients did not notice any exacerbation of their disease. About 80 female patients were enrolled in this study, of which 23 of them reported that their disease started during pregnancy and 15 patients explained that their disease got exacerbated during pregnancy, accounting for 28.7% and 18.7%, respectively. Oral contraceptive pills (OCPs) intake was in only 13.75% of female patients (Table 1).

Use of cosmetics was found in a significant number of patients. Nearly 18% of females and 3% of males gave a history of use of cosmetics at least 5 days in a week. Enquiry in association with any autoimmune disease led to the finding that 10% of the study population was on treatment for hypothyroidism.

On clinical examination, 61% of patients showed a malar type of distribution of lesion while centrofacial type was noticed in 30% and mandibular type in 9% of patients. With the help of Wood's lamp examination, patients were categorized into 4 types, of which 47% of the patients showed an epidermal pattern of pigmentation, and in 21% of cases and 30 cases, the patterns were dermal and mixed type, respectively. Nearly 2% of the patients showed an indeterminate pattern (Table 2).

**Table 1: Distribution of various characteristics of the study patients**

Characteristics	Females	Males	Total
Demographic distribution			
Number	80	20	100
Mean age	38.27	42.8	40.53
Mean duration	5.67	7.19	6.43
Mean age of onset	28.5	32.95	31.22
Socioeconomic status			
High class	4	1	5
Middle class	27	9	36
Low class	49	10	59
Genetic factors			
Family history	27	5	38
Endocrinological problems	9	1	10
Hormonal factors			
OCP/HRT use	11	-	11
Pregnancy exacerbation	15	-	15
External factors			
Sun exacerbation	19	3	22
Use of cosmetics	18	3	21
Use of sunscreen	5	1	6

OCP: Oral contraceptive pill

**Table 2: Distribution of clinical examination of the study patients**

Examination	Females	Males	Total
Distribution of melasma			
Malar	52	9	61
Centrofacial	21	9	30
Mandibular	7	2	9
Wood's lamp examination			
Epidermal	39	8	47
Dermal	16	5	21
Mixed	23	7	30
Indeterminate	2		2

## DISCUSSION

Melasma is an acquired, localized, usually symmetrical hyperpigmentation of the face, especially the forehead, malar areas, upper lip, and chin, occurring in women, particularly Fitzpatrick skin Types III and IV.<sup>1</sup> Men represent approximately 10% of the cases. In a study conducted in Brazil, the average prevalence of melasma in different parts of countries varied from 5.9% to 9.1%.<sup>9</sup> A study by Walker *et al.* in Nepal showed that melasma was the most commonly reported pigmentary dermatosis.<sup>10</sup> Melasma prevalence study among paddy field workers in India showed a prevalence of 41% by Sheno *et al.*<sup>11</sup> The average age of patients with melasma was 40.53 years in our study compared to  $37.2 \pm 9.3$  years by Achar and Rathi<sup>12</sup> and 33.45 years by KrupaShankar *et al.*<sup>13</sup> from India, and from Singapore by Goh and Dlova, it was 42.3 years.<sup>14</sup> Most patients (59%) in our study population belong to lower socioeconomic status. Melasma occurs more commonly with women. Our study showed a female-to-male ratio of 4:1, concordant with studies by Achar and Rathi<sup>12</sup> (4:1) and KrupaShankar *et al.*<sup>13</sup> (4:1). Hexsel *et al.* from Brazil and Sivayathorn from Malaysia reported higher female-to-male ratio than our study of about 39:1 and 6:1, respectively.<sup>15,16</sup> In our study, we found that about 80% of women and 20% of men have melasma. Most studies conducted in India showed almost similar results. Studies by Achar and Rathi,<sup>12</sup> KrupaShankar *et al.*,<sup>13</sup> and Sarkar *et al.*<sup>17</sup> showed 24.4%, 19.9%, and 25.8% involvement of Indian males with melasma, respectively. Pichardo *et al.* noticed a higher prevalence of melasma in Latino men up to 36%.<sup>18</sup> The mean age of onset in our study was found to be 31.22 years similar to 29.9 years reported by Achar and Rathi.<sup>12</sup> An average age of onset of melasma of 34.1 years was reported by KrupaShankar *et al.*<sup>13</sup> and 38 years by Halder *et al.* which was later than the onset of melasma noticed in our study.<sup>19</sup> Most of the patients were of Fitzpatrick skin Types III or IV. Evidence for genetic factors is the occurrence of familial cases. Nearly 38% of the study population had a positive family history, correlating with an earlier study by Resnik<sup>20</sup> and Vazquez *et al.*,<sup>21</sup> in which it varied from 20% to 70%. Achar and Rathi<sup>12</sup> reported a

familial tendency of 33.3% and KrupaShankar *et al.* reported it to be 31.1%.<sup>13</sup> Several factors have been attributed in the etiopathogenesis, notably ultraviolet light or sun exposure, hormones including oral contraceptives and hormone replacement therapy, and pregnancy. Almost 22% of our patients reported sun exposure as an aggravating factor. This is in contrast to Pathak's report,<sup>22</sup> which suggests that sunlight exacerbates melasma in all the patients, 72% as reported by Sivayathorn,<sup>16</sup> and an Indian study by Achar and Rathi<sup>12</sup> showed 55.1%. Only 6% of the study population was found to use sunscreens. Melasma is rarely reported before the onset of puberty and hormonal influence is suggested by onset or exacerbation during pregnancy.<sup>23</sup> In our study, 28.7% of the total female patients gave a history of onset during pregnancy and 18.7% of females noted pregnancy as an aggravating factor. Nearly 13.75% of females in our study population were on OCPs which is lower than those reported by Bandyopadhyay.<sup>24</sup> Other studies have reported a similar lower incidence of melasma in relation with either pregnancy or oral contraceptives. In a study by KrupaShankar, the use of oral contraceptives ranged from 2% to 23%.<sup>13</sup> Wu *et al.* and Resnik reported 8% and 34% of female patients, respectively, on OCP developing melasma.<sup>20,25</sup> Another significant association was the presence of hypothyroidism and melasma in about 10% of cases. In Achar and Rathi's study of melasma, 6% of people were suffering from thyroid disorders whereas KrupaShankar *et al.*'s study reported 11%.<sup>12,13</sup> Almost 21% of patients used cosmetics on regular basis for at least 5 days/week, correlating with the study by Grim *et al.*<sup>23</sup> There are reports of melasma developing in patients on regular cosmetic use and those who take photo toxic as well as photosensitizing drugs.<sup>26</sup> Achar and Rathi<sup>12</sup> in their study reported that increased sun, pregnancy, OCP, and cosmetic use for almost 5 times in a week can exacerbate melasma. According to the area of distribution, three main clinical patterns are seen. In the present study, malar area was most commonly involved, consistent with other studies from India, Goh and Dlova from Singapore, and Tamega from Brazil.<sup>12,14,27-29</sup> Centrofacial pattern is common in northern and eastern parts of India. This variation of results might be due to environmental or regional differences.<sup>13</sup> With the help of Wood's lamp examination, melasma is classified into four histological types depending on the depth of melanin deposition. Epidermal type where pigmentation is accentuated was found to be the most common type in which increased melanin is present in all the layers of epidermis. Dermal type has many melanophages throughout dermis and the pigmentation is not intensified. In mixed type, pigmentation is more apparent in some areas, with no change in other areas. Indeterminate type is described in individuals with skin Type VI where pigment is apparent with Wood's light examination.



## CONCLUSION

Even though the exact cause of melasma could not be identified by our study, an epidemiological view of melasma was made in our study. Among the various etiological or predisposing factors, long-term sun exposure, pregnancy, and intake of contraceptive pills definitely play a role in exacerbation and sometimes onset of melasma. Genetic factors also seem to play a role, evidence for which is the increased incidence of family history, increased incidence in certain races, and association with autoimmune disease, mainly thyroid dysfunction. Thus, melasma is a common facial melanosis with genetic predisposition and multiple environmental triggers. Sun protection definitely has a role in preventing further damage. Quality of life assessment and counseling the patient is an important aspect in the treatment of melasma.

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# Comparative Evaluation of Impact of Dental Caries, Malocclusion and Developmental Defects on Preschooler's Quality of Life

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## Abstract

**Introduction:** From the literature, it is evident that carious lesions can compromise children's quality of life. Malocclusion and developmental defects of enamel (DDE) can be considered as a public health problem due to its high prevalence. Studies investigating the impact of malocclusion and DDE on the quality of life of preschool children have shown conflicting results. It is necessary to determine the occurrence of oral problems as early as possible to diminish the impact on children's quality of life.

**Purpose:** The purpose of this study is to compare the impact of dental caries and other oral diseases such as malocclusion and developmental defects on preschooler's quality of life.

**Methods:** A total of 300 children aged 2-6 years were included in the study from different schools of South Bangalore. The parents were interviewed to answer a questionnaire on socioeconomic status and early childhood oral health impact scale (ECOHIS). Oral examination was done by a calibrated dentist under school environment.

**Results:** The dental caries, malocclusion and DDE were more likely to have a negative impact on the oral health-related quality of life (OHRQoL) Brazilian version of the ECOHIS scores.

**Conclusion:** The parent's perception of their child's oral health is strongly influenced by the presence of dental caries, malocclusion and DDE. Patient-oriented outcomes like OHRQoL will enhance the understanding of the relationship between oral and general health which will help researchers to improve the quality of life of preschool children.

**Key words:** Dental caries, Developmental defects, Malocclusion, Preschoolers, Quality of life

## INTRODUCTION

Oral diseases can negatively influence the quality of life of children and parents, causing harm in the development of routine activities, child development, and their well-being. The impact of oral health on one's quality of life is termed as oral health-related quality of life (OHRQoL). During childhood, oral changes may affect the health and quality of a child's systemic life. The most prevalent oral disease in primary dentition is dental caries which affects 50% of

preschooler.<sup>1</sup> It causes a negative impact on OHRQoL, and the most frequent consequences are impaired chewing and speech, sleep disturbances, irritability, and pain.

Malocclusion is another dental disorder in primary teeth and is considered a public health problem due to its high prevalence.<sup>2</sup> It is observed that any deviation from the "norm" can stigmatize the person and make him less acceptable socially.<sup>3</sup> Dissatisfaction with missing teeth, malalignment of teeth and peer-based teasing due to the appearance of the teeth are the factors that influence the child. According to some cross-sectional studies, malocclusion is not associated with an adverse impact on the quality of life of preschool children and their families.<sup>2</sup>

Dental abnormalities such as developmental defects of enamel (DDE) may have a negative effect on both esthetic and psychosocial factors and may affect children's

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OHRQoL. DDE are responsible for dentofacial anomalies, dental sensitivity as well as predisposition to caries. The prevalence of DDE in children ranges from 24.4% to 81.3%.<sup>4</sup> In relation to preschool children there are scarce investigation into the functional, esthetic and psychosocial implications of enamel defects, even though this abnormality is common in the primary dentition.

This study was conducted to evaluate the impact of dental caries, malocclusion and DDE on the quality of life of preschoolers.

## MATERIALS AND METHODS

The sample consisting of 300 children of both genders aged 2-6 years from public schools in South Bengaluru were included in the study. Signed written informed consent was taken from the school authorities and parents of the children. Parents answered the Brazilian version of the early childhood oral health impact scale (B-ECOHIS) and a questionnaire on socioeconomic indicators. OHRQoL instrument: The Brazilian version (B-ECOHIS) consists of 13 questions divided into a child impact section and a family impact section. The child impact section had four subscales: Child symptoms, child function, child psychology, and child self-image/social interaction. The family impact section has two subscales: Parental distress and family function. The response categories for the B-ECOHIS are coded as: 0 = Never, 1 = Hardly ever, 2 = Occasionally, 3 = Often, 4 = Very often, and 5 = Do not know.

The clinical examinations were performed by a calibrated dentist who was blind to the questionnaire in the school environment, using sterile mouth mirrors and under natural lighting. The dental caries were diagnosed based on the World Health Organization criteria (WHO 1997). Dental caries were dichotomized as absent or present. Malocclusion was diagnosed according to the presence or absence of at least one of the following alterations: Anterior open bite, and cross bite, crowding. DDE were classified according to the DDE Index.<sup>5</sup> The three types of DDE (diffuse opacity, demarcated opacity, and enamel hypoplasia) were evaluated. The recorded data were subjected to statistical analysis.

## RESULTS

This study was conducted to assess the impact of dental caries, malocclusion and DDE on preschoolers quality of life. The study consists of 300 healthy children from public schools in South Bengaluru; out of 300 children, 9 children were of 2 years (3%), 69 were 3 years (23%),

125 were of 4 years (41.6%), 89 were of 5 years (29.6%), and 8 were of 6 years (2.6%) (Table 1). The children were divided into two groups based on the presence or absence of oral diseases (dental caries, malocclusion and DDE). It was observed that 58.8% children had dental caries, 43.2% children had malocclusion and 23.6% showed the presence of DDE (Table 2).

The clinical conditions associated with the total ECOHIS, the child impact scale, and family impact scale was carried out. A significant association was observed among the total ECOHIS, the child impact section, the family impact section and some independent variables, such as child's age and dental caries, DDE, and malocclusion ( $P < 0.05$ ) (Table 3). The final multivariate adjusted models showed that children with dental caries had 0.665 and 0.137 times more likelihood of negatively impacting the child and family sections, respectively ( $P < 0.05$ ). There was no significant association between age and negative impact in the child section. The DDE and malocclusion had a negative impact on child and it was 1.622 times and 1.545 times, respectively (Table 4). The dental caries, malocclusion and DDE were more likely to have a negative impact on the OHRQoL B-ECOHIS scores.

## DISCUSSION

Oral health was always assessed based on clinical indicators in the previous years. This approach was criticized because they do not document the full impact

**Table 1: Age distribution of the children**

Age in years	Frequency (%)
2	9 (3.0)
3	69 (23)
4	125 (41.6)
5	89 (29.6)
6	8 (2.6)
Total	300 (100.0)

**Table 2: Oral health characteristics of the children**

Oral health characteristics	Frequency (%)
Dental caries	
Absent	124 (41.2)
Present	177 (58.8)
Total	300 (100)
Malocclusion	
Absent	170 (56.8)
Present	130 (43.2)
Total	300 (100)
DDE	
Absent	230 (76.4)
Present	70 (23.6)
Total	300 (100)

DDE: Developmental defects of enamel

**Table 3: Association between clinical characteristics and scores of B-ECOHIS**

Variables	Child impact section			Family impact section			Total B-ECOHIS		
	No, n	Yes, n	P	No, n	Yes, n	P	No, n	Yes, n	P
Dental caries									
Absent	124	0	0.00	123	1	0.00	124	0	0.00
Present	89	88		0	177		89	88	
Malocclusion									
Absent	83	88	0.00	51	120	0.00	83	88	0.00
Present	130	0		72	58		130	0	
DDE									0.00
Absent	142	88	0.00	88	142	0.00	142	88	
Present	71	0		35	36		71	0	
Age (years)									
2	9	0	0.00	9	0	0.00	9	0	0.00
3	67	2		67	2		67	2	
4	78	47		78	47		78	47	
5	55	34		55	34		55	34	
6	4	4		4	4		4	4	

B-ECOHIS: Brazilian version of the early childhood oral health impact scale, DDE: Developmental defects of enamel

**Table 4: Univariate and multivariate models of clinical condition**

Variables	Child impact section*			Family impact section*			Total B-ECOHIS		
	PR	95% CI	P	PR	95% CI	P	PR	95% CI	P
Age (years)									
2	0.930	0.765-1.132	0.470	0.911	0.763-1.087	0.301	0.930	0.765-1.132	0.470
3	0.930	0.760-1.138	0.481	0.939	0.828-1.064	0.323	0.930	0.760-1.138	0.481
4	0.908	0.743-1.109	0.343	1.007	0.993-1.021	0.322	0.908	0.743-1.109	0.343
5	0.948	0.774-1.162	0.607	0.997	0.989-1.004	0.386	0.948	0.774-1.162	0.607
6	1			1			1		
Dental caries									
Absent	0.665	0.627-0.706	0.000	0.137	0.115-0.165	0.000	0.665	0.627-0.706	0.000
Present	1			1			1		
Malocclusion									
Absent	1.622	1.550-1.698	0.000	0.995	0.986-1.005	0.342	1.622	1.550-1.698	0.000
Present	1			1			1		
DDE									
Absent	1.545	1.455-1.640	0.000	1.009	0.992-1.027	0.313	1.545	1.455-1.640	0.000
Present	1			1			1		

B-ECOHIS: Brazilian version of the early childhood oral health impact scale, DDE: Developmental defects of enamel, CI: Confidence interval, PR: Prevalence ratio. \* $P < 0.05$ : Significant

of the oral disease. Thus, OHRQoL measures have been introduced in health-care research.<sup>6</sup> This approach helps the health-care professional to evaluate the treatment efficacy and quality of care from the patient perspective. Unhealthy lifestyle, poor nutrition, and bad oral hygiene may lead to carious lesions in primary dentition as soon as they erupt into oral cavity.<sup>7</sup> Oral diseases during early stages of life can have a negative impact on preschoolers quality of life.<sup>8</sup> Only a few studies have been performed analyzing the negative impact of oral diseases on OHRQoL of preschool children.

Thus this study was conducted to evaluate the impact of dental caries, malocclusion and DDE on OHRQoL of 2-6 years of age and their families. A large number of children had a negative impact on their quality of life, according to parent's perception. Oral/dental pain, difficulty drinking hot or cold beverages and difficulty

eating were the most frequently answered items in the B-ECOHIS.

Results of this study showed dental caries were associated with the negative impact on quality of life for both children and family. Children with dental caries had 0.665 and 0.137 times more likelihood of negatively impacting the child and family sections, respectively ( $P < 0.05$ ). This result is consistent with other studies on preschool children reported by Bönecker *et al.*<sup>7</sup> and Ramos-Jorge *et al.*<sup>9</sup> in which they stated that dental caries were associated with a negative impact on the quality of life of preschoolers and their parents/caregivers. Tooth decay causes functional changes, such as difficulty in chewing, speech impairment, and schooling factors, such as preschool absenteeism. In addition, children with carious lesions may also display impaired psychological aspects, difficulty sleeping and irritability. These changes



result in a negative impact on the quality of children's lives, showing the importance of monitoring the oral health of preschoolers.

Malocclusion is another common occurrence in childhood. It has got both functional and esthetic effects which can, in turn, affect the quality of life. In this study, malocclusion is associated with negative impact on the quality of life of child. These children had 1.6 and 0.9 times more likelihood of negatively impacting the child and family sections, respectively. Similar results were reported by Kramer *et al.*<sup>4</sup> and Sardenberg *et al.*<sup>10</sup> in which they stated a significant impact of malocclusion on the OHRQoL of young children when compared with children without malocclusion. Contrary to the above findings, studies reported by Carvalho *et al.*,<sup>2</sup> Abanto *et al.*,<sup>11</sup> and Sousa *et al.*<sup>3</sup> stated that there is no association between malocclusion and the quality of life of preschool children. It is said that individuals with unpleasant occlusal characteristics may attract unfavorable social responses, which may leave a bad impression in early stages of life.<sup>3</sup> Esthetics appearance plays an important role in social interactions and psychological well-being, malocclusion may adversely affect the esthetics which can have a negative impact on the quality of life of children.

DDE is a common occurrence in primary dentition. They are classified as enamel hypoplasia, demarcated opacities or diffused opacities.<sup>5</sup> The main causes for DDE are absence of breast feeding, premature birth, low birth weight, and systemic conditions in childhood.<sup>12</sup> Teeth with DDE have retentive areas that will lead to formation of bacterial plaque facilitating the progression of dental caries.<sup>13</sup> Results of this study showed children with DDE had 1.5 and 1.01 times more likelihood of negatively impacting the child and family sections, respectively. These results are similar to the findings reported by Vargas-Ferreira *et al.*<sup>14</sup> in which they stated that the presence of DDE may cause negative impacts on a child's perception of oral health and on their daily performance. DDE facilitates the development of caries due to structural defects of the tooth surface, which may lead to sensitivity of the teeth followed by pain and irritability which in turn may affect the quality of life of preschoolers.

In this study, it was observed that age had no impact on children's and families quality of life. These findings are contrary to the findings reported by Corrêa-Faria *et al.*<sup>1</sup> in which they stated that age presented a significant association with negative impact of child's quality of life. Older children tend to have a greater number of dental caries as well more severe caries, which suggests a greater impact on the quality of life. Moreover, a child's ability to communicate with parents and report the effects of oral

health on the quality of life improves with the increase in age. Younger children have limitations in language and communication skills thus parents may not perceive a negative impact which can make the diagnosis more difficult.

From this study it was found that dental caries, malocclusion and DDE adversely affects the quality of life of preschoolers and their families have an impact on overall OHRQoL. These findings are contrary to the study reported by Corrêa-Faria *et al.*,<sup>1</sup> in which they stated that only dental caries was associated with negative impact on the quality of life of preschoolers whereas malocclusion and DDE did not have an impact. The present findings should be analyzed with caution because of limitation to the cross-sectional design. Longitudinal and case-control studies are needed to confirm the results obtained.

## CONCLUSION

Dental caries, malocclusion and DDE were associated with a negative impact on the quality of life of children. Knowledge about the association between oral problems and the quality of life among young children is an important tool to the early establishment of preventive and curative measures to avoid the worsening of oral problems as well as the inability to take part in routine activities and social life.

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# Role of Proton Magnetic Resonance Spectroscopy in Evaluation of Intracranial Space Occupying Lesion

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## Abstract

**Introduction:** Magnetic resonance spectroscopy (MRS) is a potential tool for differential diagnosis between brain abscesses and noninfectious lesion such as a primary brain tumor, lymphoma, brain metastasis, and tuberculoma.

**Aims and Objectives:** To evaluate the role of MRS in imaging of intracranial space occupying lesion and differentiate between benign and malignant conditions and correlate between imaging findings with histopathological findings.

**Materials and Methods:** The study was performed on whole body system 1-5 tesla GE Signa HDx magnetic resonance imaging (MRI) at MP MRI scan Centre Medical College, Jabalpur, using a dedicated head coil. Multiplanar, T1 and T2 weighted diffusion, gradient images using spin echo sequences point resolved spectroscopy chemical shift selective.

**Result:** A total of 70 patients included in our study of the space occupying lesion in the brain, 33 patients had nonneoplastic lesions. Remaining 37 patients had neoplastic lesions. 0-40 years comprising 75% of patients having nonneoplastic pathologies. Only remaining 8 patients (25%) were above the age of 40 years; the majority of patients in our study were males (67%). Only 33% patients were females. Benign pathologies were more common in females 13/23 (56% of females). In males, neoplastic pathologies were more common seen in 27 out of 47 patients (58% of males). Glioma and tuberculoma were most commonly seen in our study in 27 patients comprising 38.5% each, respectively. Mean N-acetylaspartate/creatine (Cr) levels in nonneoplastic and neoplastic category were 1.18 and 1.02, respectively, being higher in the nonneoplastic group. Mean choline/Cr levels were higher in the neoplastic group: 1.9 as compared to 1.07 seen in nonneoplastic group.

**Conclusion:** MRS is able to distinguish between neoplastic and nonneoplastic intracranial space occupying lesions on the basis of metabolites level. Tuberculoma and pyogenic abscess can be differentiated with the spectroscopic patterns.

**Key words:** Gliomas, Magnetic resonance spectroscopy, Tumors, Tuberculoma

## INTRODUCTION

Medical imaging techniques, beginning with the X-ray in 1895 and followed more recently by ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI), have provided high temporal, spatial, and contrast resolution methods to assess structure.

In 1995, a new era in neuroradiology emerged with the approval of magnetic resonance spectroscopy (MRS) by the United States FDA, as a noninvasive method providing metabolic information about the brain.<sup>1</sup> MRS enables tissue characterization on a biochemical level surpassing that of conventional MRI (c MRI). MRS does not replace c MRI but complements the information provided by it.<sup>2</sup> MRS may provide additional information as a prognostic indicator while following the progression of the disease and evaluating the response to treatment. MRS can be used to determine the degree of malignancy.<sup>1</sup>

The most common nuclei that are used: <sup>1</sup>H (proton), <sup>23</sup>Na (sodium), <sup>31</sup>P (phosphorus). Proton spectroscopy is easier to perform and provides much higher signal-to-noise ratio than either sodium or phosphorus. Proton MRS can

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be performed within 10-15 min and can be added on to conventional MR imaging protocols.

MRS enables evaluation of metabolic derangements that are specific to certain central nervous system diseases. As a general rule, as malignancy increases, N-acetylaspartate (NAA) and creatine (Cr) decrease, and choline (Cho), lactate (Lac), and lipids increase. NAA decreases as tumor growth displaces or destroys neurons. Very malignant tumors have high metabolic activity and deplete the energy stores, resulting in reduced Cr. Very hypercellular tumors with rapid growth elevate the Cho levels.<sup>3</sup>

MRS is a potential tool for differential diagnosis between brain abscesses and noninfectious lesions such as primary brain tumor, lymphoma, brain metastasis, and tuberculoma.<sup>4</sup> Lipids are found in necrotic portions of tumors, and Lac appears when tumors outgrow their blood supply and start utilizing anaerobic glycolysis. Brain abscesses destroy or displace brain tissue, so NAA is not present. Lac, cytosolic acid, alanine, and acetate are characteristic metabolites in bacterial abscesses. Toxoplasmosis and tuberculomas show prominent peaks from Lac and lipids.<sup>3</sup> When combined with c MRI and MRS may increase the diagnostic capability of MR, and thus, have a significant impact on the treatment of patients.

## MATERIALS AND METHODS

### Materials

MRS will be carried out on those patient referred to MP MRI and CT scan center from Neurology OPD/IPD or Medicine Department which are having intracranial space occupying lesions on conventional MRI.

### Methods

After taking relevant history and consent patient will be scanned on the GE Signa HDx 1.5T MRS. All patients will be followed up for operative and histopathological findings and for clinical recovery in nonoperative conditions.

### Technique

Basic method used to sample a given volume in MRS is point resolved spectroscopy (PRESS) which uses one 90° pulses and two 180° pulses to obtain a spin echo.

Water suppression is accomplished with either a chemical shift selective (CHESS) or inversion recovery (IR) technique. CHESS technique uses a series of selective 90° pulses to reduce the water signal by a factor of approximately 1000.<sup>6</sup> Water suppression techniques are used with PRESS pulse sequence acquisition. With PRESS, there is a full signal recovery and a good signal-to-noise ratio (requiring fewer signal averages). PRESS allows for sampling of large

volumes of-interest of tissue. PRESS requires a longer TE, with a long TE of 270 ms, only metabolites with a long T2 are seen, producing a spectrum with primarily NAA, Cr, and Cho. One another helpful TE is 144 ms because it inverts Lac at 1.3 ppm.<sup>2</sup> Short TE allows for identification of other metabolites such as myoinositol (MI), glutamate, glutamine, and glycine.

In our study of single voxel spectroscopy (SV spectroscopy), voxel is placed over the mass lesion to be evaluated but away from the source of susceptibility artifact, i.e., cerebrospinal fluid, hemorrhage, calcification, and lipids. Voxel size of 2 cm × 2 cm × 2 cm is used. Short echo time (TE 35 ms) first followed by SV spectroscopy with intermediate TE (144 ms) is used.

## RESULTS

A total of 70 patients included in our study of the space occupying lesion in the brain, 33 patients had nonneoplastic lesions. Remaining 37 patients had neoplastic lesions.

As evident from the Table 1, the majority of patients ( $n = 25$ ) were in the range of 0-40 years comprising 75% of patients having nonneoplastic pathologies. Only remaining 8 patients (25%) were above the age of 40 years. The minimum and maximum age of presentation was 5 and 74 years.

In the neoplastic group, trend toward higher age group was seen. Out of the 37 patients, 24 patients (65%) belong to 41-80 years was had most neoplastic pathologies. Only two patients of less than 20 years had neoplastic pathologies.

The majority of patients in our study were males (67%). Only 33% patients were females as evidence from Table 2.

Benign pathologies were more common in females 13/23 (56% of females). In males, neoplastic pathologies were more common seen in 27 out of 47 patients (58% of males).

Glioma and tuberculoma were most commonly seen in our study in 27 patients comprising 38.5% each, respectively as evident from Table 3.

Tuberculoma was a predominant lesion in the benign category comprising 82% of patients. Abscess<sup>4</sup> and neurocysticercosis as shown in Table 4.<sup>2</sup>

Glioma was the predominant pathology in the neoplastic group (73%) followed by metastasis seen in 4 of the patients ss shown in Table 5.



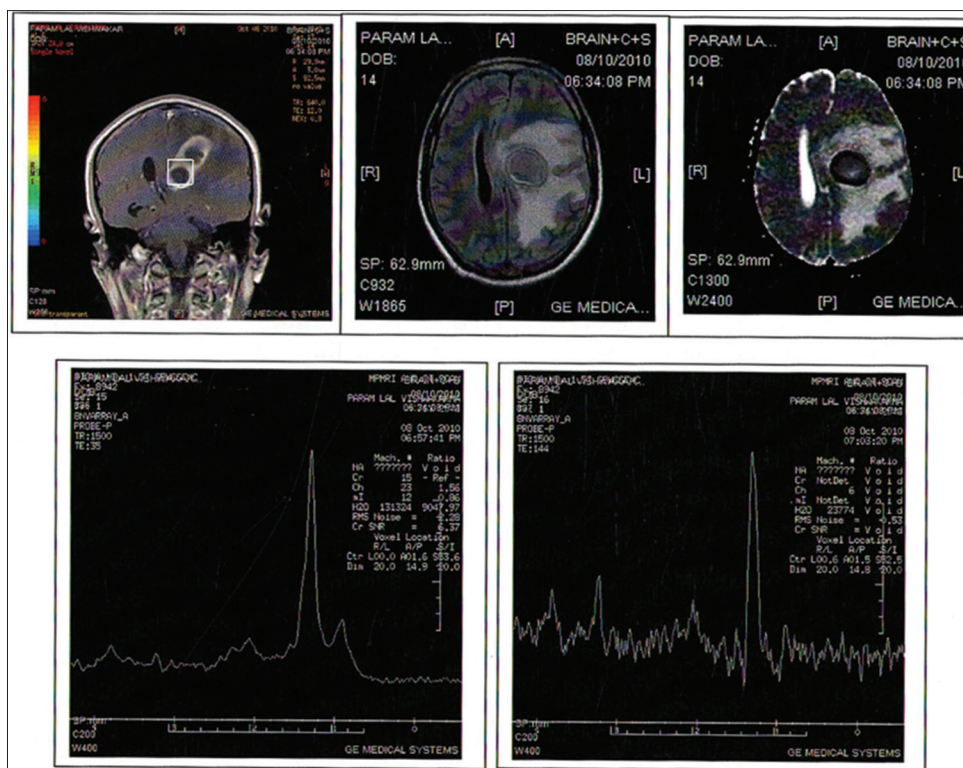


Figure 1: Case 1 – Lobulated cystic peripheral enhancing lesion with surrounding edema and diffusion restriction, spectroscopy showing very high lipid peaks with undetectable N-acetyl aspartate and cytosolic AA. Abscess

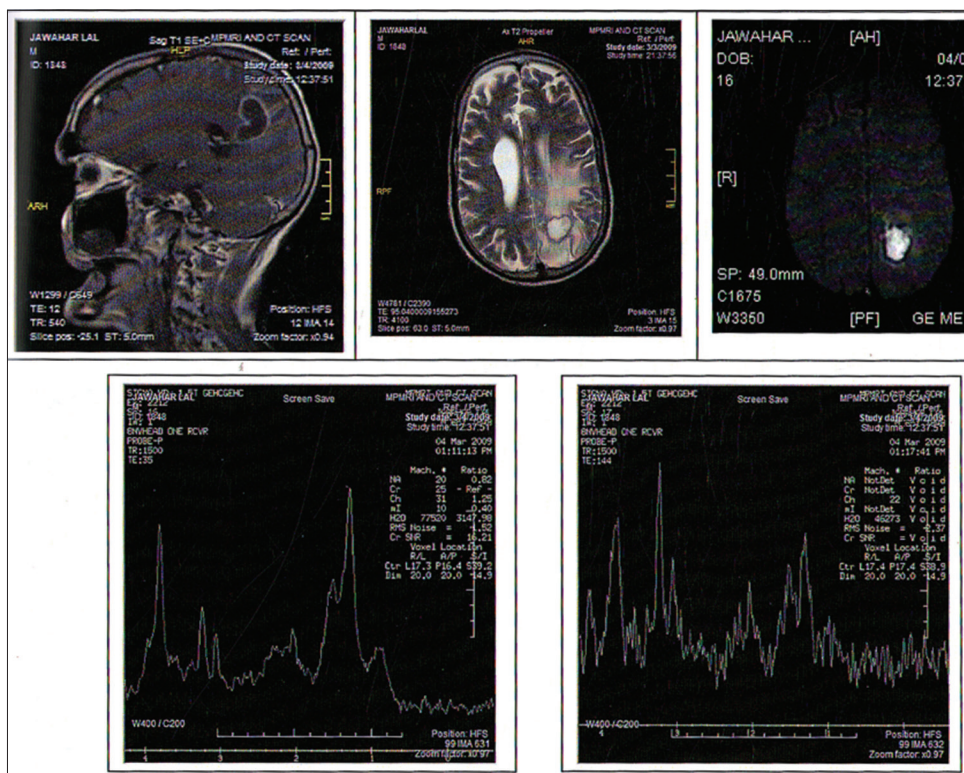
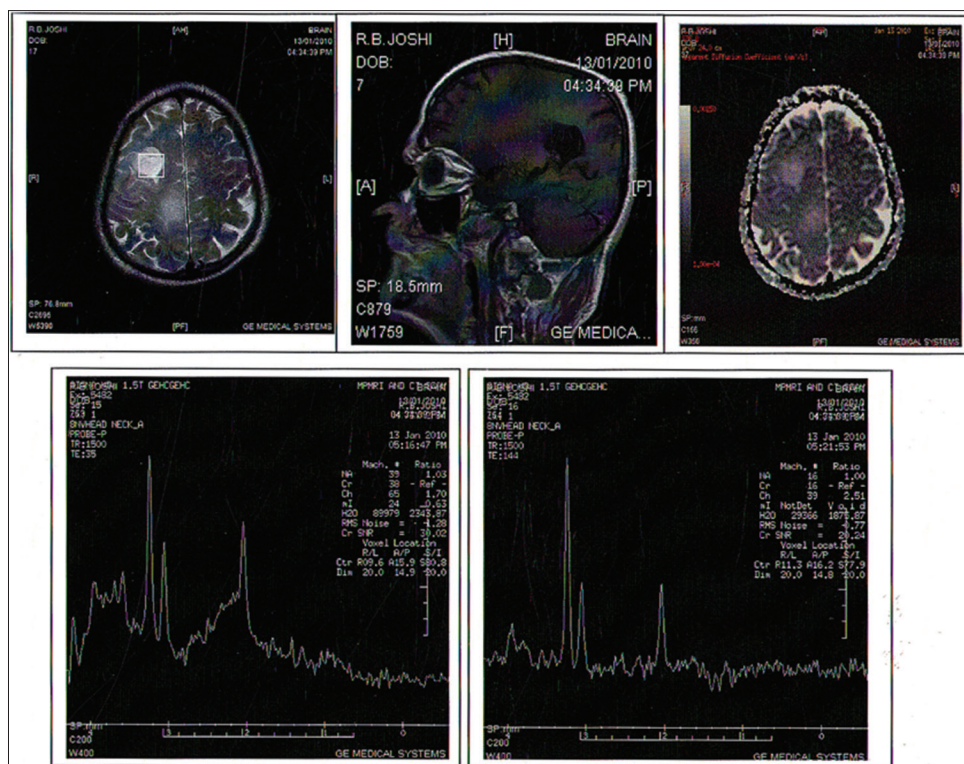


Figure 2: Case 2 – Ring enhancing lesion with diffusion restriction and prominent lipid peak with normal N-acetyl aspartate/ creatine (Cr) and choline/Cr levels s/o tuberculoma

On intravenous gadolinium, ring enhancement pattern of contrast enhancement was seen in 49 patients in

the study. Based on MRI along with spectroscopic evaluation, 25 patients were attributed to the tuberculoma.



**Figure 3: Case – 3 Cortical-subcortical T1 hypointense and T2 hyperintensity without diffusion restriction or contrast enhancement. Spectroscopy showing mild reduced N-acetyl aspartate, mild elevated choline, no lipid peak s/o low grade glioma. Biopsy turned out to be WHO Grade II astrocytoma**

Fifteen patients of high-grade glioma comprising 11 of glioblastoma multiforme (GMB) and 4 patients of anaplastic astrocytoma had ring enhancement pattern seen.

Mean NAA/Cr levels in nonneoplastic and neoplastic category were 1.18 and 1.02, respectively, being higher in the nonneoplastic group. Mean Cho/Cr levels were higher in the neoplastic group: 1.9 as compared to 1.07 seen in nonneoplastic group as evident from Table 6.

Statistically significant difference was observed in Cho/Cr and NAA/Cho levels between low- and high-grade glioma groups ( $P < 0.05$ ).

Although the values of NAA/Cr and MI were low in the high-grade glioma patients as compared with low-grade glioma group, the difference was not statistically significant  $P > 0.05$  as shown in Table 7 and Table 8. Patient of tuberculoma showed strong lipid resonances at 0.9 and 1.3.

Lac peak was seen in only one of the low-grade glioma patients while none of the high-grade glioma patient had Lac peak in the diagnostic spectra.

Presence of lipid was seen in 3 metastasis patients as shown in Table 9.

Two patients of meningioma had increased Cho peaks, and no lipid or Lac resonance was obtained in any of the patient. Both the cases of epidermoid cyst did not showed any significant alteration in metabolite except mild increased Cho levels and elevated Lac peak (Figures 1-3 and Table 1-9)).

## DISCUSSION

NAA is a neuronal marker and decreases in all tumors because of the invasiveness of tumor cells within the normal tissue. NAA accounts for the majority of the resonance at 2.01 ppm. Proton MRS-visible Cho-containing compounds include acetylCho, glycerol phosphor Cho, and phosphor Cho. Cho is increased in all tumors because of increased membrane turnover and cell proliferation. Cr/phosphocreatine, an indicator of energy metabolism, shows variable signal intensity in proton MRS of intracranial tumors.

In our study, it was possible to differentiate neoplastic pathologies from nonneoplastic conditions with as NAA levels were reduced and Cho/Cr levels were higher in neoplastic group as evident in case 3. In one of the patient with low-grade glioma had normal NAA levels. This finding could be due to lesion size being smaller than the voxel size



**Table 1: Age-wise distribution of the intracranial space occupying lesions**

Age group (in years)	Nonneoplastic	Neoplastic
0-20	11	2
21-40	14	10
41-60	6	13
61-80	2	11
81-100	0	1
Total	33	37

**Table 2: Age wise distribution**

Gender	Benign	Malignant	Total
Male	20	27	47
Female	13	10	23
Total	33	37	70

**Table 3: Etiological distribution of intracranial space occupying lesions**

Etiology	Number of cases (%)
Tuberculoma	27 (38.5)
Glioma	27 (38.5)
Abscess	4 (6)
Metastasis	4 (6)
Epidermoid	2 (3)
Meningioma	2 (3)
Neurocysticercosis	2 (3)
Lymphoma	1 (1)
Pineal tumor	1 (1)
Total	70 (100)

and due to partial voluming with normal tissue may falsely elevated NAA signal. Our findings corroborated with the findings by Poptani,<sup>6</sup> Sanghvi *et al.*<sup>7</sup>

Gliomas have been graded on the basis of NAA/Cho, Cho/Cr, NAA/Cr ratios, and Lip/Lac metabolites in the spectra. NAA/Cho and Cho/Cr ratios have shown consistency in predicting the tumor grade.<sup>8,9</sup> We observed NAA peak was significantly reduced in almost all the cases of high-grade gliomas. In remaining two cases, diagnostic spectra could not be obtained due to signal contamination due to hemorrhage. The comparison of NAA/Cho and Cho/Cr ratios in these cases of high-grade glioma with that of the low-grade gliomas provided a statistically significant difference between the two groups. These findings corroborated with the findings by Gupta,<sup>8</sup> Harting.<sup>9</sup>

Server *et al.*, recently in the year 2010, had found out that the statistically significant difference exists between NAA/Cr ratio between high- and low-grade gliomas.<sup>10</sup> However, in our study, though levels of NAA/Cr were low in high-grade tumors, this was found out to be statistically insignificant with low-grade glioma group.

**Table 4: Non neoplastic categories**

Category	Number of patients (%)
Tuberculoma	27 (82)
Abscess	4 (12)
Neurocysticercosis	2 (6)

**Table 5: Neoplastic pathologies**

Category	Number of patients (%)
Glioma	27 (73)
Metastasis	4 (11)
Epidermoid	2 (5)
Meningioma	2 (5)
Lymphoma	1 (3)
Pineal neoplasm	1 (3)
Total	37 (100)

**Table 6: Spectroscopy findings**

Metabolite ratio	Nonneoplastic	Neoplastic
NAA/Cr	1.18	1.02
Cho/Cr	1.07	1.9

NAA: N-acetyl aspartate, Cr: Creatine, Cho: Choline

**Table 7: Mean metabolites levels (mean±SD) in the low-grade versus high-grade glioma**

Grades of glioma	Metabolite levels			
	NAA/Cr	Cho/Cr	NAA/CH	MI
Low-grade glioma	0.98±0.37	1.26±0.27	0.75±0.18	0.72±0.13
High-grade glioma	0.83±0.19	2.01±0.77	0.48±0.31	0.65±0.13

NAA: N-acetyl aspartate, Cr: Creatine, Cho: Choline, SD: Standard deviation, MI: Myoinositol, CHO: choline

MI is a glial marker located in astrocytes and is a cell volume regulator. In our study, mean MI levels in the high-grade glioma were lower compared to the low-grade glioma patients. Our finding can be corroborated with the findings by Castillo *et al.* In the year 2000, published a paper correlating the levels of MI with the grading of cerebral astrocytomas. They had concluded that higher peak levels of MI were associated with lower tumor grade.<sup>11</sup> Our study also yielded same results.

Most tumor cells have low respiration and high glycolysis rates even when oxygen levels are sufficient for respiration. The high glycolytic rate results in increased accumulation of pyruvate, which converts to Lac, because there is a decrease in the tricarboxylic acid cycle activity in brain tumors. Alternatively, Lac also may be produced by anaerobic glycolysis in tumors with hypoxia. Lac levels may be present in the entire spectrum of grades of astrocytomas. Lac may arise not only from hypoxia developing within brain tumor but also seen in region of necrosis or cyst within brain tumor.<sup>6</sup>

**Table 8: Lipid lactate peak in benign pathologies**

Benign pathologies	Only lipid peak	Only lactate peak	Both lipid+lactate
Tuberculoma (n=27)	23	0	4
Abscess (n=4)	2	0	2
Neurocysticercosis (n=2)	0	2	0

**Table 9: Lipid lactate peak in neoplastic category**

Tumor category	Only lipid	Only lactate	Both lipid+lactate
High-grade glioma (n=18)	10	0	8
Low-grade glioma (n=8)	0	1	0
Mets (n=4)	3	0	0
Epidermoid (n=2)	0	2	0
Meningioma (n=2)	1	0	0
Gliomatosis cerebri (n=1)	0	0	1
Lymphoma (n=1)	0	1	0
Pineal neoplasm (n=1)	1	0	0

Lac levels were found to be increased in some of the glioma patients. 50% of high-grade glioma patients had Lac peak as against of only single patient of low-grade glioma had lac peak. In highly vascular tumor, Lac may be removed rapidly from the tumor as a result of increased blood flow; therefore, even in high-grade vascular tumors lac levels may not be seen in the Spectra. However, the presence of lac peak alone could not be used to grade the malignancy of glioma.

The presence of elevated lipids can also be used to differentiate the high- and low-grade neoplasms. In our study, elevated lipid levels were seen in all 17 patients of high-grade glioma as against low-grade glioma where no lipid peak was observed. Mobile lipids tend to be present in higher grades of neoplasms with highest levels noted in GMB. The presence of lipids in these cases suggested necrosis and higher grade of malignancy. Our findings corroborated with the findings by Poptani *et al.*<sup>8</sup> and another study by Grand *et al.*<sup>12</sup> However, elevated lipid is not the sole criteria for high-grade malignancy as lipid elevation often occurs in and necrotic centers of abscesses as evident in case 1 tuberculomas, and thus this has to be correlated with higher levels of Cho and reduced NAA found in malignancy.

Metastasis usually does not pose much of the diagnostic challenge when they are multiple based on the conventional MRI; metastases can be problematic when they are solitary because it may be difficult to distinguish them from primary brain neoplasms. Unfortunately, proton MR spectra of intracranial metastases are often nonspecific and indistinguishable from those of primary brain tumors.

Metastases patients in our study showed low NAA levels and elevated Cho levels. Theoretically, NAA should be

absent in spectra because of lack of neural components. Low levels of NAA were seen presumably secondary to voxel contamination with adjacent brain parenchyma, the presence of N-acetylated metabolites on their cell membranes or the presence of normal brain parenchyma in infiltrating lesions. Three patients with metastasis had mild increased Cho levels with resonance from lipid. This study of MRI with SV spectroscopy could not be reliably differentiated between high-grade glioma and metastasis in 5 patients although high-grade glioma patients (confirmed on histology) had more elevated Cho levels. Our findings corroborated with findings by Server *et al.* in the year 2010. However, trends toward higher values of elevated Cho/Cr were seen in the higher grade glioma patients as against mild elevation in Metastasis group in our study, and more study with the large sample is needed in the future to enable differentiation of high-grade glioma and single necrotic metastasis lesion.

Meningioma patient had marked elevation of Cho levels. Nobile lipids can be seen as also alanine although not present in all cases, detection of alanine is characteristic with meningiomas. However with lipid peak in the spectra, lac resonance can be overlapped. In our study, lipid peaks with highly raised Cho were seen in both the meningioma patients. However, no alanine peak could be attributed in the spectra. Although characteristic c MRI features usually allow confident diagnosis of these tumors, proton MRS may be useful in atypical cases. Our study had two characteristic meningioma patients with typical MRI features on conventional imaging.

As evident in case 2 prominent lipid resonances were noted in intracranial tuberculomas, with particularly important signals at the 1.3 and 0.9 ppm, corresponding to the methylene and terminal methyl groups of fatty acids, respectively. In our study, 25 of the 27 patient with tuberculoma had lipid resonance remaining two cases were showing signs of healing tuberculoma and did not had prominent lipid peak. Lipid peaks were not observed in both the neurocysticercosis patients; instead they had Lac peak in their spectra. However, this has to be evaluated with larger sample value to have a significant impression.

Three patients with bacterial abscess also had lipid/Lac peak. However, those could be differentiated from the tuberculoma patients as former showed the presence of cytosolic AA peak at 0.9 ppm in the spectra. This finding corroborated with findings by Vatsal *et al.*,<sup>13</sup> found in the year 2001.

Two patients of epidermoid cyst had prominent Lac peak in their spectra. Although we did not had any patient of arachnoid cyst in our study, this finding of the presence of



prominent Lac peak could be used to differentiate between epidermoid cyst and arachnoid cyst,<sup>14</sup> as both epidermoid cyst and arachnoid cyst are having resembling features on conventional MRI.

## CONSLUSION

MRS is able to distinguish between neoplastic and nonneoplastic intracranial space occupying lesions on the basis of metabolites level. Proton MRS is a useful and promising diagnostic modality to aid in diagnosing solid brain tumors. Cho/Cr and NAA/Cho ratios and the presence of lipid peak have potential application in pre-operative grading of gliomas. Spectrums from metastasis are in the most cases similar and hence indistinguishable from high-grade gliomas. Tuberculoma and pyogenic abscess can be differentiated with the spectroscopic patterns.

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# Efficacy of Bilateral Superior Laryngeal Nerve Block for Diagnostic Direct Laryngoscopy

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## Abstract

**Background:** Direct laryngoscopy (DLS) is a routine diagnostic procedure employed by otorhinolaryngologist which is being painful and causing severe discomfort to the patient is usually done under general anesthesia.

**Aim:** To study the efficacy of bilateral superior laryngeal nerve blocks in diagnostic DLS, a routine procedure to diagnose pathological abnormalities involving larynx.

**Materials and Methods:** A total of 40 patients scheduled for diagnostic DLS were selected, 2% lignocaine 2 ml was injected bilaterally to block superior laryngeal nerve. The success of the block was assessed by comfort of the patient, quality of analgesia, duration of blockade, and cardiovascular stability.

**Results:** There is a high success rate accounting for 82.5% (33 patients) with very less failure accounting for 17.5% (7 patients). Failed block is mostly attributed to the lack of proper skill in instituting the block during the initial period of study. Even with the successful procedure, there was a significant hemodynamic alteration which includes mild tachycardia and hypertension. This is a point of concern.

**Conclusion:** Bilateral superior laryngeal nerve block in combination with oral topical analgesia and transtracheal block has a success rate of 82.5% and provides adequate analgesia to the patients to undergo a stressful procedure of DLS.

**Key words:** Cardiovascular stability, Direct laryngoscopy, Duration of blockade, Quality of analgesia, Superior laryngeal nerve block

## INTRODUCTION

Diagnostic laryngoscopy is a diagnostic procedure used by otorhinolaryngologist in the diagnosis of tumors and other pathological conditions involving larynx and oropharynx. This diagnostic procedure being painful causes severe discomfort to the patient is usually done under general anesthesia.<sup>1</sup> Most of the patients belong to older age group and are affected with systemic disorders. This minor diagnostic procedure is risky if we subject these patients to general anesthesia. This atraumatic

procedure is associated with numerous life-threatening complications. An obstructing supraglottic mass, a displaced or narrow trachea, a head and neck tumor extending to temporomandibular joint may limit laryngoscopy and intubation.<sup>2,3</sup> Airway management with light plane of general anesthesia may cause patient discomfort, laryngospasm, and bronchospasm. Patient discomfort, laryngospasm may be overcome by muscle relaxation, but bronchospasm may be dangerous and difficult to treat.<sup>4</sup> Sympathetic and parasympathetic stimulation may cause myocardial ischemia and dysrhythmias. Sympathetic stimulation leads to hypertension and tachycardia. Light anesthesia, hypoxia or hypercarbia may predispose to dysrhythmias.<sup>5,6</sup> Sharing the airway with surgeon requires the use of small endotracheal tubes leading to narrow lumen for ventilation and tube become dislodged or obstructed. Most of the above problems are avoided if the procedure is conducted in a sedated, awake patient with intact airway reflex under regional anesthesia.<sup>2,3</sup> The

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regional technique employed to provide anesthesia of the airway is a combination of bilateral superior laryngeal nerve block with topical anesthesia of the oral cavity and transtracheal instillation of the local anesthetic through the cricothyroid membrane.

### Aim

To study the efficacy of bilateral superior laryngeal nerve blocks in diagnostic direct laryngoscopy (DLS), a routine procedure to diagnose pathological abnormalities involving larynx.

## MATERIALS AND METHODS

Totally 40 patients scheduled for diagnostic DLS were selected in the Department of Otorhinolaryngology in Kilpauk Medical College and Hospital, Chennai. An informed written consent was obtained. A good rapport was developed with patients and was explained about the procedure involved. History regarding systemic disorders such as hypertension, diabetes mellitus, ischemic heart disease, and congestive cardiac failure, was taken. A thorough examination of cardiovascular system, respiratory system, airway assessment was done. All the patients were made to gargle 2% lignocaine viscous 10 ml for 8-10 min before the procedure. Patients were shifted to operating table, and they were made in supine position. Pulse and blood pressure were recorded non-invasively. An intravenous infusion was started in one of the forearm veins. With the patient lying in supine position, the head was maximally extended and the hyoid bone was identified by palpation. Since the hyoid bone is movable, and this mobility serves as a useful identifying sign. Under strict aseptic precaution, a 21 G needle was introduced laterally and directed at the greater cornu of hyoid bone. The carotid sheath was retracted posteriorly, and the bone was contacted. The needle was then walked caudally until it slipped of the hyoid bone through the thyrohyoid membrane laterally and the laryngeal mucosa medially, where the ramifications of the internal branch of superior laryngeal nerve are present. After careful aspiration, 2% lignocaine 2 ml was injected, and the block was repeated on opposite side too. Lignocaine 4% 2 ml was injected via cricothyroid puncture at the end of maximal expiration. This provides topical anesthesia of trachea, as a cough produced by spray of lignocaine introduced directly into the trachea spreads anesthetic droplets from carina to the inferior surface of the vocal cords. The interior of the larynx is anesthetized by superior laryngeal nerve block, and topical application of local anesthetic solution to the oral cavity completed anesthesia of the upper airway. The parameters studied before and after administering the block and after DLS were pulse rate (PR), systolic blood

pressure (SBP) and diastolic blood pressure (DBP). The success of the block was assessed by the comfort of the patient during diagnostic laryngoscopy. The patients were interviewed regarding pain and discomfort after the procedure. A statistical evaluation of the changes in PR, SBP and DBP were undertaken. The efficacy of the block was evaluated by patient's response during diagnostic DLS. The statistical analysis was performed using Student's *t*-test.

## RESULTS

This study was conducted on 40 randomly chosen patients. This group consisted of 34 males and 6 females. Most of the patients were aged above 50 years, and only 8 were below 50 years.

From Table 1, it is clear that there were a significant increase in all the parameters observed after the block and during diagnostic laryngoscopy compared to the parameters before the block.

Table 2 shows significant changes in PR, SBP, and DBP before and during the block and also during DLS.

From Table 3, it was noticed that the block was more successful in patients above 50 years of age.

From the Table 4, it is clear that there is negligible difference of success rate between both sexes.

**Table 1: Distribution of hemodynamic parameters**

Parameters	Mean±SD		
	Before the block	After the block	During DLS
PR (per minute)	77.325±5.654	86.69±5.805	86.205±6.418
SBP	132.5±11.74	142.25±12.051	142.1±12.165
DBP	86.5±6.6596	92.65±6.594	92.5±7.318

DBP: Diastolic blood pressure, SBP: Systolic blood pressure, PR: Pulse rate, DLS: Direct laryngoscopy, SD: Standard deviation

**Table 2: Test of significance**

Parameters	Before verses during block		Before verses during DLS	
PR	t=7.309	P<0.001	t=6.566	P<0.001
SBP	t=3.665	P<0.001	t=3.591	P<0.001
DBP	t=4.15	P<0.001	t=3.835	P<0.001

DBP: Diastolic blood pressure, SBP: Systolic blood pressure, PR: Pulse rate, DLS: Direct laryngoscopy

**Table 3: Distribution of efficacy in age group**

Age groups	Success (%)	Failure (%)	Total
<50 years	6 (75)	2 (25)	8
>50 years	27 (84.4)	5 (15.6)	32
Total	33	7	40

**Table 4: Distribution of efficacy in gender**

Sex	Success (%)	Failure (%)	Total
Male	28 (82.4)	6 (17.6)	34
Female	5 (83.31)	1 (16.7)	6
Total	33	7	40

**Table 5: Total success rate**

Number of patients	Success (%)	Failure (%)
40	33 (82.5)	7 (17.5)

Table 5 shows that there is a high success rate accounting for 82.5% with very less failure accounting for 17.5%. Failed block is mostly attributed to the lack of proper skill in instituting the block during initial period of study. Even with the successful procedure, there was a significant hemodynamic alteration which includes mild tachycardia and hypertension. This is a point of concern.

## DISCUSSION

The study of efficacy of bilateral superior laryngeal nerve block with transtracheal block and topical anesthesia of oral cavity for diagnostic DLS was done in 40 randomly chosen patients. The aim of this study was to find the quality of analgesia, cardiovascular changes, duration of the block and patient comfort.<sup>7,8</sup> Most of the patients undergoing this procedure belong to older age group are unfit for general anesthesia due to various systemic disorders. Out of 40 patients, the procedure was successful in 33 patients with good analgesia. These patients were comfortable during laryngoscopy and minimal cardiovascular response. The duration of the blockade between 30 and 45 min. The procedure was failure in 4 patients, and these patients were distressed and unable to withstand their diagnostic procedure. Remaining 3 patients had moderate distress but

allowed laryngoscopy. They had significant cardiovascular stress response with severe tachycardia and hypertension and the procedure had to be abandoned.<sup>9,10</sup>

## CONCLUSION

In our study, we find that the bilateral superior laryngeal nerve block in combination with topical analgesia of the oral cavity and transtracheal block has a success rate of 82.5%. It does not interfere much with the cardiovascular status of the patients. This block provides adequate analgesia to the patients to undergo a stressful procedure of DLS.

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# A Study on Urinary Tract Infection Pathogen Profile and Their *In Vitro* Susceptibility to Antimicrobial Agents

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## Abstract

**Introduction:** Urinary tract infection (UTI) is a worldwide common bacterial infection, and it is important to know the common organisms and its antibiotic resistance pattern in our practicing locality, to guide us in instituting treatment.

**Aims and Objectives:** (1) To analyze and statistically evaluate the distribution of common organisms causing UTI in the community. (2) To investigate the antibiotic sensitivity pattern of the common organisms causing UTI. (3) To study the distribution of UTI among different age groups and gender. (4) To compare the sensitivity and resistance of oral with parenteral antibiotic.

**Materials and Methods:** This was an observational study over a period of 5 months, which consisted of consecutively selected patients, more than 18 years of age, visiting Sri Ramachandra Medical College and Hospital, Porur, either as outpatients or inpatients, with symptoms of UTI and with positive urinary cultures with significant colony count. Pregnant patients, patients on catheter, those with insignificant colony count and patients who were treated with antibiotics for the current complaint of UTI were excluded.

**Results:** The prevalence of *Escherichia coli* was the highest (59.4%), followed by *Klebsiella pneumoniae* (14.2%) and *Enterococcus faecalis* (11.4%). *E. coli* was most sensitive to nitrofurantoin among oral antibiotics (96.1%) and amikacin among parenteral antibiotics (98.4%), followed by piperacillin-tazobactam (97.7%) and cefoperazone-sulbactam (93.7%). *K. pneumoniae* was most sensitive to nitrofurantoin (64.3%), followed by norfloxacin (61.3%) among oral antibiotics and amikacin (93.5%), followed by piperacillin-tazobactam (90.3%) and cefoperazone-sulbactam (83.9%) among parenteral antibiotics.

**Conclusion:** This study was aimed at finding out the common organism causing UTI and its sensitivity pattern in our practicing locality. It is concluded that *E. coli* and *K. pneumoniae* were the common organisms and both were most sensitive to nitrofurantoin among oral antibiotics and amikacin among parenteral antibiotics.

**Key words:** Antibiotic sensitivity pattern, *Escherichia coli*, *Klebsiella pneumoniae*, Oral and parenteral antibiotic, Urinary tract infection

## INTRODUCTION

Urinary tract infection (UTI) is among the most common bacterial infection and account for a significant part of

the out-patient and in-patient department patients. In the pre-antibiotic era, UTI caused significant morbidity. Hippocrates, when describing a disease that appears to be acute cystitis, said that the illness could last for a year before either resolving or worsening. Nitrofurantoin, which became available in the 1950s, was the first effective antibiotic for the treatment of UTI. The most common manifestation of UTI is acute cystitis, and it is far more prevalent among women than among men, hence most clinical research on UTI has involved women. The available data demonstrate *Escherichia coli* as the most common organism responsible

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for UTI, and there is a worldwide increase in the resistance of *E. coli* to antibiotics commonly used to treat them. North American and European surveys from females with acute cystitis have documented resistance rates of >20% to trimethoprim-sulfamethoxazole and ciprofloxacin.<sup>1</sup> In community-acquired infections, there is an increase in the prevalence of uro-pathogens producing extended-spectrum  $\beta$ -lactamases leaving only few oral antibiotic options for therapy. Since resistance rates vary in each geographic region, with individual patient characteristics, it is important to know the current and local data when choosing an empirical treatment regimen.

This study was designed to find the distribution of common organisms causing UTI in males and females, who presented to Sri Ramachandra Medical College and Hospital, Porur, Chennai, with urinary tract symptoms, and to determine the antibiotic susceptibility pattern of microbial organisms isolated from the urine culture, to help in the empirical treatment and reduce antibiotic resistance.

### Aims and Objectives

1. To analyze and statistically evaluate the distribution of common organisms causing UTI in the community.
2. To investigate the antibiotic sensitivity pattern of the common organisms causing UTI in adult patients.
3. To study the distribution of UTI among different age groups and compare the same between male and female.
4. To compare the sensitivity and resistance of oral with parenteral antibiotic.

## MATERIALS AND METHODS

This was an observational study, which consisted of consecutively selected patients visiting Sri Ramachandra Medical College and Hospital, Porur, Chennai, either as outpatients or admitted as in-patients, over a period of 5 months, from April 2016 to September 2016.

### Selection Criteria for Cases

1. Hospital-based patients (in-patients and out-patients) visiting Sri Ramachandra Medical College and Hospital, Porur, Chennai, from April to September 2016, with symptoms of UTI.
2. Age more than 18 years.
3. Patients with positive urine cultures with significant colony count ( $>10^5$ ) were included in the study.

### Exclusion Criteria for Cases

1. Pregnant patients were excluded.
2. Patients on catheter were excluded.
3. Patients with urine culture showing  $<10^5$  colony count.
4. Patients who were treated with antibiotics for the current complaint of UTI.

## Methodology

Patient information was collected with the help of a questionnaire after obtaining informed consent. It included details like age, gender, diabetic profile, pregnancy status, use of catheters, recent use of antibiotics for the current complaint of UTI, etc. Clean catch mid-stream urine samples were collected for culture and sensitivity in all patients presenting with symptoms of UTI. Antimicrobial susceptibility was done by Kirby Bauer's disc diffusion method. Data was entered in Microsoft Excel spreadsheet and analyzed statistically using Statistical Package for the Social Science system. Significance testing of the difference between means was performed by Chi-square test, and correlations were assessed by Pearson coefficient. Significance was considered, if the "P" value was below 0.05.

## RESULTS

Our study group included 219 patients with positive urine cultures with a significant colony count of equal to or  $>10^5$ .

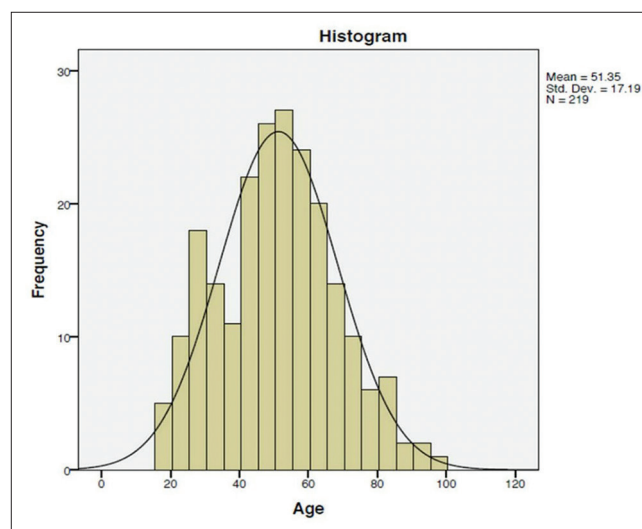
### Age Distribution

Nearly 45.2% of the patients were in the age group 40-60 years. The minimum age in the study group was 18 years, and maximum was 98 years (Table 1 and Figure 1).

**Table 1: Age distribution**

Valid (n)	219
Missing	0
Mean	51.35
Median	51.00
Mode	55
SD	17.190
Min	18
Max	98

SD: Standard deviation



**Figure 1: Age distribution**

### Sex Distribution

Out of the 219 patients who were included in the study, 111 patients were male, which comprised 50.7% and 108 patients were female, which comprised 49.3% (Figure 2).

### Diabetic Profile

While comparing the diabetic profile for our study group, 37.9% were diabetics, and 62.1% were non-diabetics (Figure 3).

### Sex Distribution within Diabetic Profile

In the diabetic group, male population was predominant (53%) when compared with females (47%). In the non-diabetic population, female population was predominant (50.7%) when compared with males (49.3%) (Figure 4).

### Distribution of Organisms Causing UTI in this Study

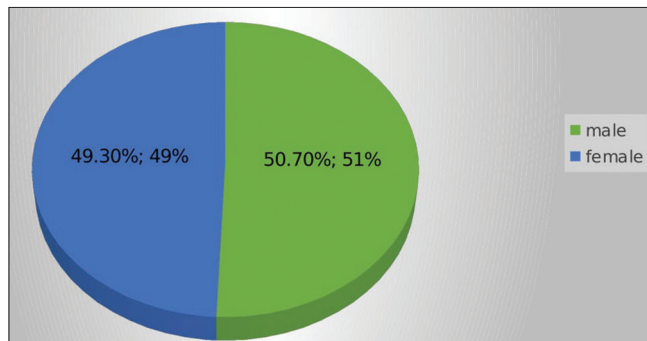
While studying the pattern of organisms grown in the urine, we noticed that the prevalence of *E. coli* was the highest. 130 out of 219 patients (59.4%) grew *E. coli* in their culture, followed by *Klebsiella pneumonia* (31 out of 219 patients [14.2%] were positive), 25 out of 219 patients (11.4%) were positive for *Enterococcus faecalis*, 5% were

positive for *Acinetobacter* species, 3.7% were positive for *Staphylococcus* species, 1.8% were positive for *Enterobacter* species and *Pseudomonas aeruginosa* each, 0.9% were positive for *Providencia* species and *Morganella* species each, 0.5% were positive for *Streptococcus* species and *Proteus mirabilis* each (Table 2 and Figure 5).

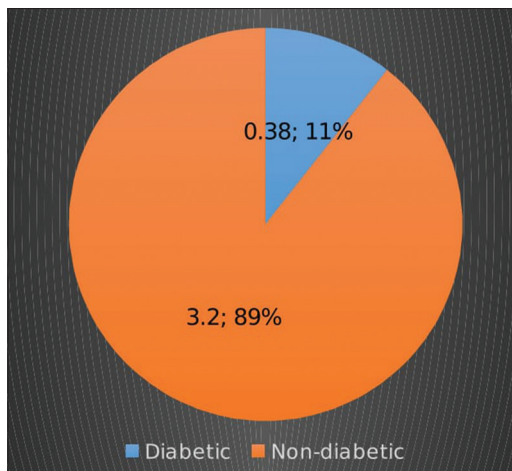
**Table 2: Distribution of organisms causing UTI in this study**

S. No	Organisms	Frequency of occurrence (%)
1	<i>Escherichia coli</i>	130 (59.4)
2	<i>Klebsiella pneumoniae</i>	31 (14.2)
3	<i>Enterococcus faecalis</i>	25 (11.4)
4	<i>Acinetobacter</i>	11 (5.0)
5	Coagulase negative <i>Staphylococcus</i>	5 (2.3)
6	<i>Enterobacter</i>	4 (1.8)
7	<i>Pseudomonas aeruginosa</i>	4 (1.8)
8	<i>Staphylococcus aureus</i>	3 (1.4)
9	<i>Morganella</i>	2 (0.9)
10	<i>Providencia</i>	2 (0.9)
11	<i>Proteus mirabilis</i>	1 (0.5)
12	<i>Streptococcus</i> species	1 (0.5)

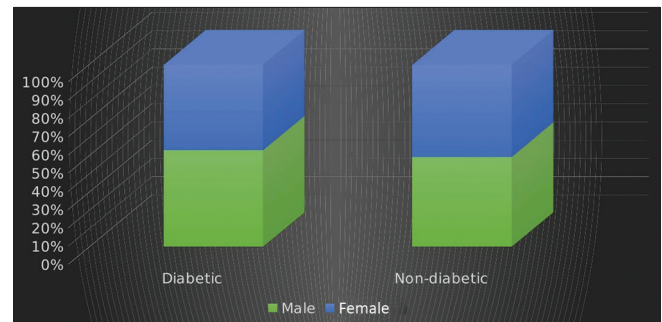
UTI: Urinary tract infection



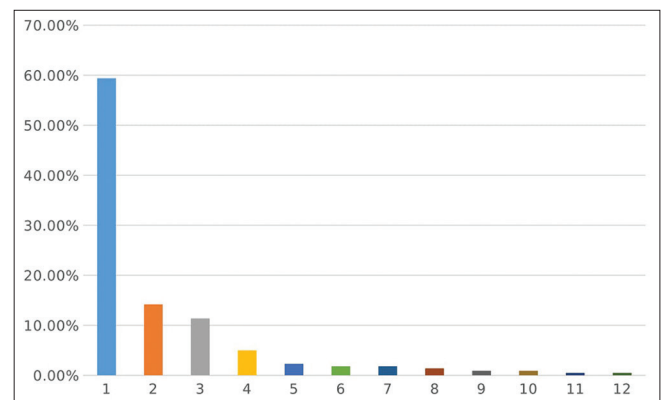
**Figure 2: Sex distribution**



**Figure 3: Diabetic profile**



**Figure 4: Sex distribution within diabetic profile**



**Figure 5: Distribution of organisms causing urinary tract infection in this study. 1 - *Escherichia coli*, 2 - *Klebsiella pneumoniae*, 3 - *Enterococcus faecalis*, 4 - *Acinetobacter*, 5 - Coagulase negative *Staphylococcus*, 6 - *Enterobacter*, 7 - *Pseudomonas aeruginosa*, 8 - *Staphylococcus aureus*, 9 - *Morganella*, 10 - *Providencia*, 11 - *Proteus mirabilis*, 12 - *Streptococcus* species**

### Sensitivity Pattern of the Oral (O) and Parenteral (P) Antibiotics Used in this Study

All 219 patients were tested for ampicillin in which 13.7% were sensitive and 86.3% were resistant. Out of the 98.2% who were tested for cefotaxime 33.5% were sensitive and 66.5% were resistant. Nitrofurantoin was tested in 95.4% patients, out of which 82.3% were sensitive. Out of the 219 patients, 85.4% patients were tested for piperacillin-tazobactam and 95.2% were sensitive, and only 4.8% were resistant. Norfloxacin was tested in 84.9% out of which 55.9% were sensitive. Amikacin was tested in 84% in which 95.1% were sensitive. 83.6% were tested for cotrimoxazole and cefoperazone-sulbactam each, out of which the sensitivity percentage was 45.9% and 90.7%, respectively. Other drugs such as ciprofloxacin, imipenem, polymyxin, tobramycin, linezolid, and vancomycin were tested in less than 15% of the study population, in which polymyxin and linezolid were sensitive in all the patients tested (Table 3).

### Oral versus Parenteral Antibiotics

On comparing the sensitivity pattern for oral antibiotics, out of 219 patients, 201 (91.8%) were sensitive to at least one oral antibiotic and 18 (8.2%) were resistant to all oral antibiotics.

Similarly, out of 219 patients tested for parenteral antibiotics, 217 (99.1%) were sensitive to at least one parenteral antibiotics, and 2 (0.9%) were resistant to all parenteral antibiotics. But the relation was not significant (Chi-square test  $P$  value 0.671) (Figure 6).

### Oral versus Parenteral Antibiotic Sensitivity Based on Age Distribution

On grouping the patients into 3 groups, based on their respective ages, 26.5% were in the age group of 18-40 years, 45.2% in 40-60 years of age and 28.3% in the age group above 60.

In the first group, 93.1% were sensitive to at least one oral antibiotic, 98.3% were sensitive to at least one parenteral antibiotic, 6.9% were resistant to all oral antibiotics, and 1.7% were resistant to all parenteral antibiotics.

In the age group between 40 and 60 years of age, 91.9% were sensitive to at least one oral antibiotic, 99% were sensitive to at least one parenteral antibiotic, 8.1% were resistant to all oral antibiotics and 1% was resistant to all parenteral antibiotics.

In the age group above 60 years, 90.3% were sensitive to at least one oral antibiotic, 100% were sensitive to at least one parenteral antibiotic and 9.7% were resistant to all oral antibiotics (Figures 7 and 8).

### *E. coli* Sensitivity Pattern to Commonly Used Antibiotics

We did an extensive study of the sensitivity and resistance pattern of the two common organisms grown in the urine culture in our study population, *E. coli* and *K. pneumoniae*, and compared their antibiotic sensitivity pattern with that of other organisms (Tables 4 and 5).

From Table 5, it is seen that *E. coli* was most sensitive to nitrofurantoin among oral antibiotics (96.1%) and

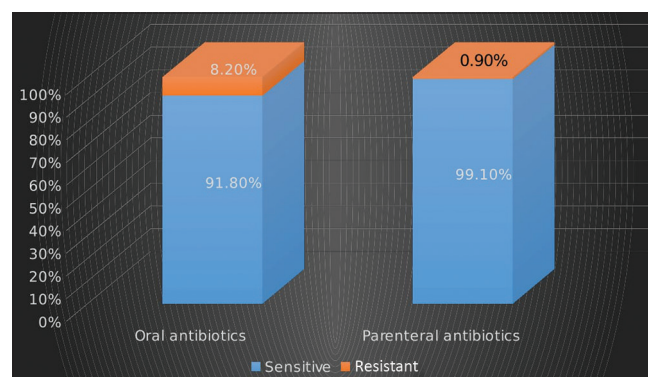


Figure 6: Oral versus parenteral antibiotics

Table 3: Sensitivity pattern of the oral (O) and parenteral (P) antibiotics used in this study

S. No	Antibiotic	Tested in	Tested in (%)	Sensitive in	Sensitivity (%)	Valid sensitivity (%)
O1	Nitrofurantoin	209	95.4	172	78.5	82.3
O2	Cotrimoxazole	183	83.6	84	38.3	45.9
O3	Norfloxacin	186	84.9	104	7.5	55.9
O4	Ciprofloxacin	32	14.6	24	10.9	75
IV1	Ampicillin	219	100	30	13.7	13.7
IV2	Amikacin	184	84	175	79.9	95.1
IV3	Cefoperazone-sulbactam	183	83.6	166	75.8	90.7
IV4	Cefotaxime	215	98.2	72	32.9	33.5
IV5	Imipenem	8	3.7	5	2.3	62.5
IV6	Piperacillin-tazobactam	187	85.4	178	81.3	95.2
IV7	Polymyxin B	7	3.2	7	3.2	100
IV8	Tobramycin	11	5	5	2.3	45.5
IV9	Linezolid	12	5.5	12	5.5	100
IV10	Vancomycin	12	5.5	11	5.0	91.7



**Table 4: Comparison of sensitivity pattern of antibiotics between *E. coli* and other organisms**

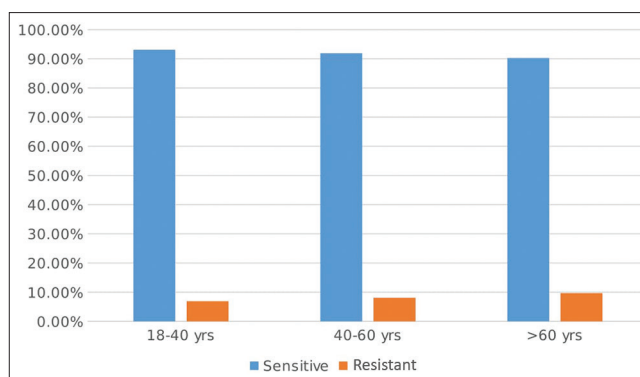
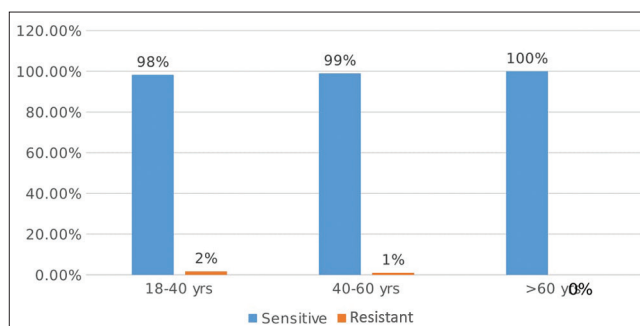
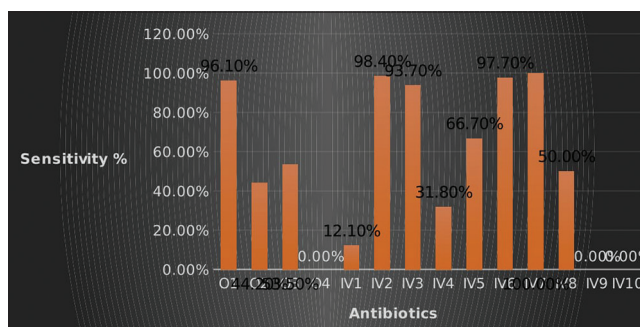
Antibiotics	<i>E. coli</i> positive	<i>E. coli</i> negative	Total	P value
Nitrofurantoin				
Resistant	5	32	37	0.0005
Sensitive	124	48	172	
Cotrimoxazole				
Resistant	72	27	99	0.472
Sensitive	57	27	84	
Norfloxacin				
Resistant	59	23	82	0.339
Sensitive	68	36	104	
Ciprofloxacin				
Resistant	1	7	8	0.078
Sensitive	0	24	24	
Ampicillin				
Resistant	116	73	189	0.128
Sensitive	14	16	30	
Amikacin				
Resistant	2	7	9	0.001
Sensitive	127	48	175	
Cefoperazone-sulbactam				
Resistant	8	9	17	0.031
Sensitive	120	46	166	
Cefotaxime				
Resistant	88	55	143	0.5
Sensitive	41	31	72	
Imipenem				
Resistant	1	2	3	0.8
Sensitive	2	3	5	
Piperacillin-tazobactam				
Resistant	3	6	129	0.01
Sensitive	126	52	58	
Polymyxin				
Resistant	0	0	0	-
Sensitive	2	5	7	
Tobramycin				
Resistant	2	4	6	0.05
Sensitive	2	3	7	
Linezolid				
Resistant	0	0	0	-
Sensitive	0	12	12	
Vancomycin				
Resistant	0	1	1	-
Sensitive	0	11	11	

*E. coli: Escherichia coli*

amikacin among parenteral antibiotics (98.4%), followed by piperacillin-tazobactam (97.7%) and cefoperazone-sulbactam (93.7%). Polymyxin was tested only in 2 patients, and it was sensitive in both these patients (Table 6 and Figure 9).

### ***K. pneumoniae* Sensitivity Pattern to Commonly Used Antibiotics**

From Table 7, it is seen that *K. pneumoniae* was most sensitive to nitrofurantoin among oral antibiotics (64.3%), followed by norfloxacin (61.3%) and cotrimoxazole (58.1%). Among the parenteral antibiotics, *K. pneumoniae* was most sensitive to amikacin (93.5%), followed by piperacillin-tazobactam (90.3%) and cefoperazone-sulbactam (83.9%). Imipenem

**Figure 7: Oral antibiotic sensitivity based on age distribution****Figure 8: Parenteral antibiotic sensitivity based on age distribution**

**Figure 9: *Escherichia coli* sensitivity pattern to commonly used antibiotics. O1 - Nitrofurantoin, O2 - Cotrimoxazole, O3 - Norfloxacin, O4 - Ciprofloxacin, IV1 - Ampicillin, IV2 - Amikacin, IV3 - Cefoperazone-sulbactam, IV4 - Cefotaxime, IV5 - Imipenem, IV6 - Piperacillin-tazobactam, IV7 - Polymyxin B, IV8 - Tobramycin, IV9 - Linezolid, IV10 - Vancomycin**

and polymyxin was tested only in 2 patients, and it was sensitive in both these patients (Table 7 and Figure 10).

## **DISCUSSION**

UTI is one of the most common bacterial infection in people visiting hospitals. UTI is far more common in females than in males, excluding infants and the elderly. In our study, male preponderance was seen (50.7%), which could be explained by the age group we included in this study (varies from 18 to 98 years), since after 50 years of

**Table 5: Comparison of sensitivity pattern of antibiotics between *K. pneumoniae* and other organisms**

Antibiotics	<i>K. pneumoniae</i> positive	<i>K. pneumoniae</i> negative	Total	P value
Nitrofurantoin				
Resistant	10	27	37	0.007
Sensitive	18	154	172	
Cotrimoxazole				
Resistant	13	86	99	0.136
Sensitive	18	66	84	
Norfloxacin				
Resistant	12	70	82	0.509
Sensitive	19	85	104	
Ciprofloxacin				
Resistant	0	8	8	-
Sensitive	0	24	24	
Ampicillin				
Resistant	31	158	189	0.017
Sensitive	0	30	30	
Amikacin				
Resistant	2	7	9	0.659
Sensitive	29	146	175	
Cefoperazone-sulbactam				
Resistant	5	12	17	0.150
Sensitive	26	140	166	
Cefotaxime				
Resistant	18	125	143	0.415
Sensitive	12	60	72	
Imipenem				
Resistant	0	3	3	0.206
Sensitive	2	3	5	
Piperacillin-tazobactam				
Resistant	3	6	9	0.166
Sensitive	28	150	178	
Polymyxin				
Resistant	0	0	0	-
Sensitive	2	5	7	
Tobramycin				
Resistant	2	4	6	0.154
Sensitive	0	5	5	
Linezolid				
Resistant	0	0	0	-
Sensitive	0	12	12	
Vancomycin				
Resistant	0	1	1	-
Sensitive	0	11	11	

*K. pneumoniae: Klebsiella pneumoniae***Table 6: *E. coli* sensitivity pattern to commonly used antibiotics**

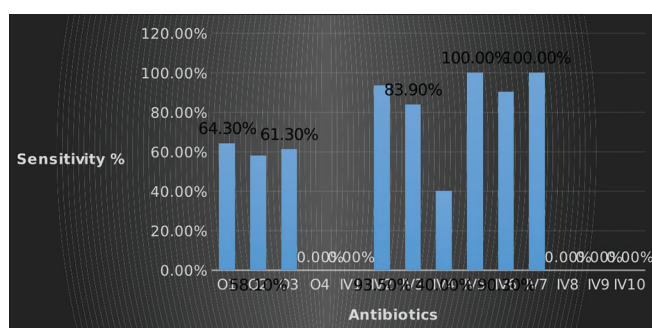
S. No	Antibiotics	<i>E. coli</i> sensitive in	<i>E. coli</i> resistant in	Tested totally in	% sensitivity of <i>E. coli</i>
O1	Nitrofurantoin	124	5	129	96.1
O2	Cotrimoxazole	57	72	129	44.2
O3	Norfloxacin	68	59	127	53.5
O4	Ciprofloxacin	0	1	1	0
IV1	Ampicillin	14	116	130	12.1
IV2	Amikacin	127	2	129	98.4
IV3	Cefoperazone-sulbactam	120	8	128	93.7
IV4	Cefotaxime	41	88	129	31.8
IV5	Imipenem	2	1	3	66.7
IV6	Piperacillin-tazobactam	126	3	129	97.7
IV7	Polymyxin	2	0	2	100
IV8	Tobramycin	2	2	4	50
IV9	Linezolid	0	0	0	0
IV10	Vancomycin	0	0	0	0

*E. coli: Escherichia coli*

**Table 7: *K. pneumoniae* sensitivity pattern to commonly used antibiotics**

S. No	Antibiotics	<i>K. pneumoniae</i> sensitive in	<i>K. pneumoniae</i> resistant in	Tested totally in	% sensitivity of <i>K. pneumoniae</i>
O1	Nitrofurantoin	18	10	28	64.3
O2	Cotrimoxazole	18	13	31	58.1
O3	Norfloxacin	19	12	31	61.3
O4	Ciprofloxacin	0	0	0	0
IV1	Ampicillin	0	31	31	0
IV2	Amikacin	29	2	31	93.5
IV3	Cefoperazone-sulbactam	26	5	31	83.9
IV4	Cefotaxime	12	18	30	40
IV5	Imipenem	2	0	2	100
IV6	Piperacillin-tazobactam	28	3	31	90.3
IV7	Polymyxin	2	0	2	100
IV8	Tobramycin	0	2	2	0
IV9	Linezolid	0	0	0	0
IV10	Vancomycin	0	0	0	0

*K. pneumoniae*: *Klebsiella pneumoniae*



**Figure 10: *Klebsiella pneumoniae* sensitivity pattern to commonly used antibiotics. O1 - Nitrofurantoin, O2 - Cotrimoxazole, O3 - Norfloxacin, O4 - Ciprofloxacin, IV1 - Ampicillin, IV2 - Amikacin, IV3 - Cefoperazone-sulbactam, IV4 - Cefotaxime, IV5 - Imipenem, IV6 - Piperacillin-tazobactam, IV7 - Polymyxin B, IV8 - Tobramycin, IV9 - Linezolid, IV10 - Vancomycin**

age, obstruction due to prostatic hypertrophy becomes common in men, and the incidence of UTI increases among men as well.

The most common organisms causing UTI in our study were *E. coli* (59.4%), followed by *K. pneumoniae* (14.2%), *E. faecalis* (11.4%), *Acinetobacter* species (5%), and *Staphylococcus* species (3.7%). The data is comparable to other studies where the common causative organisms in uncomplicated UTI are *E. coli* (34.4-67.0%), followed by *Enterococcus*, *Pseudomonas*, *Enterobacter*, *Klebsiella*, and *Staphylococcus*.<sup>2-6</sup>

In a study conducted in West Bengal, India, regarding patterns of antibiotic susceptibility of bacteria causing UTI, *E. coli* was the most common uropathogen (67.1%), followed by *Klebsiella* species (22%) and *Pseudomonas* species (6%). Penicillin was least effective against *E. coli* and maximum susceptibility was recorded for the drugs belonging to fourth-generation cephalosporin. *Klebsiella* species were maximally resistant to broad-spectrum penicillin, followed by aminoglycosides and third generation

cephalosporins.<sup>7</sup> Fourth generation cephalosporin and macrolide were the most susceptible antibiotic in their study,<sup>7</sup> whereas, our study showed nitrofurantoin, amikacin, piperacillin-tazobactam and cefoperazone-sulbactam as the most common sensitive antibiotics.

Another study conducted in Delhi, showed that the common organisms causing community-acquired UTI were *E. coli* (68%), *Klebsiella* (16.9%) and *Proteus* (5.5%). Meropenam was the most sensitive antibiotic (100%) followed by piperacillin-tazobactam (90.2%), amikacin (75.6%) and nitrofurantoin (65.7%).<sup>8</sup>

In a study conducted in Karnataka,<sup>9</sup> a total of 181 diabetics (83 males and 98 females) and 124 non-diabetic subjects (52 males and 72 females) with UTI and significant colony count were studied. Asymptomatic bacteriuria was one of the common presentation (30%) of both diabetic and non-diabetic patients, and the prevalence of pyelonephritis in diabetic patients was significantly higher ( $P = 0.04$ ) when compared to non-diabetic patients.

In conclusion, when patients present with symptoms of UTI, laboratory tests are necessary to make a diagnosis, identify the organisms and to provide appropriate antibiotic treatment. But empirical antibiotic has to be administered while awaiting culture reports. The appropriate antibiotic can be added by the clinician only when the data regarding the uropathogen and their antibiotic susceptibility in that locality is available for them. This study concludes that *E. coli* (59.4%) and *K. pneumoniae* (14.2%) were the common organisms and both were most sensitive to nitrofurantoin among oral antibiotics and amikacin among parenteral antibiotics.

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# Morphological Variations of Human Placentae in Preterm Labor, Pregnancy-induced Hypertension, and Gestational Diabetes Mellitus

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## Abstract

**Background:** Preterm birth is one of the primary causes of perinatal mortality and morbidity. Pregnancy-related conditions causing preterm labor are associated with gross morphological changes in placenta, the fetomaternal organ which is vital for maintaining pregnancy and for promoting intrauterine growth of the fetus.

**Objectives:** To study the morphological variations of human placenta in preterm labor, to compare the findings of the study with the morphology of human placenta of normal pregnancies, and to correlate the morphologic changes of the placenta in preterm labor with fetal outcome.

**Materials and Methods:** A cross-sectional study was conducted among 695 placentae delivered from the Department of Obstetrics and Gynaecology, Dr. Somervell Memorial CSI Medical College, Karakonam, during a period of 6-month from June 2016. The gross morphological and histological examinations of placentae were performed.

**Results:** There were 50 preterm placentae including 30 from pregnancy-induced hypertension (PIH), 10 from gestational diabetes mellitus (GDM), and 2 from anemic pregnant mothers. The preterm placentae from PIH showed a significant reduction in placental weight, diameter and thickness and significantly more incidence of infarction, retroplacental hematoma, and calcification. Histologically, placentae in PIH showed significantly large number of syncytial knots, cytotrophoblastic proliferation, fibrinoid necrosis, and villus hyalinization. Newborn babies of mothers with PIH showed significant reduction of birth weight and low Apgar score. 50% of the preterm placentae from GDM were heavier, paler, and thick.

**Conclusion:** Prominent risk factors of preterm labor were PIH and GDM. PIH showed significant differences in various parameters of placental morphology and histology and fetal outcome.

**Key words:** Fetal outcome, Gestational diabetes mellitus, Placenta, Pregnancy induced hypertension, Preterm labor

## INTRODUCTION

The human placenta is the vital organ for maintaining pregnancy and promoting development of the fetus in utero.<sup>1</sup>

Placenta is an intrauterine fusion of fetal and maternal tissues for the purpose of physiological transfer of nutrients and oxygen from mother to fetus and transfer of waste products of metabolism from fetus to mother for continuation of fetal life. The intrauterine existence of fetus is dependent on this vital organ. Placenta has been considered as a valuable indicator for fetal and maternal diseases and conditions.<sup>2</sup>

Many maternal diseases or disorders are associated with high perinatal morbidity and mortality and gross pathological changes in placenta.<sup>1</sup> Abnormal placenta adversely affects the fetal outcome.<sup>3</sup>

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As placenta is the mirror of maternal and fetal status, complications in pregnancy reflect in the placenta in a significant way both macroscopically and microscopically.<sup>4,6</sup>

Preterm birth<sup>7</sup> is the primary cause of perinatal mortality and morbidity. The American College of Obstetricians and Gynaecologists (2016)<sup>7</sup> defined preterm labor or premature labor as regular contractions of the uterus resulting in changes in the cervix that start before 37 weeks of pregnancy. Changes in the cervix include effacement and dilation so that the fetus can enter the birth canal.

Globally, perinatal mortality rate<sup>8</sup> is 49.6 per 1000 live births. One of the major causes of perinatal mortality is preterm birth and it accounts for 6-10% of all births. Preterm labor has become a significant public health issue leading to perinatal mortality in developing countries.<sup>9</sup>

Among the various factors,<sup>9</sup> pregnancy-induced hypertension (PIH) and gestational diabetes mellitus (GDM) are two important high-risk factors for preterm birth. Other factors that increase the risk of preterm birth include the following:

- Having a previous preterm birth
- Having a short cervix
- Short interval between pregnancies
- History of certain types of surgery on the uterus or cervix
- Multiple pregnancy and Antepartum hemorrhage
- Lifestyle factors such as low prepregnancy weight of the mother, smoking or substance abuse during pregnancy
- Anemia complicating pregnancy.

Hypertension in pregnancy is responsible for 5-8% of all maternal deaths.<sup>10</sup> Hypertensive disorders of pregnancy are strongly associated with fetal growth retardation and prematurity leading to perinatal morbidity and mortality.<sup>4,6</sup>

GDM<sup>11</sup> is defined as any degree of glucose intolerance with onset or first recognition during pregnancy. In women with average or high-risk (marked obesity, personal history of GDM, glycosuria, or a strong family history of diabetes), the plasma glucose concentration 1 h after a 50 g oral glucose load (glucose challenge test), followed by a diagnostic oral glucose tolerance test on the women exceeding the glucose threshold value ( $>140$  mg/dl) at glucose challenge test confirms the diagnosis. GDM is a pregnancy-related condition causing high maternal morbidity and increased risk of perinatal morbidity and mortality.

Anemia exerts profound changes on the maternal circulatory system and has serious effects on both mother and fetus. Anemia in mother leads to hypoxia which results in low birth weight of baby and premature delivery.

The prevalence of these risk factors of preterm labor shows geographical variations.

This research work has been conducted with the objectives to find the prevalence of preterm labor and to study the morphological variations of human placenta in conditions leading to preterm labor at Dr. Somervell Memorial CSI Medical College, Karakonam, a health-care facility in rural South Kerala, India.

### Objectives

- To study the morphological variations of human placenta in preterm labor
- To compare the findings of the study with those of human placentae of normal pregnancies
- To correlate the morphologic changes of placenta in preterm labor with fetal outcome.

## MATERIALS AND METHODS

A cross-sectional study was conducted among placentae from 659 pregnant ladies admitted in the labor room, Department of Obstetrics and Gynaecology, Dr. Somervell Memorial CSI Medical College, Karakonam, South Kerala, India, during a period of 6-month from June 2016.

Placentae from those pregnant women who delivered before 37 weeks of pregnancy were considered as the preterm group. Placentae from mothers having normal, uncomplicated pregnancy formed the normal group.

### Inclusion Criteria

Those pregnancies with preterm labor.

### Exclusion Criteria

All pregnant mothers with a history of hypertension or diabetes mellitus detected before pregnancy.

Before the study, approval from the Institutional Ethics Committee and permission from the Head of the Department of Anatomy and Head of Department of Obstetrics and Gynecology were obtained. Informed consent was taken from the parents of the newborns.

### Definitions

- Pregnant mothers who had blood pressure at or above 140/90 mm of Hg on at least two occasions 6 h apart diagnosed for the first time after 20 weeks of gestation, with or without edema and/or proteinuria formed the PIH group.
- Mothers having a fasting plasma glucose level  $>126$  mg/dl, or an occasional plasma glucose  $>200$  mg/dl detected for the first time after pregnancy were included as having GDM.

- Pregnant mothers with hemoglobin (Hb) level <11 g/dl formed the anemic group. According to the WHO<sup>12</sup> classification, anemic group was divided into 3 groups:
  - Group a - Mild anemia (Hb level 11-10 g/dl)
  - Group b - Moderate anemia (Hb level 10-7 g/dl)
  - Group c - Severe anemia (Hb level <7 g/dl).

#### Method of Data Collection using Pretested Schedule

Clinical findings of mothers were collected from case sheets, along with recording of their obstetric and medical history. Their investigation reports were noted (blood sugar, urea, creatinine, Hb levels, urine for albumin, pus cells, and ophthalmic examinations). Mothers were considered to be hypertensive if the blood pressure was 140/90 or above mm of Hg. Mothers with blood sugar levels higher than normal as per definition were considered to be having gestational diabetes.

Placentae were collected immediately after vaginal delivery and cesarean section and were washed in running tap water. The placenta along with cord were coded. Any abnormality of cord and membranes was noted and were cutoff by sharp scissors. The placenta were cleaned and excess water was removed with blotting paper. Then, placenta were immersed in 10% formalin.

Examination of placenta was done for gross and histological studies.

Size, shape, surface area and thickness of placenta, number of cotyledons, presence of infarction, calcification, and site of insertion of umbilical cord were noted. The placental weight was taken using standard weighing machine.

Placental tissues were taken from the following sites for histological studies.

- Margins – at 12, 3, 6, 9 O' clock positions
- Near the insertion of the umbilical cord
- Center of the placenta
- Umbilical cord at placental junction and cut end
- Infarcted area if any
- Fibrotic area if any.

Placental tissues were stained and examined under microscope for number of syncytial knots, fibrinoid necrosis, cytotrophoblastic cell proliferation, calcification, and hyalinization of villi in the preterm group in comparison to normal group.

Neonatal outcome in the form of birth weight, Apgar score, presence of any congenital anomalies, need for neonatal resuscitation, and admission to newborn intensive care unit were noted. Fetal-placental weight ratio was calculated in each case.

Statistical analysis was made using Chi-square test and Student's *t*-test.

## RESULTS AND DISCUSSION

Among 695 placenta delivered from the Department of Obstetrics and Gynaecology, Dr. Somervell Memorial CSI Medical College, Karakonam, during a period of 6-month from June 2016, 50 placenta were from preterm labor. The gross morphological and histological findings of preterm placenta were compared with a normal group of significantly comparable maternal age and parity.

The prevalence of preterm labor was 7.19% in this study (Table 1).

Prominent risk factors of preterm labor in this study were PIH (60%) and GDM (20%) (Table 2) (Figure 2).

In this study, 26.7% hypertensive placenta were irregular in shape (Figure 2). A study conducted by Agarwal *et al.*<sup>13</sup> did not show a significant variation of shape in hypertension.

The incidence of infarction among placenta of the PIH was 36.7% and the same of the nonhypertensives was 6.7% in the present study.

Udaina *et al.*<sup>4</sup> and Majumdar and Dasgupta,<sup>5</sup> and Corrêa *et al.*<sup>6</sup> made similar observation in their study.

In this study, the presence of infarction was related to low birth weight and intrauterine death (IUD) of fetus (Table 3).

**Table 1: Distribution of placenta-based on term of delivery**

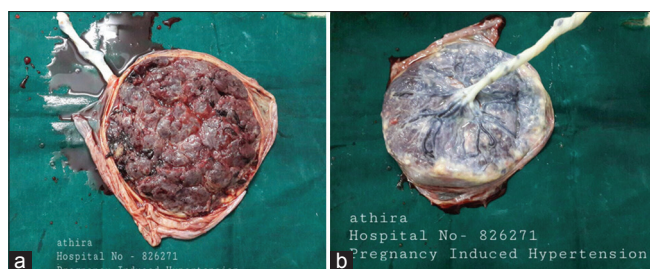
Category	Number of placenta (%)
Term	645 (92.806)
Preterm	50 (7.194)
Total	695 (100)

**Table 2: Distribution of preterm placenta (N=50) and risk factors**

Risk factor of preterm labor	Number of cases (%)
Pregnancy induced hypertension	30 (60)
Gestational diabetes mellitus	10 (20)
Low prepregnancy weight of mother	4 (8)
Anemia	2 (4)
Multiple (twin) gestation	1 (2)
Antepartum hemorrhage	1 (2)
Cervical incompetence	1 (2)
Hypothyroidism	1 (2)
Total	50 (100)

**Table 3: Gross appearance of placentae (normal vs. pregnancy induced hypertension)**

Placental features	Component	N (%)		“Z”	Significance
		Pregnancy-induced hypertension	Normal		
Shape	Discoid	22 (73.3)	30 (100)	5.894	$P < 0.001$
	Irregular	8 (26.7)	0 (0.0)		
Presence of hematoma	Yes	2 (6.7)	0 (0.0)	1.433	$P > 0.05$
	No	28 (93.3)	30 (100)		
Presence of infarction	Yes	11 (36.7)	2 (6.7)	2.821	$P < 0.01$
	No	19 (63.3)	28 (93.3)		
Presence of calcification	Yes	17 (56.7)	7 (23.3)	2.635	$P < 0.01$
	No	13 (43.3)	23 (76.7)		

**Figure 1: Preterm placenta from twin gestation****Figure 2: (a and b) Placenta from pregnancy-induced hypertension (maternal and fetal aspect)**

Placental features such as placental weight, diameter, thickness, and number of cotyledons were significantly less in PIH (Figure 3) compared to normal group (Table 4).

Similar findings were reported from other studies<sup>5,6,13</sup> also. In the studies by Udaina *et al.*,<sup>4</sup> Sheetal *et al.*,<sup>14</sup> Virupaxi *et al.*,<sup>15</sup> Dadhich *et al.*,<sup>16</sup> Barker *et al.*,<sup>17</sup> Londhe and Mane,<sup>18</sup> and Eriksson *et al.*<sup>19</sup> placental weight was seen significantly reduced in the PIH group.

Dadhich *et al.*<sup>16</sup> and Pandure and Ghosh<sup>20</sup> observed that both diameter and thickness of placenta were significantly reduced in the hypertensive placentae.

In the present study, fetal-placental weight ratio was not showing statistically significant relation between the two groups. Another study<sup>21</sup> by Vijayalakshmi and Kittali has reported increased F/P weight ratio in the hypertension complicating pregnancy.

#### Insertion of Umbilical Cord

Udaina *et al.*,<sup>4</sup> Majumdar and Dasgupta,<sup>5</sup> and Vijayalakshmi and Kittali<sup>21</sup> observed that marginal insertion of cord was significantly associated with hypertensive placentae.

In the PIH group of this study, five placentae showed abnormal insertion of cord. Among them, four placentae showed marginal insertion (Figure 4) and one showed velamentous insertion while the placentae of normotensive group showed central insertion of umbilical cord. There was insignificant association between insertion of umbilical cord and PIH ( $P > 0.05$ ).

#### Histology of Placenta in PIH

Placentae in PIH showed significantly large number of syncytial knots, cytotrophoblastic proliferation, fibrinoid necrosis, and villus hyalinization compared to normal group in this study.

Many other studies<sup>4,6</sup> show similar finding.

In this study, Apgar score of new born babies was found to be significantly low in the hypertensive group ( $P < 0.001$ ) (Table 5).

The means of Apgar score of babies at birth of PIH and nonhypertensive groups were  $6.9 \pm 1.8$  and  $9 \pm 0$  and the same at 5 min were  $8.5 \pm 0.8$  and  $10 \pm 0$ , respectively (Table 6).

Similar finding was observed by Majumdar and Dasgupta<sup>5</sup> and Duley.<sup>22</sup>

There were two cases of IUDs in the PIH group.

Similar finding was observed by Pandure and Ghosh<sup>20</sup> who found that preterm labor and preterm birth associated with increased fetal mortality.



**Table 4: Gross morphology of placentae (normal vs. pregnancy induced hypertension)**

Placental features	Pregnancy induced hypertension		Normal		Difference of means	't'	df	Significance
	N	Mean±SD	N	Mean±SD				
Placental weight	30	455.7±59.9	30	516.7±25.7	60.3	5.073	58	P<0.01
Placental diameter	30	14.1±0.7	30	19.1±0.9	5.0	24.459	58	P<0.001
Placental thickness	30	1.9±0.9	30	2.4±0.1	0.5	3.023	58	P<0.01
Cotyledons	30	16.1±2.5	30	19.1±1.2	3.0	6.080	58	P<0.001
Fetal-placental ratio	30	5.5±1.9	30	5.6±0.7	0.1	0.193	58	P>0.05

SD: Standard deviation

**Figure 3: Placenta from pregnancy-induced hypertension****Figure 4: Marginal insertion of umbilical cord**

### Comparison of Placentae in Normal versus Gestational Diabetes

This study was found that in gestational diabetes; there was increased birth weight of babies. The placentae of gestational diabetic mothers showed significant increase in size, weight, and volume in the present study (Figures 5 and 6).

Radaelli *et al.* (2003), Segregur *et al.* (2009), and Fahima Akhter *et al.*<sup>9</sup> found that placentae of diabetic mothers show significant increase in size, weight, volume, area, thickness, diameter, and circumference than those of normal mothers.

**Table 5: Comparison of pregnancy outcome (normal vs. PIH)**

Pregnancy outcome	Component	N (%)		"Z"	Significance
		PIH=30	Normal=30		
Mode of delivery	Vaginal	18 (60.0)	27 (90.0)	2.860	P<0.01
	LSCS	12 (40.0)	3 (10.0)		
Type of birth	Live	28 (93.3)	30 (100)	1.468	P>0.05
	IUD	2 (6.7)	0 (0.0)		
NICU admissions	Yes	9 (30.0)	0 (0.0)	3.586	P<0.001
	No	21 (70.0)	30 (100)		

PIH: Pregnancy-induced hypertension, NICU: Neonatal intensive care, LSCS: Lower segment cesarean section, IUD: Intrauterine fetal death

Furthermore, placentae from diabetic mothers showed significant increase in villous edema, fibrin deposition, calcification, and congestion of blood vessels.

### Comparison of Placentae in Normal versus Anemia

In this study, the placental weight and volume were reduced in anemia (Hb 9 g/dl) complicating pregnancy. Chavez and Corral M (2003) stated that there is increase in placental weight and placental weight/newborn baby weight ratio in placenta from anemic pregnancies. Huang *et al.* (2001) stated that placental volume was significantly increased in anemic group and the uniform enlargement of placenta was a physiological compensatory growth.

## CONCLUSION

The prevalence of preterm labor was 7.19% in the present study. Prominent risk factors of preterm labor were PIH and GDM. 60% of preterm placentae from PIH were delivered by early induction for the sake of mother and new born. PIH showed significant differences in various parameters of placental morphology and histology and fetal outcome. There were two cases of preterm IUD in the PIH group. In GDM, there was increased birth weight of babies. Placentae from pregnancy with combined PIH and GDM were normal in size and volume. The preterm placentae of gestational diabetic mothers showed significant increase in size, weight, and volume in the present study. Examination of the placenta

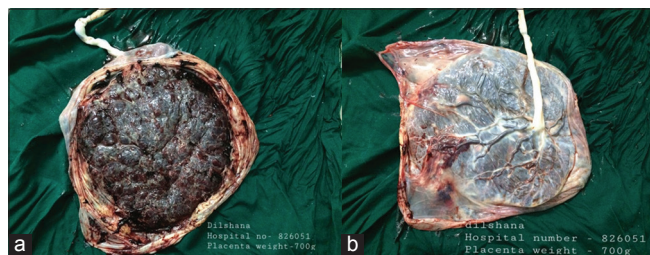
**Table 6: Comparison of fetal outcome (normal vs. PIH)**

Variable	PIH=30		Normal=30		Difference of means	“t”	df	Significance
	N	Mean±SD	N	Mean±SD				
Birth weight	30	2.5±0.7	30	2.9±0.4	0.4	2.973	58	P<0.01
Apgar score at birth	28	6.9±1.8	30	9±0	2.1	6.294	56	P<0.001
Apgar score at 5 min	28	8.5±0.8	30	10±0	1.5	10.13	56	P<0.001

PHI: Pregnancy-induced hypertension, SD: Standard deviation



**Figure 5: Placenta from gestational diabetes mellitus (weight 750 g)**



**Figure 6: (a and b) Placenta from gestational diabetes mellitus**

gives valuable information about the perinatal health of the new born baby and the mother.

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# Pattern of Lipid Profile Abnormality in Subjects with Prediabetes

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## Abstract

**Introduction:** Diabetes is one of the most prevalent diseases in the world. Diabetes mellitus is a metabolic disorder characterized by hyperglycemia. Worldwide, the prevalence is increasing dramatically over decades.

**Materials and Methods:** It is a cross-sectional case-control study. The sample size: 100 cases and 100 age and sex matched controls meeting inclusion criteria of this study from outpatients and inpatients of K R Hospital, Mysore.

**Results:** The overall presence of abnormal serum total cholesterol (TC), low-density lipoprotein (LDL), triglycerides (TGs), very LDL (VLDL), TG/high-density lipoprotein (HDL) ratio, and LDL/HDL ratio with statistical significance is tabulated in tables.

**Conclusion:** TC, LDL, TG, and VLDL were significantly raised in prediabetics as compared to normal healthy subjects whereas HDL was significantly lower in prediabetics as compared to normal healthy subjects.

**Key words:** Cholesterol, diabetic dyslipidemia, prediabetics

## INTRODUCTION

Diabetes is one of the most prevalent diseases in the world. Diabetes mellitus (DM) is a metabolic disorder characterized by hyperglycemia. Worldwide, the prevalence is increasing dramatically over decades. The International Diabetes Federation predicts 592 million diabetes individuals by 2035. India holds second place among countries with the greatest number of individuals with diabetes. There were 69.1 million cases of diabetes in India. Diabetes is seventh leading cause of death as per statistics in 2010. According to ICMR INDIAB study phase<sup>1</sup> showed the prevalence of diabetes in Tamil Nadu was 10, 4%, Jharkhand 5.3% Chandigarh 13.6%, and Maharashtra 8.4%. Except in Chandigarh, the prevalence of prediabetes was higher in urban areas in all age groups.

Prediabetes or intermediate hyperglycemia is classified as impaired fasting glucose (IFG) = fasting plasma glucose (FPG) = 5.6-6.9 mmol/L, impaired glucose tolerance (IGT) with plasma glucose 7.8 – 11 mmol/L after oral glucose challenge or hemoglobin A<sub>1c</sub> of 5.7 - 6.4%. Prediabetes individuals are at high risk of developing diabetes, and aggressive management of cardiovascular risk factors such as hypertension and dyslipidemia should be ensured.

The vascular complications of DM can be microvascular (retinopathy, nephropathy, and neuropathy) and macrovascular complications (coronary heart disease, peripheral vascular disease, and cardiovascular disease [CVD]). Macrovascular complications are similar to nondiabetics at a greater frequency.

Dyslipidemia increases macrovascular complications in prediabetes and diabetics. The prevalence of dyslipidemia ranged from 75.7% in urban Maharashtra to 87.2% in urban Chandigarh, and 76.5% in rural Tamil Nadu to 81.1% in rural Chandigarh. The prevalence of coronary artery disease was higher among diabetic subjects compared to normal with Maharashtra having the highest prevalence. Diabetic dyslipidemia commonly includes

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hypertriglyceridemia and reduced high-density lipoprotein (HDL) and increased small density low-density lipoprotein (LDL) particles.

Prediabetics have deranged lipid profile as compared to normal subjects and hence more prone to develop cardiovascular mortality.<sup>1-6</sup>

## MATERIALS AND METHODS

- Study design: Cross-sectional case-control study
- Sample size: 100 cases and 100 age and sex matched controls meeting inclusion criteria of this study from outpatients and inpatients of K R Hospital, Mysore
- Duration of study: 6 months from 20<sup>th</sup> August 2016 to 20<sup>th</sup> January 2017.

### Inclusion Criteria

1. IFG - FPG levels of 100-125 mg/dl
2. IGT - 2 h oral glucose tolerance test (OGTT) values of 140-199 mg/dl.

### Exclusion Criteria

1. Age <18 years
2. Patients diagnosed with Type 1? Type 2 diabetes
3. Patients with known thyroid dysfunction
4. Patient already on lipid lowering drugs
5. Pregnancy.

The study was initiated after clearance from the Institutional Ethics Committee. Biochemistry measurements including fasting blood sugar, 2 h OGTT, serum total cholesterol (TC), triglyceride (TG), HDL, and LDL, and very LDL (VLDL) were done. Normal levels of lipids were considered as per National Cholesterol Education Program ATP III classification (Table 1).

### Statistical Analysis

Statistical analysis was performed using descriptive statistics and inferential statistics, using Chi-Square test, odd's ratio, Pearson's correlation coefficient, and multiple regression analysis. The software used in this analysis was SPSS version 17.0 and Graph Pad Prism version 5.0. A  $P < 0.05$  was considered as a level of significance.

## RESULTS

The overall presence of abnormal serum TC, LDL, TGs, VLDL, TG/HDL ratio, and LDL/HDL ratio with statistical significance is given in Table 2.

## DISCUSSION

### TC

In our study, mean value of TC for cases ( $190.58 \pm 47$  mg/dL) was more than controls ( $105.92 \pm 22.2$  mg/dL) (Table 2).  $P$  value was 0.00 ( $P < 0.05$ ), (Table 3) i.e., significant. Similarly, Williams *et al.* studied data from National Health and Nutrition Examination Survey done in 1999-2000. The mean TC of the prediabetic subjects were higher (174.2 mg/dL) than the controls (157.5 mg/dL). They concluded that adolescents with IFG had significantly high TC than adolescents with normal fasting glucose (NFG).<sup>7</sup>

### LDL

In our study, mean value of LDL for case ( $124 \pm 32.49$  mg/dL) (Table 2) was more than controls ( $38 \pm 13.82$  mg/dL).  $P$  value was 0.00 ( $P < 0.05$ ), (Table 3) i.e., significant.

**Table 1: NCEP ATP III classification of lipid levels**

Risk	LDL-c	HDL-c		TGs	Cholesterol
		Male	Female		
High	$\geq 160$	$< 40$	$< 50$	$\geq 200$	$\geq 240$
Borderline	$\geq 130-169$	40-59	50-69	150-199	200-239
Desirable	100-129	$> 60$	$> 70$	$< 150$	$< 200$
Optimal	$< 100$				

LDL-c: Low-density lipoprotein-cholesterol, HDL-c: High-density lipoprotein-cholesterol, TGs: Triglycerides, NCEP: National Cholesterol Education Program

**Table 2: LDL/HDL ratio with statistical significance**

Parameters	Group	N	Mean $\pm$ SD	SEM
TC	Experimental	50	190.5800 $\pm$ 47.05407	6.65445
	Control	50	105.9200 $\pm$ 22.24157	3.14543
TGs	Experimental	50	129.1400 $\pm$ 36.60490	5.17671
	Control	50	91.5800 $\pm$ 19.20256	2.71565
HDL	Experimental	50	27.2800 $\pm$ 9.55124	1.35075
	Control	50	39.7200 $\pm$ 9.63844	1.36308
LDL	Experimental	50	124.0400 $\pm$ 32.49676	4.59574
	Control	50	38.9340 $\pm$ 13.82266	1.95482
VLDL	Experimental	50	49.2160 $\pm$ 13.90339	1.96624
	Control	50	24.2440 $\pm$ 6.98141	0.98732

LDL: Low-density lipoprotein, VLDL: Very low-density lipoprotein, HDL: High-density lipoprotein, TGs: Triglycerides, SD: Standard deviation, SEM: Standard error of mean, TC: Total cholesterol

**Table 3: Lipid profile in cases and controls**

Parameters	t-test for equality of means			
	t	df	Significant (two-tailed)	Mean difference
TC	11.502	98	0.000	84.66000
TGs	6.425	98	0.000	37.56000
HDL	6.483	98	0.000	12.44000
LDL	17.041	98	0.000	85.10600
VLDL	11.350	98	0.000	24.97200

LDL: Low-density lipoprotein, VLDL: Very low-density lipoprotein, HDL: High-density lipoprotein, TGs: Triglycerides, TC: Total cholesterol



Similarly, Rahbar *et al.* reported that prediabetics are at higher risk of having increased level of LDL-cholesterol.<sup>8</sup> Furthermore, Magge *et al.* observed that obese prediabetic adolescents have a significantly more atherogenic lipoprotein profile compared with obese normoglycemic peers.<sup>9</sup>

Similarly, Miyazaki *et al.* observed high LDL levels in prediabetic subjects. Moreover, they stated that the lipid profile in IFG/IGT appears to be very similar to “diabetic dyslipidemia” in T2DM.<sup>10</sup> Shin *et al.* also found a statistically significant difference in LDL between nondiabetes controls ( $n = 172$ ) and prediabetes subjects ( $n = 138$ ) with a mean LDL  $134 \pm 34.6$  mg/dL and  $150.5 \pm 38.0$  mg/dL, respectively. They proved that there was a positive correlation between raised blood glucose and LDL.<sup>11</sup>

### HDL

In our study, mean value of HDL for case ( $27.28 \pm 9.55$  mg/dL) was lower than controls ( $39.72 \pm 9.63$  mg/dL) (Table 2).  $P$  value was 0.000 ( $P < 0.05$ ), i.e., (Table 3) significant. Similarly, Rahbar *et al.* showed that prediabetics are at higher risk of having a low level of HDL-cholesterol. Impaired lipid profile, i.e., dyslipidemia is commonly associated with CVD in Type 2 diabetes and can also occur in prediabetics.<sup>8</sup> Similarly, Miyazaki *et al.* observed low HDL levels in prediabetic subjects than controls.<sup>10</sup> Shin *et al.* also concluded that there is statistical significant difference in mean HDL between nondiabetes controls ( $n = 172$ ) and prediabetes ( $n = 138$ ) subjects with a mean HDL (mg/dl)  $54.7 \pm 13.3$  and  $49.9 \pm 11.6$  mg/dl, respectively. They proved that there is a positive correlation between raised blood glucose and HDL.<sup>11</sup>

### TGs

Mean value of TG for case ( $129 \pm 36.6$  mg/dL) was higher than controls ( $91.58 \pm 19.20$  mg/dL) (Table 2).  $P$  value was 0.000 ( $P < 0.05$ ), i.e., significant. Similarly, Rahbar *et al.* showed that prediabetics are at higher risk of having high TG.<sup>8</sup> Furthermore, Barzi *et al.*, Gaziano *et al.*, Kansal *et al.*, and Boizel *et al.* observed that TG levels were significantly higher in IFG/IGT compared to NFG/normal glucose tolerance.<sup>12-14</sup> Similarly, Miyazaki *et al.* in their study observed raised TG levels in prediabetic subjects.<sup>10</sup>

### VLDL

In our study, mean value of VLDL for case ( $49.21 \pm 13.90$  mg/dL) was more than controls ( $24.34 \pm 6.98$  mg/dL) (Table 2).  $P$  value was 0.000 ( $P < 0.05$ ), i.e., (Table 3) significant. Kansal *et al.* showed that VLDL levels were significantly higher in prediabetics.<sup>15-23</sup>

## CONCLUSION

TC, LDL, TG, and VLDL were significantly raised in prediabetics as compared to normal healthy subjects whereas HDL was significantly lower in prediabetics as compared to normal healthy subjects. These prediabetics are highly prone for cardiovascular complications. Through this study, we recommend screening of prediabetics for dyslipidemia to prevent early cardiovascular complications.

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# Retroperitoneal Soft Tissue Sarcoma: An Analysis of Surgical and Adjuvant Chemotherapy

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## Abstract

**Introduction:** Soft tissue sarcomas are a rare and heterogeneous group of tumors that arise from the supporting skeletal tissue.

**Aim:** To study the epidemiology, various presentation, and the response to the surgery and adjuvant chemotherapy.

**Materials and Methods:** A prospective observational study on retroperitoneal sarcoma was conducted in the Department of Surgical Oncology.

**Results:** A total of 21 patients were taken in the study and the age incidence is mainly in the 5<sup>th</sup> decade as with other study. The major histopathological examination of retroperitoneal sarcoma was liposarcoma followed by leiomyosarcoma.

**Conclusion:** Most of the tumors occur in the 5<sup>th</sup> decade, and surgery was the mainstay of treatment. Only primitive neuroectodermal and rhabdomyosarcoma showed good results with chemotherapy.

**Key words:** Retroperitoneal sarcoma resection of tumor, Soft tissue sarcoma, Tumor grade

## INTRODUCTION

Soft tissue sarcomas are the most frequent sarcomas. They are a rare and heterogeneous group of tumors that arise from the supporting extraskelatal tissues.<sup>1</sup> Soft tissue sarcomas are disease of adulthood, occurring most commonly in persons between 30 and 60 years of age. The sole exception is rhabdomyosarcoma, which occurs in young children. Each of the various soft tissue sarcomas has a unique morphology, biological behavior, and characteristics.<sup>2</sup> The clinical, radiographic, and surgical management of most soft tissue sarcomas is identical, regardless of histogenesis. The treatment of soft tissue sarcoma has become multidisciplinary, as advances in biology, imaging, surgery, chemotherapy, and radiotherapy have improved the outlook for these patients who have these malignancies.<sup>3</sup> Fifteen percent of adult

soft tissue sarcomas occur in the retroperitoneum. Most retroperitoneal tumors are malignant, and about one-third are soft tissue sarcomas. The most common sarcomas occurring in the retroperitoneum are liposarcomas, malignant fibrous histiocytomas, and leiomyosarcomas. The size at presentation depends on the location. Tumors in the proximal extremities and retroperitoneum are often quite large, whereas distal extremity tumors are often small. The anatomic site of the primary disease represents an important variable that influences treatment and outcome. Soft tissue sarcomas of the extremities account for about 50% of all sarcomas, gastrointestinal (GI) sarcomas for 25%, retroperitoneal sarcomas for 15-20%, and head and neck for 9%.<sup>4</sup>

## Aim

The aim of the study was to study the stage of the disease at presentation, incidence of various pathological types, and incidence of the grade of the tumor.

## MATERIALS AND METHODS

This prospective observational study was conducted in the Department of Surgical Oncology, Government

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Royapettah Hospital, Chennai. Patients admitted for retroperitoneal sarcoma were included in the study. The institutional ethics committee approval and informed consent were obtained. Histories such as abdominal mass, its duration, presence of pain and its duration, other symptoms, and family history were recorded. Previous history of surgery, biopsy if any, and treatment were taken. Physical examination was done to note site, size of swelling, and presence or absence of metastases. Chest X-ray, computed tomography (CT) abdomen, and CT chest were taken in all patients. Histopathology, grade, and margin status were noted. Histopathology is compared with previous reports.

## RESULTS

Retroperitoneal sarcoma consisted of 0.16% of all cancers admitted in the institute (Table 1).

Retroperitoneal sarcoma forms 9.85% of all soft tissue sarcomas (Table 2).

In this study, incidence of retroperitoneal sarcoma was seen more in males than in females in a ratio of males females 2.5:1 (Table 3).

According to literature,<sup>4</sup> the most common histopathologic types in the retroperitoneum are liposarcoma (40%), leiomyosarcoma (25%), malignant peripheral nerve sheath tumor (MPNST), and fibrosarcoma. Approximately 55% of retroperitoneal liposarcomas are well differentiated and low grade, with tumors in roughly 40% of patients showing

dedifferentiated, high-grade histologic features at primary presentation. In this study, the results are the same as that of literature with liposarcoma (52.38%) being the most common histopathology (Table 4).

As per literature, the peak incidence is in the 5<sup>th</sup> decade of life although they can occur in any age group.<sup>5</sup> The study findings bide with literature results with peak incidence in 5<sup>th</sup> decade, accounting about 33.33% of the all age groups (Table 5).

Most of the retroperitoneal sarcoma are large at the time of presentation and are considered as deep tumors according to the AJCC staging. All belong to T2b. The average size of the tumor at presentation 15.19 cm. The median size of retroperitoneal sarcoma is 25 cm. As per literature, most of the retroperitoneal sarcoma was seen in Stage III accounting to 62%. Only one case was found to be in Stage IV in this study. At the time of presentation, the majority were primary tumors but few of them were recurrent (Table 6).

Out of the two recurrent cases, one of them was a case of 2<sup>nd</sup> time recurrence and the other 3<sup>rd</sup> time recurrence (Table 7).

**Table 1: Prevalence of retroperitoneal sarcoma**

Cancers	Number (%)
Retroperitoneal sarcoma	21 (0.16)
Other	12990 (99.83)
Total	13011 (100)

**Table 2: Distribution of soft tissue sarcoma**

Cancers	Number (%)
Retroperitoneal sarcoma	21 (9.85)
Other soft tissue sarcoma	192 (90.14)
Total	213 (100)
Sex ratio	

**Table 3: Gender wise distribution**

Sex	Frequency (%)
Male	15 (71.42)
Female	6 (28.57)
Total	21 (100)

**Table 4: Pathological presentation**

Histopathology	Frequency (%)
Liposarcoma	11 (52.38)
Leiomyosarcoma	4 (19)
PNET	3 (14.3)
Rhabdomyosarcoma	1 (4.7)
MPNST	2 (9.5)
Total	21 (100)

MPNST: Malignant peripheral nerve sheath tumour, PNET: Primitive neuroectodermal tumour

**Table 5: Age wise distribution**

Age groups	Frequency (%)
<20	2 (9.5)
21-30	4 (19)
31-40	1 (4.7)
41-50	7 (33.33)
51-60	3 (14.3)
61-70	3 (14.3)
>70	1 (4.7)
Total	21 (100)

**Table 6: Stage wise presentation**

Stage	Frequency (%)
IA	-
IB	7 (33.33)
IIA	-
IIB	-
III	13 (62)
IV	1 (4.7)



Management and work up plan of the recurrences were managed like as for primary tumors. Most patients present with an asymptomatic abdominal mass. On occasion, pain is present, and less common symptoms include GI bleeding, incomplete obstruction, and neurologic symptoms related to retroperitoneal invasion or pressure on neurovascular structures. Weight loss is uncommon, and incidental diagnosis is the norm. Some of the patients came with more than one complaint. Abdominal pain was the major complaint most of the patients in this study accounting about 47.6%. Neurologic symptoms were found to be high 42.85% when compared to the literature values 27% (Table 8).

In this study, only one case was incompletely resected and in literature incomplete resection is acceptable only in case of a retroperitoneal sarcoma with well-differentiated liposarcoma as the histopathology. In such cases, the long-term survival is significantly increased, whereas in other cases, incomplete resection has same survival rates as those without surgery. Out of the 8 cases which had complete resection, 3 cases were positive for margins. These cases were subjected to postoperative radiotherapy (Tables 9 and 10).

**Table 7: Recurrence presentation**

Presentation	Frequency (%)
Primary	19 (90.47)
Recurrence	2 (9.52)
Total	21 (100)

**Table 8: Symptoms at presentation**

Symptoms	Frequency (%)
Abdominal pain	10 (47.6)
Abdominal mass	6 (28.5)
GI bleed	1 (4.7)
Neurologic	9 (42.85)
GI: Gastrointestinal	

**Table 9: Management**

Treatment	Frequency (%)
Complete resection	8 (35)
Incomplete resection	1 (4.7)
Inoperable	6 (28.5)
Metastasis	1 (4.7)
Chemotherapy without surgery	5 (23.8)

**Table 10: Margin of resection**

Margin	Frequency (%)
Positive	3 (37.5)
Negative	5 (62.5)
Total	8 (100)

In a study of 28 patients with liposarcomas, adjacent organ resection was carried out in more than half the cases, with partial or total resection of the kidneys in 60%, colon in 50%, and adrenal glands in 35%. Although nephrectomy was performed in 60% of cases, the kidney itself was rarely involved. Nevertheless, the encompassment of the kidney and the involvement of the hilar renal vasculature make the resection of the kidney often necessary.

In this study, 11 cases went in for adjacent organ resection. Nephrectomy was the most common procedure done along with the resection of the tumor. Left kidney removal (55.55%) was more common than right kidney removal (11.11%). Most common bowel loops to be resected was descending colon. In most of the cases, descending colon was completely removed and distal 2/3<sup>rd</sup> transverse colon was anastomosed to either sigmoid colon or rectum. The majority of cases which are inoperable are due to vascular involvement (19%). Vascular structures commonly involved are inferior vena cava and common iliac veins (Table 11).

In this study, no vascular resection and reconstruction was done (Table 12). Such cases were given postoperative radiotherapy, but overall survival was the same. Radiotherapy helped in local control only in few patients and tumor was progressive in some cases. Out of the 21 cases, 12 cases (57.14%) had previous biopsy done. Pre-operative biopsy is required in case of high suspicion when there is chance of the retroperitoneal tumor being a lymphoma or primitive neuroectodermal tumor (PNET) where such radical resection is not at all required as they are curable by chemotherapy alone. In this study, high-grade tumors accounted for 66.66% (Table 13).

**Table 11: Adjacent organs involvement**

Adjacent organs removed	Frequency (%)
Kidney	6 (66.66)
Bowel loops	5 (55.55)
Total	11 (100)

**Table 12: Vascular resections**

Blood vessels	Frequency (%)
SVC	2 (50)
Common iliac vein	2 (50)
Total	4 (100)

SVC: Superior vena cava

**Table 13: Grade of the tumour**

Grade	Frequency (%)
High	14 (66.66)
Low	7 (33.33)
Total	21 (100)

According to literature, most of the retroperitoneal sarcoma was low-grade, well-differentiated tumors unlike the reports of this study. In this study, 5 cases had adjuvant and neoadjuvant chemotherapy. Especially, PNET, MPNST, and rhabdomyosarcoma responded well to chemotherapy.

## DISCUSSION

Retroperitoneal sarcoma forms 10-20% of the soft tissue sarcomas according to Mettlin *et al.*, but in this study, it accounts for 9.85% of soft tissue sarcomas, most of it occurs in males than in females in a ratio of 2.5:1.<sup>5</sup> As with other series, the age incidence is mainly in the 5<sup>th</sup> decade. The major histopathology of the retroperitoneal sarcoma is liposarcoma followed by leiomyosarcoma.<sup>6</sup> Majority of the cases at the time of presentation were about 15 cm in diameter and most belonged to Stage III (62%). Abdominal pain, discomfort, and neurologic pain were the most common presenting complaints. The majority were primary tumors and only 9.52% being recurrent tumors. About 35% of tumors were completely resectable and 28.5% were inoperable due to involvement or proximity to vascular structures. Only one case of metastasis was reported. Nearly 62.5% of operated cases were margin negative. Most of the tumors were high-grade tumors (66.66%).<sup>7</sup> Most of the resections involved adjacent organ removal with bowel loops and kidney being the common adjacent organs removed. Kidney (66.66%) removal was slightly more common than bowel removal (55.55%). Vascular involvement was seen in 19% of the cases. Only primitive neuroectodermal tumor and rhabdomyosarcoma showed good results with chemotherapy. Radiotherapy had no significant role in controlling local spread as well as on survival benefits.<sup>8-10</sup>

## CONCLUSION

Most of the tumor occurs in the 5<sup>th</sup> decade and surgery was the mainstay of treatment. Only primitive neuroectodermal and rhabdomyosarcoma showed good results with chemotherapy.

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# Histopathological Spectrum of Neoplastic and Non-neoplastic Breast Lesions: A Two Years Study

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## Abstract

**Introduction:** Lump in the breast is a sensitive issue for female patients. Timely and accurate diagnosis of a breast lump can not only alleviate anxiety but also early intervention can be lifesaving. In India, breast cancer forms the second most common malignancy after cervical cancer and is detected in 20/1,00,000 women.

**Purpose:** Many studies have been done and published on the histopathology of breast lesions. The present study was done in collaboration with Department of General Surgery to know the histopathological spectrum of breast lesions at SVS Medical College, Mahbubnagar.

**Materials and Methods:** A total of 168 cases of breast lesions were evaluated, including benign and malignant cases. Relevant clinical data were recorded in a pro forma. Appropriate areas were selected from the specimens received, and after processing, sections were made from them. These were stained with hematoxylin and eosin and observed under microscope.

**Results:** The results were analyzed, which show that the benign breast disease (82.7%) is much more common than the malignant lesions (16%). Moreover, among all the lesions, fibroadenoma (50.5%) was seen to be the most common one.

**Conclusion:** This study emphasizes the importance to recognize benign lesions and to distinguish them from carcinoma - *in situ* and invasive breast carcinomas. It is also important to assess a patient's risk of developing breast cancer so that the most appropriate treatment modality for each case can be established.

**Key words:** Benign, Breast, Fibroadenoma, Histopathology, Malignant

## INTRODUCTION

Lump in the breast is a sensitive issue for female patients. Timely and accurate diagnosis of a breast lump can not only alleviate anxiety but also early intervention can be lifesaving. Breast lesions have gained increasing importance and attained global attention because of increasing mortality and morbidity caused by breast cancer, which has become one of the leading causes of death among women. Awareness is widespread among women regarding lump in the breast.

Breast neoplasms are heterogeneous. Benign breast lesions being more common than malignant tumors. The

incidence of benign breast lesions begins to rise during the second decade of life, peaks in the fourth and fifth decades. Increased risk of breast cancer is associated with proliferative and atypical lesions. Diagnostic modalities such as mammography, ultrasonography, and fine-needle aspiration cytology are being increasingly used.

In India, breast cancer forms the second most common malignancy after cervical cancer and is detected in 20/1,00,000 women. Many studies have been done and published on the histopathology of breast lesions. The present study was done to know the histopathological spectrum of breast lesions at SVS Medical College, Mahbubnagar.

## MATERIALS AND METHODS

This study was done for 2 years (July 2014-June 2016) in the Department of Pathology, SVS General Hospital, to study the frequency and histopathological spectrum of various breast lesions. Total number of cases included

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under the study were 168, out of which biopsy specimens accounted for 15 cases, lumpectomy specimens were 141, and mastectomy specimens were 12 in number.

Relevant clinical data regarding age, history, and examination were recorded in a pro forma. The lesions were identified, surgically resected, and sent for histopathological examination. Gross examination of the specimens was recorded. Standard grossing techniques were followed, and sections were given. They were then fixed in 10% formalin for 24-48 h. An automatic processor was used for further processing of tissue blocks. This was followed with dehydration using ethyl alcohol (70% alcohol for 1 h × two changes, 90% alcohol for 2 h × two changes, and 100% alcohol for 2 h × two changes). Clearing in two changes of xylene for one hour each was done. Tissues were impregnated in two changes of paraffin wax with a melting point of 56°C for 3 h. Following this, embedding of the tissues was done in paraffin wax using L-shaped metallic molds. These blocks were put in the refrigerator for 4-6 h. Each block was cut on a rotary microtome. About 3-4 µm thick sections were obtained and placed in a water bath with a temperature of 5°C below the melting point of wax. Cut ribbons of tissues were placed on albumenized glass slides and stained with hematoxylin and eosin (H and E).

#### Rapid Hematoxylin and Eosin Staining Procedure

Adopted from Culling CFA, Dunn WL. Handbook of Histopathologic and Histochemical Techniques. 3<sup>rd</sup> ed. p. 210.

- 95% ethanol – 2 dips
- Distilled water – 5 dips
- Harris hematoxylin – 2 min
- Tap water – 3 dips
- Acid alcohol – 2 dips
- Tap water – 2 dips
- 1% eosin – 10 dips
- 95% Alcohol – 2 changes of 5 dips each
- Absolute alcohol – 2 changes of 5 dips each
- Xylene – 2 changes of 5 dips each

- Mount with DPX
- Results – nuclei stain purple, cytoplasm stains pink.

## RESULTS

Total cases – 168.

Results of the study are shown in Tables 1-3 (Charts 1-3 and Figures 1-6).

Following this study, it is observed that the incidence of benign breast disease (82.7%) is higher than breast malignancies (16%). The most common cause of breast lump in this series remained fibroadenoma (50.5%), followed by fibrocystic change (17.8%). Age range in this study is 13-90 years, with mean age being 33.63 years.

## DISCUSSION

The mean age in our study which is 33.63 years is found to be much lower compared to that in the western literature where the mean age is 54 years. Reported frequency of fibroadenoma in England<sup>1</sup> is 7.7% and in the USA,<sup>2</sup> it is 8.5%. In our study, it is 50.5%. It is also identified as the most common breast lesion in the study from PNS Shifa, Naval Hospital, Karachi, where it constituted 25%, followed by fibrocystic change 22.5% and carcinoma 18.7%. The high frequency of fibroadenoma in Indian females is similar to what has been observed in colored American,<sup>3</sup> African,<sup>4</sup> and Pakistani<sup>5</sup> females and in contrast with the lower frequency in the Western Caucasian females. These findings are seen to be consistent with other studies in India.<sup>6</sup> Fibrocystic change is the most common reported lesion in the UK and USA, with 37% in the UK<sup>1</sup> and 33.9% in the USA.<sup>7</sup> In Saudi Arabia,<sup>8</sup> it is reported to be 24.1%, and in our study, it is 17.8%.

The series by Anyanwu<sup>9</sup> 20 years ago reported only a case of phyllodes tumor, but no case of granulomatous mastitis

**Table 1: Incidence of various breast lesions in the study is as follows**

Incidence of various lesions			
Inflammatory	Benign epithelial lesions	Malignant epithelial lesions	Stromal tumors
Chronic suppurative mastitis-8	Non-proliferative breast lesions Cysts-18 Adenosis-9 lactating adenoma-3	Carcinoma - <i>in situ</i> -4	Fibroadenoma-85 (including 16 complex fibroadenoma cases)
Granulomatous maslitis-3	Proliferative breast lesions without atypia Epithelial hyperplasia-5 Papilloma-1	Paget's disease-2 (with underlying ductal carcinoma)	Phyllodes tumor-6 Benign phyllodes-2 Borderline phyllodes-2 Malignant phyllodes-2
Duct ectasia-1	Proliferative breast lesions with atypia Atypical ductal hyperplasia-3 Atypical lobular hyperplasia-1	Invasive carcinoma Ductal carcinoma (NOS)-14 Medullary carcinoma-2 papillary carcinoma-1 Lobular carcinoma-1 Mucinous carcinoma-1	

NOS: Not otherwise specified



**Table 2: Age distribution of various breast lesions**

Age (years)	Inflammatory	Benign lesions	Borderline	Malignant lesions
10-20	0	34	0	0
21-30	3	34	0	2
31-40	6	39	0	2
41-50	4	14	2	13
51-60	1	2	0	5
61-70	0	1	0	3
71-80	0	0	0	2
81-90	1	0	0	0

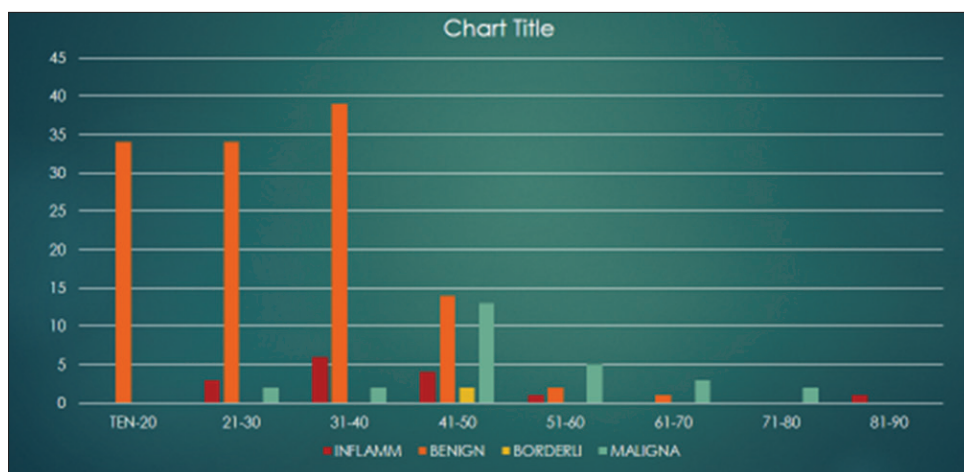
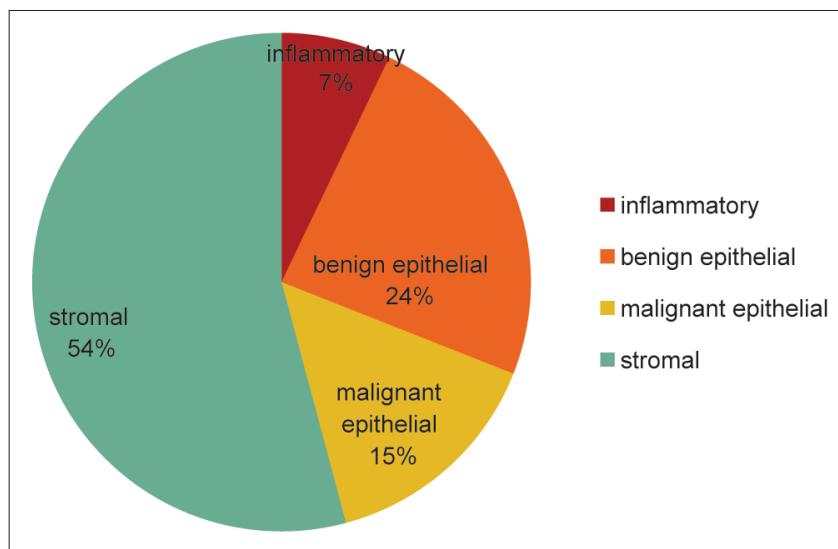
**Table 3: Incidence of various types of complex fibroadenoma**

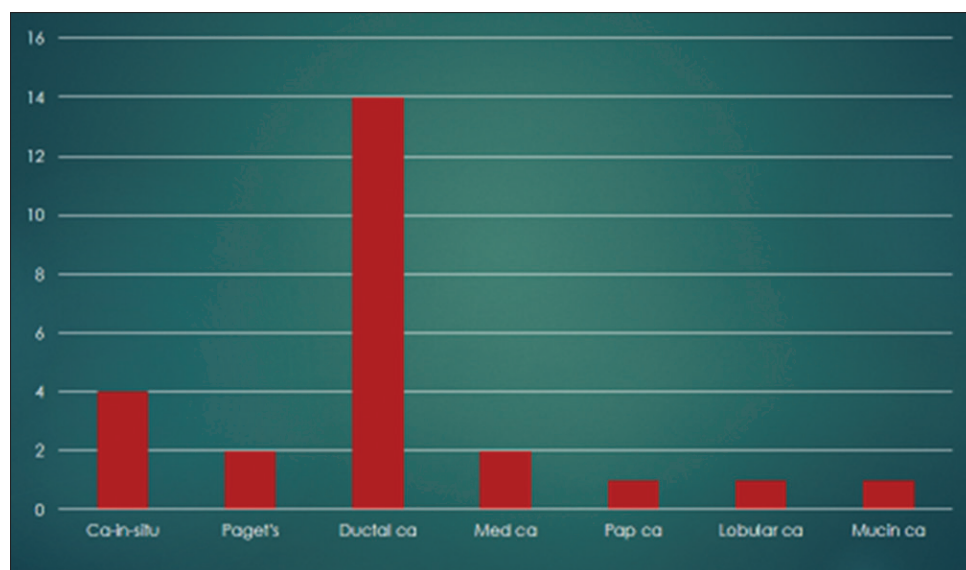
Type of complex fibroadenoma	Number (%)
Adenosis and cystic change	8 (50)
Focal epithelial hyperplasia	2 (12.5)
Sclerosing adenosis	3 (18.75)
Apocrine metaplasia	3 (18.75)

was reported. Furthermore, Akhator<sup>10</sup> reported only one case of phyllodes tumor with 2 cases of granulomatous mastitis. Our study reported 6 cases of phyllodes tumors, showing an incidence of 3.5%, which is well within the 2-4.4% reported in various other studies. In the present study, fibroadenoma - 85 (50.5%), is the most common benign lesion which is corresponding to Kulkarni *et al.*'s study<sup>11</sup> in which fibroadenoma accounted for 62.32% of benign lesions. In the current study, infiltrating ductal carcinoma (56%) is the most common malignant lesion which is similar to the observations of Kumar.<sup>12</sup> In the study, it is observed that benign lesions are more common (83.4%) in  $\leq 40$  years age group, whereas malignant lesions are more common (85.1%) in  $>40$  years age group, which correspond to the findings of Kumar.<sup>12</sup>

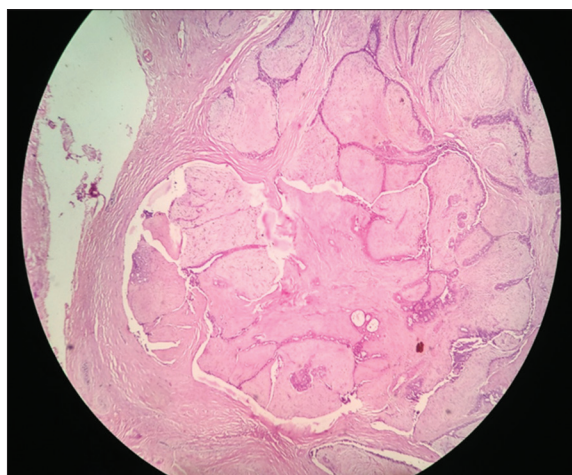
## CONCLUSION

In the present study, the most common benign lesion is fibroadenoma - 50.5%. The most common malignant

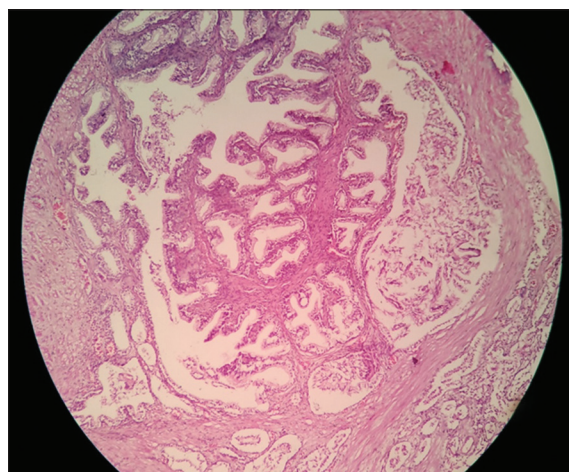
**Chart 1: Age distribution of various breast lesions****Chart 2: The frequency of incidence of various types of breast lesions**



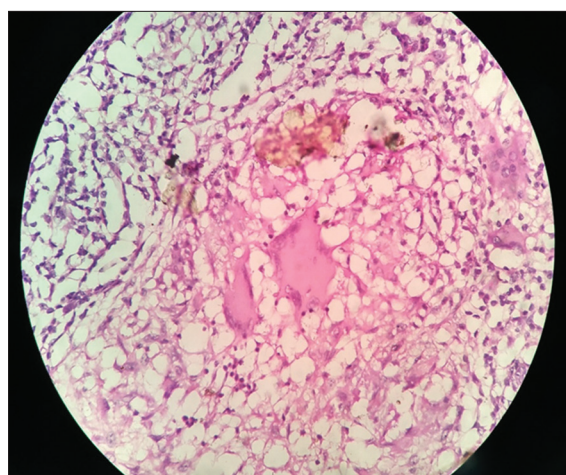
**Chart 3: Incidence of various malignant epithelial lesions of breast**



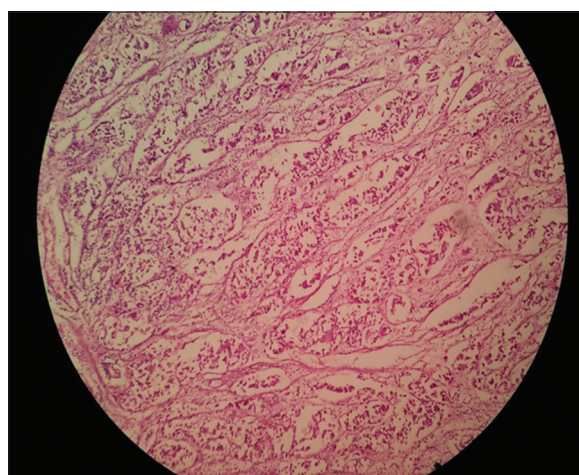
**Figure 1: Fibroadenoma**



**Figure 3: Intraductal papilloma**

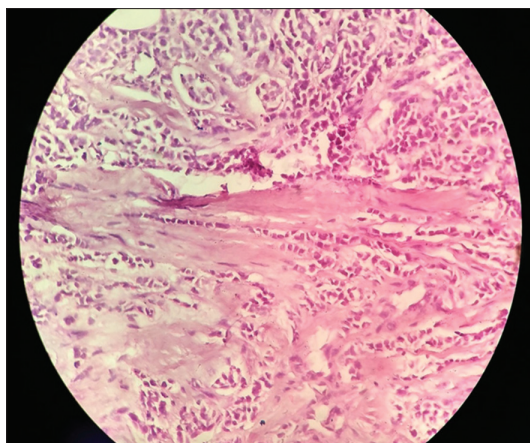


**Figure 2: Granulomatous mastitis**

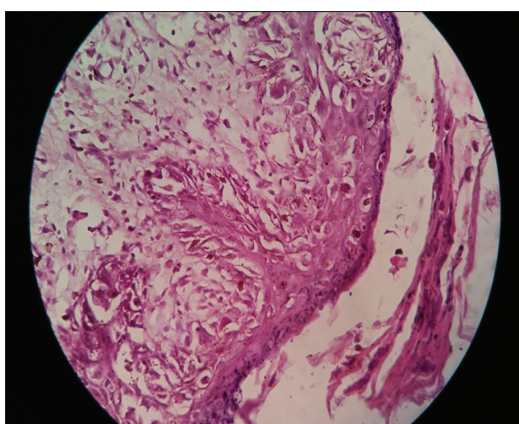


**Figure 4: Ductal carcinoma (not otherwise specified)**





**Figure 5: Lobular carcinoma**



**Figure 6: Paget's disease**

lesion is infiltrating ductal carcinoma - 56%. Peak incidence of benign lesions is in the age group of

31-40 years, and peak incidence of malignancy is seen in 41-50 years.

This study emphasizes the importance to recognize benign lesions and to distinguish them from *in situ* and invasive breast carcinomas. It is also important to assess a patient's risk of developing breast cancer so that the most appropriate treatment modality for each case can be established.

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# Chronic Autoimmune Urticaria and Efficacy of Autologous Serum Therapy

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## Abstract

**Introduction:** Chronic idiopathic urticaria (CIU) is defined as widespread, short-lived wheals occurring daily or almost daily for more than 6 weeks, with no obvious cause. Approximately, 30-40% of patients with CIU have chronic autoimmune urticaria. Autologous serum skin test (ASST) is a simple *in vivo* screening test for detecting patients with autoimmune urticaria. Autologous serum therapy (AST) has been found fairly effective in chronic urticaria.

**Aim:** To study the prevalence of chronic autoimmune urticaria using ASST and epidemiological pattern of the disease and to evaluate the efficacy of AST in the disease.

**Materials and Methods:** A prospective, interventional study was conducted between October 2009 and September 2011. 200 consecutive patients who attended our outpatient department were selected for the study. ASST was done with patient's serum and AST was given intramuscularly every week for 9 consecutive weeks, and the results were studied.

**Results:** Among 200 patients, 85 were males and 115 were females. 47 were positive and 153 were negative for ASST. No statistically significant difference was seen with age and sex distribution, atopy, number of wheals, and wheal size, and statistically significant difference was seen with angioedema, pruritus score, average hold time use, duration of wheals, and total severity score (TSS) among ASST positive and ASST negative patients. AST was given to 46 ASST positive patients. At the end of treatment, none had severe TSS, 9 patients were free from symptoms, and the majority had only mild TSS.

**Conclusion:** In patients with chronic autoimmune urticaria, AST is a cheap, cost-effective, and potentially curative modality of treatment.

**Key words:** Autologous serum skin test, Autologous serum therapy, Histamine-releasing autoantibodies, Total severity score

## INTRODUCTION

Urticaria commonly called as “hives” has a long and rich history dating back to the 10<sup>th</sup> century BC.<sup>1</sup> Urticaria is a distressing dermatosis of skin characterized by transient erythematous edematous wheals which are very itchy. Activation of cutaneous mast cells liberates various mediators predominantly histamine which increases the

permeability of capillaries and venules which in turn produces urticaria. Chronic idiopathic urticaria (CIU) is defined as widespread, short-lived wheals occurring daily or almost daily for at least 6 weeks, with no obvious cause. Approximately, 30-40% of patients with CIU have histamine-releasing autoantibodies directed against either high-affinity immunoglobulin E (IgE) receptor or less frequently IgE itself and are categorized as having chronic autoimmune urticaria. The presence of autoantibodies may be important clinically in severely affected, treatment-resistant patients where immunomodulatory drugs may be helpful.<sup>2</sup> The autologous serum skin test (ASST) is a simple *in vivo* screening test for detecting patients with autoimmunity, which has a sensitivity of 70% and specificity of 80%.<sup>3</sup> A positive test is suggestive but not diagnostic of an autoimmune basis. Confirmation is needed by

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testing the patient's serum for anti-FcεRIα or the anti-IgE autoantibodies. Basophil histamine release assay is the gold standard for detecting functional autoantibodies.<sup>4</sup> However, it is available only in a few research centers and cannot be used routinely. CIU can be extremely disabling in its severe form and can be difficult to treat with conventional antihistaminic and need immunomodulators. Autologous serum therapy (AST), a modified form of autologous whole blood therapy, has been found to be fairly effective in chronic urticaria.<sup>5</sup> We had the opportunity to study the various clinical parameters in patients with chronic autoimmune urticaria, the role of ASST in these patients, and the efficacy of AST in the management of these patients.

### Aims

To study the clinico-epidemiologic features in a patient with positive or negative ASST and to evaluate the efficacy of AST in patients with chronic autoimmune urticaria.

## MATERIALS AND METHODS

This prospective cohort study was conducted in the Department of Dermatology, Madras Medical College. Informed consent and Institutional Ethics Committee approval were obtained. 200 consecutive patients of CIU (defined by having at least 2 episodes per week for more than 6 weeks) who attended our dermatology outpatient department were selected for the study. Other causes of urticaria were excluded by history and clinical examination. Pregnant and lactating mothers, children less than 12 years, patients who had taken antihistaminic within the past 3 days to 1 week, and who have taken steroids within 30 days to 3 months were excluded from the study. Severity of the disease based on history was graded with various scores such as a number of wheal, pruritus, frequency of wheal, duration of wheal, size of wheal, and score for antihistamine use. Total severity score (TSS) was calculated by adding the various scores, and patients' disease severity was graded according to TSS (Table 1).

AST was given to ASST positive patients who were willing for weekly injections and regular follow-up. AST was given for 9 consecutive weeks and was asked to follow up after 3 months. Repeat scoring and TSS were calculated at the follow-up.

**Table 1: TSS**

TSS score	Grade
0	Clear
1-6	Mild
7-12	Moderate
13-18	Severe

TSS: Total severity score

## RESULTS

Of the total 200 patients, 85 (42.5%) were males and 115 (57.5%) were females. 153 (76.5%) patients were ASST negative and 47 (23.5%) patients were ASST positive. There was no statistically significant difference seen in sex distribution ( $P = 0.504$ ), age distribution ( $P = 0.535$ ), duration of disease ( $P = 0.142$ ), association with atopy ( $P = 0.852$ ), number of wheals score ( $P = 0.926$ ), and wheal size score ( $P = 0.057$ ) among ASST positive and ASST negative patients. Statistically significant difference was seen in angioedema ( $P = 0.002$ ), frequency score ( $P < 0.001$ ), pruritus score ( $P = 0.022$ ), average hold time (AHT) use ( $P < 0.001$ ), duration of wheals ( $P = 0.0015$ ), and mean TSS ( $P < 0.001$ ) among the two groups. Out of the 47 ASST positive patients, only 44 patients completed 9 weeks of AST. 1 patient denied treatment and 2 patients dropped out. Out of 44 patients who completed AST, 9 had complete clearance, 31 had mild symptoms, and 4 had moderate symptoms based on TSS at the end of treatment. 7 out of 9 patients who had complete clearance, remained clear during follow-up, 1 patient lost to follow-up, and 1 patient relapsed back to have severe symptoms. None of the patients reached their baseline TSS value in the follow-up period (Table 2).

## DISCUSSION

In our study with 200 CIU patients, the prevalence of patients with autoimmune urticaria was 23.5%. The prevalence of ASST in patients of chronic urticaria ranges from 25% to 60%. Historically, Grattan *et al.* were the first to use ASST to differentiate chronic autoimmune urticaria from CIU.<sup>6</sup> Study done by Bajaj *et al.* among 394 patients, ASST positivity was 49.5%.<sup>5</sup> Godse conducted study on 45 patients and found 26.67% were ASST positive.<sup>7</sup> Out of 96 patients, 53% were positive in a study by Asero *et al.*<sup>8</sup> The prevalence of ASST positivity in our study was little lower compared to other studies.

In our study, male to female ratio among ASST positive and negative groups was 0.8:1 and 1:1.42, respectively, which was comparable with the study conducted by Vohra *et al.* where it was 1:1.25 and 1:2.07, respectively.<sup>9</sup> Mean age in ASST positive and negative groups was  $36.77 \pm 15$  and  $35.42 \pm 13$  years, respectively, which was comparable with the study conducted by Azim *et al.* where it was  $34 \pm 10$  and  $30 \pm 11$  years.<sup>10</sup> Mean duration of disease in our study among ASST positive and negative patients was  $4.36 \pm 3$  and  $3.8 \pm 3$  years, which was comparable with studies conducted by Staubach *et al.*<sup>11</sup> Association with atopy was seen in 30-28% patients of ASST positive and negative patients, respectively, which was in concordance with study

**Table 2: TSS after 9 weeks of ASST**

Time	Number of patients	TSS (Mean)	TSS grade in number of patients			
			Clear	Mild	Moderate	Severe
Baseline	44	13.68	0	1	18	25
End of treatment	44	3.68	9	31	4	0
Follow-up	41	3.98	7	25	8	1

TSS: Total severity score, ASST: Autologous serum skin test

conducted by Bajaj *et al.*,<sup>5</sup> where it was 46.7% and 38.5%, respectively, and with study conducted by De Swerd *et al.* where it was 32-31%, respectively.<sup>12</sup> No statistical difference was seen in the above parameters in our study and also in other studies.

In our study, 59.57-33.98% of ASST positive and negative patients had angioedema, where the difference was statistically significant. In studies conducted by Vohra *et al.* and Azim *et al.*, it was 59% and 52% and 46.7% and 40%, respectively, where the difference was not significant.<sup>9,10</sup> In our study, the frequency score of 3 among ASST positive and negative patients was 68% and 21.56%, respectively, which was statistically significant ( $P < 0.001$ ) and was comparable to another study conducted by George *et al.* ( $P = 0.038$ ).<sup>13</sup> There was no statistically significant difference seen in number of wheals score among ASST positive and negative patients, which was comparable to studies conducted by Bajaj *et al.* and Sabroe *et al.*<sup>5,14</sup> Significant difference was seen in the mean values for pruritus score,  $2.3 \pm 0.6$  and  $1.98 \pm 0.7$  and AHT use score,  $2.59 \pm 0.6$  and  $1.42 \pm 0.8$  among ASST positive and negative patients, which was in concordance with the study conducted by Staubach *et al.* and Sabroe *et al.*<sup>11,14</sup> Statistically insignificant results between ASST positive and negative groups was seen for wheal size score ( $P = 0.0623$ ), which was similar to studies conducted by Bajaj *et al.* and Staubach *et al.*<sup>5,11</sup>

The majority of ASST positive patients had severe TSS score, while the majority of ASST negative patients had moderate TSS score in our study, which was significant. Study by Bajaj *et al.* with similar scoring system showed no significant difference in mean TSS between two groups.<sup>5</sup>

Mean baseline TSS value of 44 AST completed patients was 13.68, and at the end of treatment, it was 3.68 in our study. This was a significant reduction in mean TSS. Although there was an increase in actual TSS during follow-up in some patients, it did not reach baseline values. Only a few studies with AST on chronic urticaria patients are available. Staubach *et al.* used autologous whole blood for therapy.<sup>11</sup> Bajaj *et al.* used AST and found that ASST positive patients had a dramatic decline in severity score and lower TSS score compared to ASST negative patients.<sup>5</sup> Since only limited studies are conducted on chronic urticaria patients

using AST, large-scale placebo-controlled randomized studies with longer follow-up period are needed to know the efficacy.

## CONCLUSION

Prevalence of autoimmune urticaria among patients with chronic urticaria was 23.5%. ASST is a simple, cost-effective, easy to perform screening test which can be done as an outpatient procedure to identify autoimmune etiology, in patients previously categorized as having CIU. AST is a cheap, cost-effective, and potentially curative modality of treatment with no side effects in patients with chronic autoimmune urticaria. Especially, in those patients with severe intensity who often require steroids and immunomodulators which are well known for their adverse effects on long-term use, AST emerges to be a better therapeutic option.

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# Clinical Presentation and Histopathology of Childhood Leprosy

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## Abstract

**Background:** Leprosy is one of the oldest diseases of mankind. It is well-documented in children with an incidence of 13.3%, as immune system is not fully developed. 75% of cases regress spontaneously without treatment.

**Aim:** To study incidence, duration, spectrum, reactions, deformity, slit skin smear (SSS) and skin, and nerve biopsy in childhood leprosy.

**Materials and Methods:** Leprosy cases from 0 to 14 years age who attended Department of Dermatology and Leprosy of Government General Hospital, Chennai, were collected for 2 years (study period).

**Results:** During the study period of 2 years, total numbers of childhood leprosy cases were 46. Most number of cases was seen in 10-14 years age group - 36 cases (78.3%). Most common spectrum is borderline tuberculoid 27 cases (58.7%). Percentage of cases in household contact was 19.6%. Type 1 reaction was seen in 3 children. Type 2 reaction was not seen. The deformity was seen in 5 children. SSS was positive in only 4, all of them were borderline leprosy cases.

**Conclusion:** Leprosy still occurs in children in sizable and constant proportion, even though the prevalence rate has reduced below one per thousand and we are in the run for total eradication of leprosy.

**Key words:** Borderline leprosy, Childhood leprosy, *Mycobacterium leprae*

## INTRODUCTION

Leprosy is a chronic disease caused by *Mycobacterium leprae*, infectious in some cases, and affecting the peripheral nervous system, skin, and certain other tissues.<sup>1</sup> It has been a major public health problem in many developing countries for centuries. Children are believed to be the most vulnerable group to *M. leprae* infection and clinical manifestation is often seen in adolescence or young adulthood following the long incubation period. Leprosy in children has epidemiological significance and is considered as index of the prevalence of disease. It forms

an important link in the study of natural evolution of disease. India represents about 76% of global burden. The overall prevalence of leprosy in India has declined from 5.27/10000 in the year 2000 to 1.34 in 2005, still, it constitutes a sizable health problem in pediatric age group with incidence of 13.3%. Childhood leprosy forms an important link in the study of natural evolution of disease. The spectrum of disease is usually incomplete in children. It is rare under 2 years of age.<sup>2</sup> It is often unrecognized, and 75% cases regress spontaneously without any treatment. The youngest age reported for occurrence is 3 weeks in Martinique. The youngest case of tuberculoid leprosy confirmed by histopathology was infant of 2.5 months old.<sup>3</sup> In children it is equally prevalent in both sexes. Childhood leprosy usually responds rapidly to treatment. Reactions, relapses are not uncommon.<sup>4</sup> Ocular leprosy, deformities, infectivity, poor tolerance to drugs, and special variants like Histoid leprosy are rare in children. The worldwide prevalence of disease has decreased dramatically, since the inception of elimination

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plan, but the disease deduction rate has remained almost constant over last 10 years with the high rate of infection (17%) in children.

### Aim

To study incidence, duration, spectrum, reactions, deformity, slit skin smear (SSS) and skin, and nerve biopsy in childhood leprosy.

## MATERIALS AND METHODS

This prospective observational study was conducted in the Department of Dermatology, Government General Hospital, Chennai. Childhood (0-14 years) leprosy cases were screened, complete history of presenting complaints, duration of illness, history of contact, treatment, Bacillus Calmette–Guérin vaccination, were taken from the informant usually parents. A complete general and dermatological examination regarding the morphology, number, size, site, color, anesthesia, margins, surface, satellite lesions and general clearing of skin lesions and involvement of peripheral truncal nerves, and cutaneous nerves were done. Reactions and deformities were also noted. Slit smear examination was done from a minimum of three sites (If there was a single lesion, i.e., from the lesion and both ear lobes and from a minimum of four sites if there was more than one lesion, i.e., from both ear lobes and two skin lesions). A SSS examination was performed using standard techniques. Stained by Ziehl–Neelson stain and graded by Ridley's scale for bacteriological index. A skin biopsy was obtained using local anesthesia, following consent and stained with hematoxylin and eosin for histopathological examination. Nerve biopsy was done and stained with hematoxylin and eosin and Fite-Faraco staining in the case of pure neuritic leprosy.

## RESULTS

A total number of childhood leprosy cases is 46. Of these, 36 (78.3%) were in 10-14 years age and 7 (15.2%) were in 5-9 years. The age of onset, in most cases, 29 cases (63%) was 10-14 years. Borderline tuberculoid is seen in 27 cases (58.7%). Only 4 (8.7%) cases of borderline lepromatous leprosy were seen and no lepromatous leprosy. Pure neuritic leprosy is seen in 5 (10.9%) children. 2 presented with foot drop, 1 with claw hand and trophic ulcer and 1 with ulnar nerve abscess and clawing of right little finger. Single skin lesion was the most common presentation in 22 cases (47.8%). Ulnar (27 cases, unilateral in 22 and bilateral in 5) is most common truncal nerve and radial cutaneous (13 cases, unilateral in 7 and bilateral in 6) is most common peripheral nerve involved. Type 1 reaction was

seen in 3 cases. Type 2 reaction is not seen. Deformities were seen in 5 children. Claw hand, foot drop, and trophic ulcer were the deformities encountered. Ocular and Histoid leprosy is not seen.

## DISCUSSION

The incidence of leprosy is higher in 10-14 years of age and 30-60 years of age group. A total number of childhood leprosy cases (0-14 years) seen was 46 during the study period of 2 years. Of the 46 patients, 36 (78.3%) were in 10-14 years age group, 7 (15.2%) were in 5-9 year age group, and 3 (6.5%) were in 0-4 year age group. Age distribution reflects a clear preponderance of older children because of relatively long incubation period. Incubation period may be as short as few months as long as 20 years or more. On an average it is between 2 and 5 years.<sup>5</sup> The youngest patient seen in the study was a 4-year-old girl who had borderline tuberculoid leprosy with age of onset at 3 years. Two more children of 4 years old, one with intermediate leprosy and another with tuberculoid leprosy with age of onset of 3 years 6 months and 3 years 9 months, respectively, were also seen in the study. The age of onset, (obtained by subtracting the duration of disease from age of patient) in most cases, 29 cases (63%) was 10-14 years among the children in the study group (0-14 years). There was a preponderance of boys (31 cases over 15 cases, with a male-female ratio of 2.07:1). This observation is similar to most of earlier studies, and it could be because of environmental and socio-cultural factors such as greater exposure in boys.

Duration of disease at the time of detection in most of the cases was found to be less than or equal to 1 year. Overall 9 children gave a history of contact with a leprosy patient within the household, father being the index cases in 4 cases and mother in 2 cases. Borderline tuberculoid is most common type seen in children.<sup>6,7</sup> In our study, borderline tuberculoid is seen in 27 cases (58.7%). Only 4 cases of borderline lepromatous leprosy were seen and no lepromatous leprosy was seen indicating clearly the spectrum is incomplete. It is a paradox that children with poor cell-mediated immunity rarely presents with multibacillary disease. Claw hand is most common deformity followed by trophic ulcer, foot drop, and wrist drop.<sup>7</sup> Pure neuritic leprosy was seen in 5 children. 2 presented with foot drop, other with numbness below the right knee, 1 with claw hand and trophic ulcer, and 1 with ulnar nerve abscess and clawing of right little finger.

The clinical presentation in most cases was hypopigmented skin lesions with or without sensory impairment. Single skin lesion is more common followed by 2 to 3 and more than 4 is rare.<sup>2</sup> In our study, single skin lesion was the most common presentation in 22 cases (47.8%). The sites for

the development of single lesion are predominantly seen on the exposed parts.<sup>8-12</sup> Similarly, exposed parts such as forearm, face, knee, and leg were the most common sites involved in 15 cases (68%) than covered parts such as back, arms, buttocks, and thighs in 7 cases (32%). Some of earlier studies observed an increased incidence of single skin lesion over gluteal region. In this study among 22 patients presented with a single skin lesion, 6 had lesions over forearm (common site) followed by cheeks in 5 cases. The most common morphology of the lesions seen were macules, patches, plaques, and usually hypopigmented followed by erythematous and copper colored lesions. Size of lesion varied from <1 cm - 45\*15 cm involving most of lower limb, the largest lesion in the study. Ichthyosis and traumatic fissure were seen in few cases. Of the peripheral truncal nerves, ulnar nerve was the most common nerve involved followed by lateral popliteal, posterior tibial, and median nerve. Radial cutaneous nerve was the most common cutaneous nerve involved followed by greater auricular, sural, supraorbital, and supraclavicular nerves. Involvement of lateral, intermediate and medial cutaneous nerves of thigh was seen in one case.

Type 1 reaction was seen in 3 cases of whom 2 had borderline lepromatous leprosy and 1 had borderline tuberculoid leprosy. Type 2 reaction was not seen. Relapse was seen in a case of 10-year-old boy who presented with increase in size of skin lesion 2 years after completion of paucibacillary treatment. Deformities were seen in 5 children. Claw hand, foot drop, and trophic ulcer were the deformities encountered. 14-year-old male child, the case of pure neuritic leprosy had claw hand both sides and trophic ulcer right foot. 14-year-old male child, case of borderline tuberculoid leprosy had left side claw hand and left foot drop. 11-year-old male child, a case of pure neuritic leprosy, had clawing right little finger. 12-year-old female child (pure neuritic leprosy) had left foot drop. 6-year-old female child (pure neuritic leprosy) had left foot drop. Ocular leprosy among children is rare and nonblinding.<sup>4</sup> Ocular involvement was not seen in any of the cases. Special variants like Histoid leprosy were also not seen.

The frequently encountered differential diagnosis was polymorphic light eruption, pityriasis alba, tinea versicolor, early vitiligo, resolving morphea, and post-inflammatory hypopigmentation. A case of ganglion, mimicking nerve

swelling, along the course of lateral popliteal nerve was also seen.

SSS was positive in only 4 cases; all of them were borderline lepromatous cases. Histopathological examination of skin and nerve biopsy was very useful in establishing the diagnosis.

## CONCLUSION

The most common age of occurrence is 10-14 years. Incidence was more among male than female. Single skin lesion, occurring over exposed parts is the common presenting feature. Ulnar nerve is most commonly involved truncal nerve, and radial cutaneous nerve is most commonly involved cutaneous nerve. Borderline tuberculoid is the most common spectrum. Leprosy toward lepromatous pole is rare. Reactions, relapse, and deformities are rare. Leprosy still occurs in children in sizable and constant proportion, even though the prevalence rate has reduced below one per thousand and we are in the run for total eradication of leprosy.

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# Comparison of Antioxidant Status Levels and the Impact of Oxidative Stress in Spontaneous Inevitable Abortion With Normal Pregnancy and Healthy Non Pregnant Women

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## Abstract

**Introduction:** One major cause for spontaneous and threatened abortion is oxidative stress (OS). Spontaneous abortion might be associated with OS in the maternal circulation.

**Purpose:** This study is conducted to note the effect of OS during pregnancy and to explore the OS and antioxidant status in the maternal circulation in spontaneous inevitable abortion and in normal pregnancy.

**Materials and Methods:** Ferric reducing antioxidant power (FRAP), serum uric acid, total protein (TP), albumin, glucose, and cholesterol were measured among 126. Woman presenting with spontaneous inevitable abortion (No. 42, Group IA), Group IA after 48 h of abortion (No. 42 Group IB), age-matched normal pregnant woman (No. 42, Group II), and normal non-pregnant woman (No. 42, Group III).

**Results:** The mean age of the subjects in Groups I-III was 26.5, 27.09 and 26.76 years. FRAP value and uric acid levels are much lower among the women presenting with spontaneous inevitable abortion ( $P < 0.001$ ). FRAP value and uric acid level were much higher among the healthy pregnant woman controls and non-pregnant woman controls ( $P = 0.01$ ).

**Conclusion:** When and uric FRAP acid value compared between, non-pregnant, normal pregnancy and spontaneous inevitable abortion by the student *t*-test, there was a significant difference in the mean value ( $P < 0.01$ ). Improving the antioxidant status by supplementation during pregnancy might be useful in preventing OS related disorders.

**Key words:** Ferric reducing ability of plasma, Oxidative stress, Spontaneous abortion, Total antioxidant status, Pregnancy

## INTRODUCTION

The ability to propagate life by the process of reproduction is a boon to mankind as well as to all life forms. However, disorders of pregnancy such as placental-related disorders, miscarriage, and preeclampsia affect around a third of human pregnancies causing termination of the

pregnancy. Before the end of the first trimester, 30-50% of conceptions end in spontaneous abortion (SAb). Oxidative stress (OS)-induced damage had played a major role in SAb, idiopathic recurrent pregnancy loss, hydatidiform mole, defective embryogenesis, and drug-induced teratogenicity.<sup>1</sup> OS-induced placental dysfunction is a common cause of polygenic etiologies of abortion, recurrent pregnancy loss, defective embryogenesis, hydatidiform mole, and drug-induced teratogenic effect. The aim of this study was to look at the association between OS and spontaneous inevitable abortion. Hence, the study “comparison of antioxidant status levels and the impact of oxidative stress in spontaneous inevitable abortion with normal pregnancy and healthy non pregnant women” was taken up to determine the total antioxidant (TAO) status of plasma

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by FRAP and uric acid level. (Halliwell and Gutteridge, 1985; Berlett and Stadtman, 1997 (Smith and Lawing, 1983; Berlett and Stadtman, 1997; Nyyssonen *et al.*, 1997) state that uric acid conceivably acts as a powerful antioxidant in plasma. The antioxidant in highest concentration in human blood is uric acid, which provides about half of the TAO capacity of human serum.

## REVIEW OF LITERATURE

### SAb

SAb, also known as miscarriage, refers to a pregnancy that ends spontaneously before the fetus has reached a viable gestational age.<sup>1</sup> The loss of a pregnancy before 20 weeks was known as early pregnancy loss. Recurrent pregnancy loss was defined as three or more consecutive pregnancy losses before 20 weeks of gestation.<sup>2</sup>

### Spontaneous Inevitable Abortion

Gross rupture of membranes evidenced by leaking of amniotic fluid, in the presence of cervical dilatation signals almost certain abortion. If, however, the gush of vaginal discharge was followed by bleeding, pain, or fever, then the abortion considered as inevitable. Spontaneous inevitable abortion SAb is the most common complication of early pregnancy.<sup>3</sup> The frequency decreases with increasing gestational age. Around 80% of clinically recognized pregnancies will undergo SAb within the first 12 weeks of gestation.<sup>4-6</sup>

### Pathogenesis

Miscarriage and pre-eclampsia are the most common disorders of human pregnancy. Ultrasound imaging has enabled the events during early pregnancy visualized *in vivo*. As a result, a new understanding of the early maternofetal relationship has emerged and a new insight into the pathogenesis of these disorders. In miscarriage, there is rapid and generalized placental tissue degeneration, in preeclampsia, the placental damage is progressive and it was compensated for some time depending on the severity of the initial placental defect and the intrinsic placental antioxidant capacity.<sup>7,8</sup>

### Pregnancy - A State of OS

Pregnancy is a state of OS arising from increased placental mitochondrial activity and production of reactive oxygen species (ROS). The placenta produces ROS includes nitric oxide, carbon monoxide, superoxide anion, and peroxynitrite, which have pronounced effects on the placental function including trophoblast proliferation and vascular reactivity. In the first trimester, the establishment of blood flow into the intervillous space was associated with a burst of OS. Evidence for this OS includes decreased

activity of antioxidants, increased lipid peroxides and isoprostanes.

### OS in Early Pregnancy

Early anatomical and histopathological studies have exclusively focused on defective villous development in early pregnancy loss.<sup>9</sup> There is now clear evidence that miscarriages are placentation disorders and that the villous changes described previously are the consequences, rather than the cause.<sup>10</sup> In about two-thirds of early pregnancy failures, there is anatomical evidence of abnormal placentation is by a thinner and fragmented trophoblast shell, incomplete plugging of the lumen at the tips of the spiral arteries and decreased cytotrophoblast invasion of the endometrium.<sup>11,12</sup> This is associated with the absence of physiological changes in most spiral arteries and leads to a premature onset of the maternal circulation throughout the entire placenta. Entry of excessive maternal blood into the intervillous space has two effects: (i) A direct mechanical effect on the villous tissue, which becomes progressively entangled inside the large intervillous blood thrombi and (ii) a widespread and indirect O<sub>2</sub>-mediated trophoblastic damage and increased apoptosis.<sup>13-15</sup>

The consequences are placental degeneration with complete loss of function of syncytiotrophoblast and detachment of the placenta from the uterine wall. Any factor that causes abnormally high and fluctuating concentrations of O<sub>2</sub> will have a harmful on the early villous tissue. In this review, we have presented the current evidence regarding the role of OS in pregnancy and SAb, assessment of OS by assaying TAO status by FRAP assay and uric acid levels.

## MATERIALS AND METHODS

Following the approval of the Institutional ethical committee, this study was carried out over a period of 6-12 months in a tertiary care hospital. Where 126 adult (21-25 years) women gave their consent to take part in the study. The participants are divided into four subgroups. (i) Those patients presenting with SAb ( $n = 42$  Group IA), (ii) Group IA patients after 48 h of SAb ( $n = 42$  Group IB), (iii) healthy age-matched normal pregnant woman ( $n = 42$  Group II), and (iv) healthy age-matched non-pregnant woman ( $n = 42$  Group III). All subjects with H/O DM, HT, thyroid disorders and prior abortions was eliminated from this study. Blood samples are collected under aseptic conditions from the anterior cubital vein, 3 ml was kept for estimation of FRAP. The remaining sample was placed in a sterile vial without any anticoagulant at 37°C for clot formation. After clot retraction serum was separated. Uric acid (UA, ref. 3.5-7 mg/dl), albumin (Al, ref. 3.5-5 g/dl), TP (TP, ref.



6.0-8.00 g/dl), glucose (GLU, ref. 80-110 mg/dl), and total cholesterol (CHO, ref. 150-200 mg/dl) levels were measured by commercially available kits on automated analyzer XL300.

### Measurement of Plasma TAO Status-FRAP Assay

An imbalance of oxidants and antioxidants within the human body, in which either high oxidants or antioxidant protection is low, it will lead to a state of “OS.” This is associated with a variety of chronic degenerative diseases. With the standard FRAP assay, an increase in antioxidants should result in an increase FRAP value. FRAP assay, one of the most sensitive and specific assay. Tests which measure the combined antioxidant effect of the non-enzymatic defense in biological fluids will be useful in providing an index of ability to resist oxidative damage. TAO status was measured by FRAP assay of Benzie and Strain (1996).<sup>16,17</sup> FRAP assay uses antioxidants as reductants in a redox-linked colorimetric method, employing an easily reduced oxidant system present in stoichiometric excess. The relative activity of individual serum antioxidants and their estimated contribution to plasma FRAP: Uric acid - 61.7%, albumin - 7.26%, tocopherol - 5.84%, ascorbic acid - 10.1%, bilirubin - 4.34%, and others - 10.76.

### Statistical Analysis

Demographic and clinical variables were given in frequencies with their percentages. Mean and standard deviations for them was calculated. FRAP and uric acid was analyzed using Student's independent *t*-test. Maternal age, gestational age, and weight were analyzed using one-way analysis of variables F-test and multiple comparisons were analyzed using the Bonferroni *t*-test. Pearson correlation (*r*) is used to assess the degree of association between variables in different groups. *P* < 0.05 was considered statistically significant.

## RESULTS

Comparison of observed biochemical parameters among all the subjects was presented in Tables 1-5. Comparison of mean FRAP value and mean uric acid level among various groups were plotted in Figures 1 and 2. Demographic and clinical variables were presented in Table 6. The mean age of the subjects among Groups I-III was 26.5, 27.09 and 26.76 years. From the study, we find that the mean value of FRAP assay for the various study groups as Group IA (women with spontaneous inevitable abortion) mean  $0.322 \pm 0.688$  mMFe (II)/L, Group IB (after 48 h of abortion) mean  $0.706 \pm 0.670$  mMFe (II)/L, Group II (normal pregnant women) mean  $0.829 \pm 0.129$  mMFe (II)/L, and Group III (normal non-pregnant women) mean  $1.020 \pm 0.195$  mMFe (II)/L. Comparison of the mean level of FRAP among women with spontaneous inevitable abortion (Group IA), after

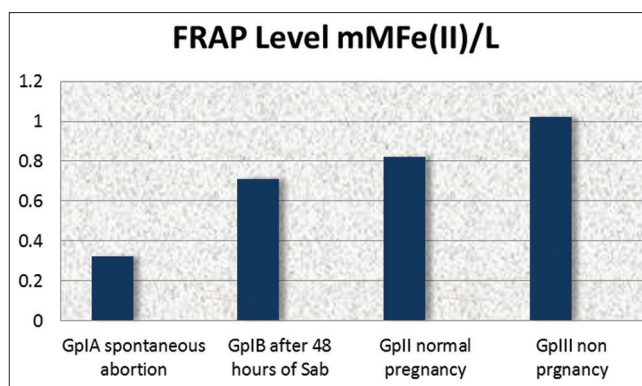


Figure 1: Comparison of mean plasma ferric reducing antioxidant power value among study groups

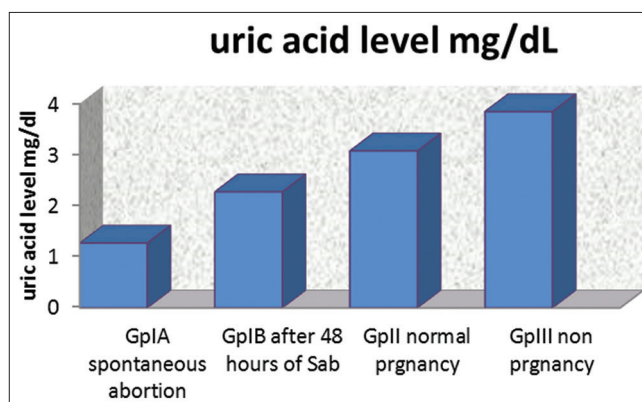


Figure 2: Comparison of mean serum uric acid value among study groups

48 h of abortion (Group IB), normal pregnant women (Group II), and normal non-pregnant women (Group III). FRAP value is expressed as mMFe (II)/L. On comparison FRAP mean level of Group IA ( $0.322 \pm 0.688$ ) with Group IB ( $0.706 \pm 0.670$ ), it was found that FRAP value was very low at the time of abortion, and it increases after 48 h of expulsion of the abortus, it is represented by, a significant increase in FRAP value (*P* = 0.001). When the mean FRAP value of Group IA was compared with Groups II and III it was much higher in Group II, highest in Group III and the difference was highly significant (*P* = 0.001). FRAP mean of Group II ( $0.829 \pm 0.129$ ) is compared with Group III ( $1.020 \pm 0.195$ ) it was higher in Group III, and the difference was significant (*P* = 0.001).

The mean uric acid levels in the study groups were found as Group IA ( $1.277 \pm 0.260$  mg/dl), Group IB ( $2.578 \pm 0.398$  mg/dl), Group II ( $3.073 \pm 0.605$  mg/dl), and Group III ( $3.843 \pm 0.737$  mg/dl). The mean uric acid level of Group IA compared with Group IB ( $2.578 \pm 0.398$ ). It was very low at the time of the abortion and it increases after 48 h of the expulsion of the abortus (*P* = 0.001). When the mean uric acid level of Group IA compared with Groups II and III it was much higher in the Group II, and highest in

**Table 1: Comparison of mean plasma FRAP value among study groups**

Groups	n	Mean FRAP value mM/L	Standard deviation	Group IA versus Group IB	Group IA versus Group II	Group IA versus Group III	Group II versus Group III
Group IA	42	0.32150	0.068824	$t=25.97$	$t=22.48$	$t=21.88$	$t=5.29$
Group IB	42	0.70648	0.067026	$P=0.001$	$P=0.001$	$P=0.001$	$P=0.001$
Group II	42	0.82881	0.128997				
Group III	42	1.02002	0.195045				

FRAP: Ferric reducing antioxidant power

**Table 2: Comparison of mean serum uric acid level among study groups**

Groups	n	Mean uric acid mg/dl	SD	Group IA versus Group IB	Group IA versus Group II	Group IA versus Group III	Group II versus Group III
Group IA	42	1.2771	0.26055	$t=17.73$	$t=17.68$	$t=21.27$	$t=5.23$
Group IB	42	2.5779	0.39764	$P=0.001$	$P=0.001$	$P=0.001$	$P=0.001$
Group II	42	3.0729	0.60460				
Group III	42	3.8431	0.73710				

SD: Standard deviation

**Table 3: Comparison of mean values of Group-IA versus Group-IB**

Group and means	FRAP mM/L	Uric acid mg/dl	Total protein gm/dl	Albumin gm/dl	Glucose mg/dl	Cholesterol mg/dl
Group IA Mean±SD	0.32±0.07	1.28±0.26	5.95±0.35	3.17±0.19	86.26±5.59	181.66±34.06
Group IB Mean±SD	0.71±0.07	2.57±0.40	6.40±0.44	3.62±0.18	83.55±5.54	181.19±32.96
P	0.001 HS	0.001 HS	0.001 HS	0.001 HS	0.03 S	0.03 S

P-value: HS: Highly significant, S: Significant, NS: Not significant, FRAP: Ferric reducing antioxidant power, SD: Standard deviation

**Table 4: Comparison of mean values of Group-IA versus Group-II**

Group and means	FRAP mM/L	Uric acid mg/dl	Total protein gm/dl	Albumin gm/dl	Glucose mg/dl	Cholesterol mg/dl
Group IA Mean±SD	0.32±0.07	1.28±0.26	5.95±0.35	3.17±0.19	86.26±5.59	181.66±34.06
Group II Mean±SD	0.82±0.12	3.07±0.60	6.45±0.47	3.47±0.20	87.02±4.78	158.88±24.031
P	0.001 HS	0.001 HS	0.001 HS	0.001 HS	0.50 NS	0.95 NS

FRAP: Ferric reducing antioxidant power

Group III and the differences were significant ( $P = 0.001$ ). Similarly, when the mean of Group II was compared with Group III it was higher in the Group III, and the difference was significant ( $P = 0.001$ ). This suggests that the women with SAb were initially having severe OS, which is reflected by a reduction in the level of FRAP and uric acid. On removal of the stress (expulsion of the abortus), the antioxidant status improves, as observed by the rise of FRAP and uric acid level after 48 h. Tables 1 and 2 show the mean values of FRAP and uric acid of the various groups. Tables 3-5 show the comparison of mean values of FRAP, uric acid, TP, albumin, and cholesterol in Groups IA, IB, II, and III. Demographic and clinical data of the subjects were shown in Table 6. There were no differences in mean age, gestational age, gravidity, and mean weight between patients with SAb and controls. As seen in Table 1, plasma TAO levels of patients with SAb was found significantly

lower than those of healthy pregnant women and healthy non-pregnant women of the same reproductive age group. OS was significantly higher in the patients with spontaneous inevitable abortion, which is reflected as a reduction in FRAP value ( $0.32 \pm 0.07$ ) mMFe (II)/L, the healthy pregnant women had lower values of FRAP ( $0.83 \pm 0.13$ ) mMFe (II)/L than non-pregnant women ( $1.02 \pm 0.19$ ) mMFe (II)/L. When FRAP value compared among normal pregnancy and abortion by Student's t-test, there was a significant difference in the mean ( $P < 0.01$ ) showing that there is an association of OS in SAb.

## DISCUSSION

OS is the imbalance among pro-oxidants and antioxidants it is been shown in several female reproductive pathologies.

**Table 5: Comparison of mean values of Group-II versus Group-III**

Group and means	FRAP mM/L	Uric acid mg/dl	Total protein gm/dl	Albumin gm/dl	Glucose mg/dl	Cholesterol mg/dl
Group II						
Mean±SD	0.82±0.12	3.07±0.60	6.45±0.47	3.47±0.20	87.02±4.78	158.88±24.031
Group III						
Mean±SD	1.02±0.19	3.84±0.73	6.20±0.40	3.43±0.52	87.11±7.19	161.26±35.04
P	0.001 HS	0.001 HS	0.01 S	0.63 NS	0.94 NS	0.71 NS

FRAP: Ferric reducing antioxidant power

**Table 6: Demographic and clinical variables**

Basis	Group I (n=42) pregnant women at the time of abortion	Group II (n=42) normal pregnant women	Group III (n=42) normal non-pregnant women
Mean maternal age (years)	26.5	27.09	26.76
Mean gestational age (weeks)	12.90	16.33	-
Primigravida	20	22	-
Multigravida	22	20	-
Mean weight (kg)	49.23	49.54	48.73

Various literatures have documented that significant rise in OS during pregnancy. Adequate uteroplacental circulation is one prime need for a successful pregnancy. Placenta-related disorders of pregnancy affect around a third of human pregnancies and primarily include miscarriage and pre-eclampsia. This study was up to look at the association among OS and spontaneous inevitable abortion. From the study, we found that the FRAP value, as an indicator of TAO status, as well as the uric acid value both are much decreased in the women with SAb initially. After the expulsion of abortus, the OS is removed and the antioxidant status was improved an increase shows that in the FRAP as well as that of uric acid. Increases in these two parameters are highly significant. As seen in Table 1, plasma TAO level of patients with SAb is much lower than that of healthy pregnant women and healthy non-pregnant women of the same reproductive age group. This suggests that OS plays an important role in spontaneous inevitable abortion. This finding correlates with the findings of studies conducted by Barrington *et al.*<sup>18</sup> The decrease in the uric acid levels at the time of abortion and its rise after 48 h suggests that the antioxidants are used at the time of OS. The TAO status as measured by FRAP also shows a similar pattern. This finding correlates with the studies of Jauniaux *et al.* 2000.<sup>19</sup> It is known that during pregnancy, there is a lot of stress on the women, both physical and emotional. Metabolically this reflects as OS and there is a need for an increase in need of antioxidants during pregnancy. TP and Albumin values found to increase in SAb cases after 48 h of expulsion. This increase is probably due to the removal of OS (The products of conception and the toxic metabolites associated). We did not observe any statistical difference in the values of the other parameters (glucose and cholesterol) among all the study groups.

## CONCLUSION

The antioxidant status of women with spontaneous inevitable abortion compared with healthy pregnant women and non-pregnant women. TAO status measured by FRAP in the plasma and the uric acid level were found much lower in women with spontaneous inevitable abortion than the normal pregnant women. After 48 h of abortion, both FRAP and uric acid level rose significantly. This suggests that the OS was to a certain extent; however, the values are still lower than that of normal pregnant as well as healthy non-pregnant women. The normal pregnant women also had a lower level of antioxidants than non-pregnant women. This suggests pregnancy itself is a stressful condition for the women. The role of OS is becoming increasingly important as there is new cumulative evidence suggesting that OS is involved in conditions such as abortions, preeclampsia, hydatidiform mole, fetal teratogenicity, preterm labor, and intrauterine growth retardation. OS is involved in causing an adverse effect on natural fertility, with a definite role in varied aspects of assisted conception. Optimizing various techniques in the ART laboratory may be an effective strategy to intercept OS in IVF/ICSI and IVM settings.

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# Breast Fibroadenomas in a Tertiary Care Hospital: A Prospective Observational Study

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## Abstract

**Introduction:** Breast cancer is a well-known type of cancer in the women both in the developed as well as in developing countries. The incidence of breast cancer is increasing in the developing country due to increase life expectancy, increase urbanization and adoption of western lifestyle. The majority of breast lumps are benign, but finding a breast lump understandably creates considerable patient anxiety. Some benign tumors can become malignant but it's rare.

**Aim:** To study the incidence of breast lumps, effectiveness of conservative management in the selected cases of fibroadenoma breast, incidence of various lumps with respect to breast segments and to study the bilaterality of the benign breast lumps.

**Materials and Methods:** Patients with breast lumps were included in the study. Ethical committee clearance and informed consent from the patients were obtained. The site of lump and extend of disease was recorded. Fine needle aspiration cytology was done routinely and selected cases submitted for excision biopsy.

**Results:** The most common lesion was fibroadenoma breast which was present in 35 patients (35%), 25 patients (25%) reported to have fibroadenosis, and 8 patients (8%) had giant fibroadenoma. In this study group, 70% of the patients attained menarche by the age of 13.

**Conclusion:** Although benign breast lesions are more common among female population than malignant lesion, the frequency of breast cancer is increasing rapidly across the global. It is important to screen females at a younger age to detect early breast cancer.

**Key words:** Breast, Cancer, Female, Lump, Tumor

## INTRODUCTION

The breast has always been a symbol of womanhood and the ultimate fertility. Human beings are classified as mammals because of the presence of “mamma” or the breast. Breast has a lot of importance even though it is a modified sweat gland not only for its lactating function but also for a cosmetic reason. It is the organ teased day in and day out by various hormones and it is the one which is influenced by various endocrinological challenges

posted on it.<sup>1</sup> Breast is one of the most puzzling areas of surgical diseases resulting from undue but understandable perception with carcinoma at the expense of benign conditions. Benign breast disorders are a heterogeneous group of lesions that clinically and radiologically span the entire spectrum of breast abnormalities.<sup>2</sup> Some benign disorders that mimics breast cancer need a biopsy or an excision to make this distinction. The breast or mammary glands are important for the survival of the newborn and thus of the species. Nursing of the young in the animal kingdom has many physiologic advantages for the mother, such as aiding postpartum uterine involution as well as for the neonate in terms of breast feeding of neonate and may have interfered with its physiologic role. It has become increasingly apparent that advantages of nursing are substantial for both mother and child.<sup>3</sup> Until a few years ago, it was believed that a breast tumor should be excised and histologically examined to determine the pre-

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operative assessment alone was associated with too much uncertainty now benign breast lump can be diagnosed with the help of fine needle aspiration cytology (FNAC), Trucut biopsy, ultrasonography (USG), and assure the patients of its benign course.<sup>4</sup>

### Aim

To study the incidence of breast lumps, effectiveness of conservative management in the selected cases of fibroadenoma breast, incidence of various lumps with respect to breast segments and to study the bilaterality of the benign breast lumps.

## MATERIALS AND METHODS

This prospective observational study was conducted in the Department of Surgery, Government Rajaji Medical College Hospital. Patients with breast lumps were included in the study. Ethical committee clearance and informed consent from the patients were obtained. The site of lump and extend of disease was recorded. FNAC was done routinely and selected cases submitted for excision biopsy. In this study, only benign clinical lumps were discussed in detail. Male patients also included.

## RESULTS

A total of 100 patients were studied, 91% of female patients followed by 9% of male patients. 40% of female patients are in 21-30 years followed by 37% in 31-40 years. 67% of male patients are in between 10 and 20 years (Figure 1 and Table 1).

The most common lesion was fibroadenoma breast which was present in 35 patients (35%), 25 patients (25%) reported to have fibroadenosis, and 8 patients (8%) had giant fibroadenoma (Table 2).

In this study group, 70% of the patients attained menarche by the age of 13. The general populating statistics show 13 years of age of menarche is around 41.2%, which is lesser than this study group. In this study, 25% of cases presenting with menstrual irregularities such as menorrhagia, dysmenorrhea, and scanty menstruation. Hence, there may be a role of ovarian hormones in the development of benign breast lumps (Table 3).

In this study group upper outer quadrant is more commonly affected, least common is lower inner quadrant. In this study, bilateral/unilateral ration of benign breast lumps 1:2.3, bilateral lumps in male breast (18%), bilateral lumps in female breast (29%) (Table 4).

Among the 14 cases of nipple discharge, 2 cases were duct ectasia, and 12 cases were fibroadenosis; the discharge was subjected for cytological study, no malignant cell found in the cytology. Among 36 patients, cyclical and non-cyclical pain in assessed with Cardiff breast pain chart, 25 patients with cyclical pain are responded well to E.P.O. and hormonal treatment (Table 5).

All cases of breast lumps were subjected to FNAC, and the results were analyzed and correlated with clinical exam and ultrasonogram. Since only benign cases are taken for our study, after histopathological exam only 3 cases are found to be malignant. In this study, we have the sensitivity of 97%.

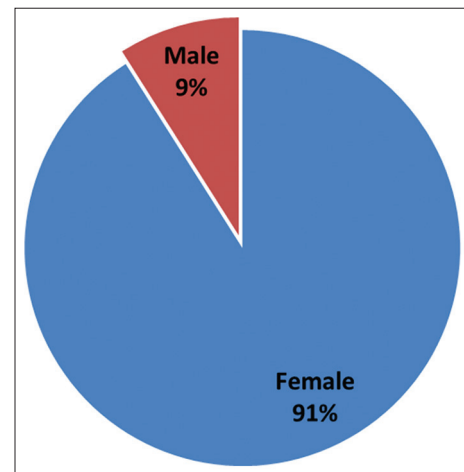


Figure 1: Gender distribution of study patients

Table 1: Age distribution of patients with benign breast lumps

Age in years	Male	Female
10-20	6	11
21-30	2	36
31-40	1	33
41-50	0	10
51-60	0	1
Total	9	91

Table 2: Distribution of various types of breast lumps

Types of breast lump	Number of patients
Fibroadenoma	35
Fibroadenosis	25
Giant fibroadenoma	8
Cystosarcoma phylloides	6
Gynecomastia	9
Breast cyst	8
Tramatic fat necrosis	5
Antibioma	2
Duct ectasia	2

**Table 3: Relationship various benign breast lumps with reproductive age group in females**

Lesions	Menstruation <40 years	Perimenopausal 40-50 years	Post-menopausal 50 years
Fibroadenoma	30	5	-
Fibroadenosis	25	-	-
Giant fibroadenoma	7	1	-
Cystosarcoma phylloids	4	2	-
Breast cyst	6	2	-
Traumatic fat necrosis	3	-	-
Antibioma	2	-	-
Sclerosing adenosis	2	-	-
Duct ectasia	1	-	1
Total	80	10	1

**Table 4: Incidence of various lumps with respect to different breast segment**

Quadrant	Percentage (%)
Upper outer	37
Upper inner	12
Lower outer	10
Lower inner	8
Central	15
More than one quadrant	18
Total	100

**Table 5: Distribution of clinical features**

Symptoms	Number of cases
Lump	100
Nipple discharge	14
Pain	36

In our study, it has a very limited role, only four doubtful cases with suspicion of malignancy core cut biopsy done, in all cases' results are only benign breast lump. USG is very useful in female <35 years and in very large breast, it aid in the aspiration of breast cysts, in our study of 8 breast cyst USG is used in aspiration, USG is also useful in the diagnosis of doubtful breast lumps.

About 15 cases if fibroadenoma are treated conservatively and followed up for 2 years. For other cases excision biopsy done, giant fibroadenoma was excised. Only one case of fibroadenoma, which was previously diagnosed as benign, is turned to be malignant. Some cases of fibroadenosis undergone excision biopsy, others treated medically. For 2 cases of duct ectasia Hadfield's surgery done. Breast cyst is aspirated and followed up for 6 months, there is no recurrence. Nine gynecomastia cases which are all idiopathic are treated by Webster's procedure. Cystosarcoma phylloides are treated with excision, with 1 cm margin of normal breast tissue, two cases of malignancy after histopathological examination is treated accordingly, for two cases of traumatic fat necrosis excision biopsy done.

## DISCUSSION

Although benign breast lumps are most common than malignant ones, females who present to the private medical center with complaints of breast lump suffer anxiety due to the fear of it turning out to be a malignant lesion. Thus, it is important to investigate these patients according to standard protocols to relieve their stress.<sup>5</sup> Most breast lumps are not breast cancer, there is always a chance that a lump may be breast cancer, even in younger women. Khan *et al.* also noted in their study that lump in the breast was more common on the left side with 57.5% of their patients than on the right side, i.e., 42.5%.<sup>6</sup>

Biopsy was performed to all the patients reporting with breast lump. As shown in Table 2, the study is found to be the most common lesion was fibroadenoma breast which was present in 35 patients (35%), 25 patients (25%) reported to have fibroadenosis, and 8 patients (8%) had giant fibroadenoma. Fibroadenoma is one of the most common lesions among young woman. It is a breast lump where tissues and ducts around a milk producing lobe grow and thickens over it. Fibroadenomas are benign tumors made up of both glandular breast tissue and stromal (connective) tissue.<sup>7</sup>

Internationally, Jamal reported that fibroadenoma was the most common breast lesion in their population in Jeddah, Saudi Arabia where it was present in 47% of the females.<sup>8</sup> Fibroadenoma is not common breast lesion everywhere because, in Nepal, it was the least common lesion, present in 21.6% of the female patients.<sup>9</sup> The use of birth control pills before age 20 is linked to the risk of fibroadenomas. Women with fibroadenomas have an increased risk of breast cancer which is about 11/2 to 2 times the risk of women with no breast changes.<sup>7</sup>

Fibrocystic disease is a condition in where it occurs due to thickening of tissue or cyst and it is mostly benign. In this study, fibrocystic disease is the second most common lesion to fibroadenoma with 17 patients (34%). Whereas

Lakhana and Khalid reported fibrocystic disease to be more common in their study.<sup>10</sup>

## CONCLUSION

Although benign breast lesions are more common among the female population than malignant lesion, the frequency of breast cancer is increasing rapidly across the global. It is important to screen females at a younger age to detect early breast cancer. Internationally mass awareness should be created regarding detection of early breast cancer and to foster knowledge about the medical and socioeconomic implications of a common public health issue.

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# Ultrasonographic Evaluation of Cervical Lymphadenopathy with Cytological Correlation

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## Abstract

**Introduction:** Cervical lymphadenopathy is one of the most common causes of mass in head and neck region; there are various causes of CL common among them are reactive, tuberculosis, metastasis, and lymphoma.

**Aims and Objectives:** The aims and objectives of this study were to study and differentiate between neoplastic (malignant) and nonneoplastic (reactive and tubercular) cervical lymph nodes by high-resolution ultrasonography. To correlate between ultrasound and fine needle aspiration cytology (FNAC) in cervical lymphadenopathy.

**Material and Methods:** Data were collected from a total of 80 cases referred for an ultrasound of neck to the Department of Radiodiagnosis, NSCB Medical College, Jabalpur, from December 2015 to December 2016, with 5-10 MH linear transducer using SIEMENS ultrasound machine. Lymph nodes were assessed using gray scale and color Doppler parameters such as nodal level and site, size, shape, L/S ratio, border, hilum, echotexture, necrosis, matting, and angioarchitecture. A provisional diagnosis was suggested after the ultrasound examination, and these findings were correlated with FNAC/histopathological findings.

**Results:** In our study, out of 45 non-neoplastic nodes (reactive and tubercular), only 40 nodes were identified as non-neoplastic (reactive/tubercular) on ultrasound prior to FNAC/histopathology. Out of 35 possible neoplastic (malignant nodes) detected on ultrasound, only 29 lymph nodes turned out to be neoplastic on FNAC/histopathology. Lymph node with oval shape (L/S ratio >2) echogenic hilum, homogenous echotexture, and hilar vascularity was considered as significant parameters in detecting non-neoplastic (reactive) lymph nodes, which showed matting with soft tissue edema. Nodes which were round shape (L/S ratio <2), absent hilum, heterogeneous echotexture, hilar, capsular vessels, and mixed vascularity were considered as significant parameters in detecting neoplastic (malignant) lymph nodes. Correlation of sonographic findings with FNAC/histopathological findings was performed. Sensitivity and specificity of ultrasound in differentiating neoplastic from non-neoplastic cervical lymphadenopathy was found to be 90% and 74%, respectively.

**Conclusions:** This study concludes that ultrasonographic examination proved as a valuable primary investigation to identify lymph nodes and differentiate non-neoplastic and neoplastic lymphadenopathy.

**Key words:** Cervical lymphadenopathy, Ultrasonography, Malignant

## INTRODUCTION

Cervical lymphadenopathy is one of the most common causes of mass in head and neck region; there are

various causes of CL common among them are reactive, tuberculosis, metastasis, and lymphoma.

Ultrasonographic criteria for distinguishing neoplastic and non-neoplastic lymph nodes have been studied under site, shape, size, echogenicity, hilum, matting, nodal border, long/short axis ratio, intranodal necrosis, and angioarchitecture.<sup>1</sup>

Ultrasonographic features that help to identify abnormal nodes as well as giving clues to neoplastic nodes are heterogeneous echogenicity, absent hilum, invasion, and

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intranodal necrosis. The shape is the best method to attempt the differentiation between neoplastic and non-neoplastic lymph nodes. The long/short diameter ratio of lymph node provides excellent criteria for differentiation between neoplastic and non-neoplastic cervical lymphadenopathy.<sup>2</sup>

By using color/power Doppler sonography can further characterize lymph nodes as non-neoplastic (reactive, tubercular) and neoplastic. The non-neoplastic (reactive) nodes show increased central hilar vascularity, with radial symmetry whereas, neoplastic (malignant) nodes show absent hilar vascularity and increased peripheral vascularity.<sup>1</sup>

## MATERIALS AND METHODS

In this study, 80 patients age between 12 and 60 years with cervical lymphadenopathy referred for ultrasonography of neck to the Department of Radiodiagnosis, NSCB Medical College, over a period of December 2015 - December 2016 are included in this study. All scans carried out on 5-10 MHz linear transducer using SIEMENS ultrasound-guided (USG), Philips machine.

### Inclusion Criteria

1. All patients coming for ultrasound neck.
2. Patients more than 12 years of age of either sex.

### Exclusion Criteria

1. Moribund patients.
2. No fine needle aspiration cytology (FNAC) available.
3. Patient with no evidence of cervical lymphadenopathy on ultrasound.

Common ultrasound scan planes used in the examination of cervical nodes in different regions of the neck.

Regions	Scan plane(s)
Submental	Transverse
Submandibular	Transverse
Parotid	Transverse and longitudinal
Upper cervical	Transverse
Middle cervical	Transverse
Lower cervical	Transverse
Supraclavicular fossa	Transverse
Posterior triangle	Transverse and longitudinal

The criteria that are followed in this study to differentiate between reactive, tubercular, and neoplastic (malignant) lymph nodes (Table 5):

1. Distribution includes levels and side;
2. Number;
3. Size;
4. Shape includes L/S ratio;
5. Echogenic hilum - wide, narrow, and absent;

6. Border - sharp and unsharp;
7. Homogeneity and heterogeneity;
8. Central necrosis and cystic necrosis;
9. Matting;
10. Vascularity and angioarchitecture: Hilar vessels, peripheral vessels, mixed vessels, focal absence of perfusion and absence of perfusion.

Non-neoplastic lymph nodes include reactive and tubercular. Lymph node oval shape, echogenic hilum, homogenous echotexture, matting, L/S ratio >2, and hilar vascularity were considered as reactive lymphadenopathy. Nodes hypoechoic, round without echogenic hilum, intranodal cystic necrosis, nodal matting, and adjacent soft tissue edema were considered tubercular lymphadenitis.

Round shape, absent hilum, heterogeneous echotexture, sharp borders, L/S ratio <2, capsular vessels (peripheral), mixed vascularity, displacement of vessels, and focal absence of perfusion were considered in detecting neoplastic lymph nodes. Since there was no difference between primary malignancy and metastasis sonologically, results of the examination were grouped as malignant under neoplastic category.

### USG Guided FNAC

The most promising contribution of ultrasound is in the guidance of FNAC in non-palpable lymph nodes. Under aseptic precaution and ultrasound guidance, 21/22 gauge needle with syringe is introduced into enlarged abnormal lymph nodes, and sample is sent for analysis.

## RESULTS

In our study most common no. of cases seen in age group (13-20) as shown in Table 1, out of 45 non-neoplastic nodes (reactive and tubercular), only 40 nodes were identified as non-neoplastic (reactive/tubercular) on ultrasound before FNAC/histopathology. Out of 35 possible neoplastic (malignant nodes) detected on ultrasound, only 29 lymph nodes turned out to be neoplastic on FNAC/histopathology. Lymph node with oval shape (L/S ratio >2) echogenic hilum, homogenous echotexture, and hilar vascularity were considered as significant parameters in detecting non-neoplastic (reactive) lymph nodes, which showed matting with soft tissue edema. Nodes which were round shape (L/S ratio <2), absent hilum, heterogeneous echotexture, hilar, capsular vessels, and mixed vascularity were considered as significant parameters in detecting neoplastic (malignant) lymph nodes. Correlation of sonographic findings with FNAC/histopathological findings was performed. Sensitivity and specificity of ultrasound in differentiating neoplastic from

non-neoplastic cervical lymphadenopathy was found to be 90% and 74%, respectively.

Our study had a high sensitivity of 91.3%, specificity of 75.93%, positive predictive value of 91.11%, and also a negative predictive value of 76.36% in differentiating neoplastic from non-neoplastic lymphadenopathy (Table 4).

Table 10 shows most of benign, reactive, tubercular and malignant lymph nodes showing lymph node perfusion, which is not significant and nonspecific criteria.

On USG at level I an oval lymph node with maintained Hilum and hilar vascularity suggestive of reactive lymph node confirmed on FNAC (Figure 1).

**Table 1: Age distribution**

Age groups (in years)	Number of cases
13-20	17
21-30	11
31-40	13
41-50	15
51-60	7
61-70	9
>70	8

**Table 2: Diagnosis of cervical lymphadenopathy on USG**

Diagnosis on USG	Number of lymph nodes
Malignant	35
Tubercular	21
Reactive	24
Total	80

USG: Ultrasound-guided

**Table 3: Diagnosis of cervical lymphadenopathy on FNAC/histopathology**

Diagnosis on USG	Number of lymph nodes
Malignant	29
Tubercular	21
Reactive	30
Total	80

USG: Ultrasound-guided, FNAC: Fine needle aspiration cytology

**Table 4: Comparison of USG diagnosis with FNAC diagnosis**

USG diagnosis	FNAC diagnosis			
	Malignant	Tubercular	Reactive	Total
Malignant	20	10	3	35
Tubercular	5	8	8	21
Reactive	4	3	17	24
Total	29	21	30	80

$\chi^2=110.2$ ,  $P<0.001$ , USG: Ultrasound-guided, FNAC: Fine needle aspiration cytology

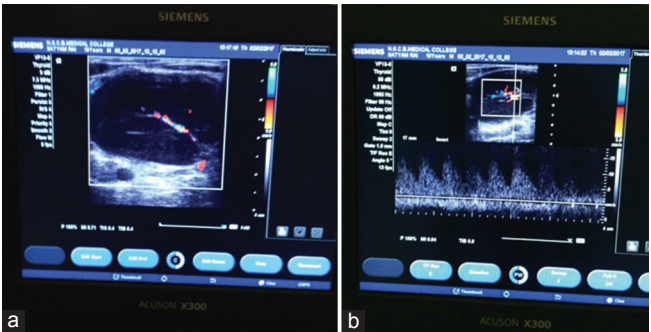
On USG oval lymph node with maintained Hilum and hilar vascularity suggestive of reactive lymph node but on FNAC it was proved to be malign CM ant (Figure 2).

# DISCUSSION

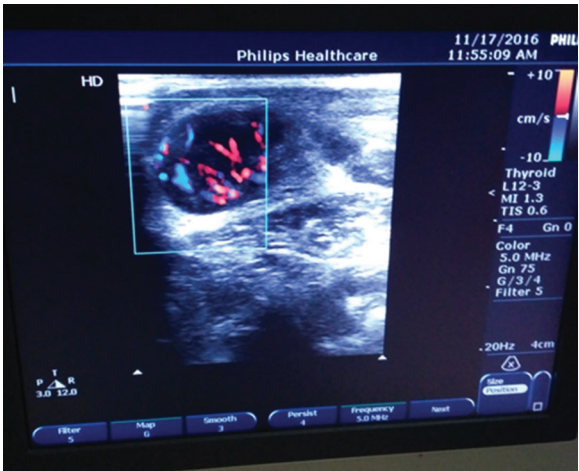
Ultrasound is preferred over computed tomography (CT) and magnetic resonance imaging (MRI) in evaluation cervical lymphadenopathy.

1. In differentiating benign and malignant lymph nodes, the size cannot be considered as sole criteria.
2. The presence of central nodal necrosis is thought to be one of the most specific signs of metastatic involvement with a specificity of 95-100%. In CT, the nodal necrosis is observed as central low attenuation. Infection and other causes can also appear as a central nodal necrosis on CT.<sup>3</sup>
3. Finally, CT and MRI are expensive and not readily accessible for repeated use during follow-up of the patients.

Ultrasonography is cost-effective, easily available, radiation free, non-invasive, safe and is primary investigation to



**Figure 1: (a and b) 15-year-old male presented with swelling in neck**



**Figure 2: 65-year-old male presented with swelling in neck**



**Table 5: Distribution of L/S ratio on USG to FNAC/histopathology diagnosis**

Category	L/S<2	L/S>2	Total
Malignant (%)	22 (75)	7 (24)	29
Tubercular (%)	9 (44)	12 (57)	21
Reactive (%)	12 (40)	18 (60)	30
Total (%)	43 (53)	37 (47)	80

$\chi^2=23.26$ ,  $P<0.001$ , USG: Ultrasound-guided, FNAC: Fine needle aspiration cytology

**Table 6: Distribution of border according to USG in comparison with FNAC/histopathology diagnosis**

Category	Sharp border (%)	Unsharp border (%)	Total
Malignant	19 (65)	10 (34)	29
Tubercular	8 (38)	13 (61)	21
Reactive	12 (40)	18 (60)	30
Total	39 (48.8)	41 (51.2)	80

$\chi^2=4.4$ ,  $P=0.11$ , USG: Ultrasound-guided, FNAC: Fine needle aspiration cytology

**Table 7: Distribution of lymphnode echotexture according to USG in comparison with FNAC/histopathology diagnosis**

Category	Homogenous (%)	Heterogeneous (%)	Total
Malignant	10 (34)	19 (65)	29
Tubercular	15 (71)	6 (28)	21
Reactive	23 (76)	7 (23)	30
Total	48 (60)	32 (40)	80

$\chi^2=16.38$ ,  $P<0.001$ , USG: Ultrasound-guided, FNAC: Fine needle aspiration cytology

**Table 8: Hilar vascularity on USG diagnosis with hilar vascularity on FNAC/histopathology diagnosis**

Category	Present (%)	Absent (%)	Total
Malignant	7 (24)	22 (75)	29
Tubercular	3 (14)	18 (85)	21
Reactive	22 (73)	8 (26)	30
Total	32 (40)	48 (60)	80

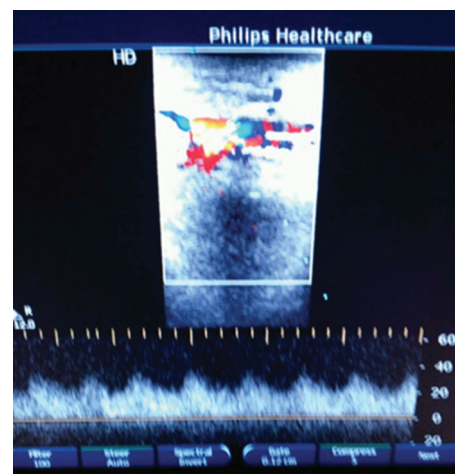
$\chi^2=42.68$ ,  $P<0.001$ , USG: Ultrasound-guided, FNAC: Fine needle aspiration cytology

**Table 9: Capsular vascularity on USG diagnosis with hilar vascularity on FNAC/histopathology diagnosis**

Category	Present (%)	Absent (%)	Total
Malignant	3 (10)	26 (89)	29
Tubercular	1 (4.7)	20 (95)	21
Reactive	3 (10)	27 (90)	30
Total	7 (8.7)	73 (91.2)	80

$P=0.04$ , USG: Ultrasound-guided, FNAC: Fine needle aspiration cytology

differentiate malignant, tubercular, and reactive cervical lymphadenopathy.<sup>3</sup> Ultrasound examination of the lymph nodes can be done in all planes so that exact nodal size and shape can be evaluated.<sup>4</sup>



**Figure 3: Tubercular lymph node with absent hilum showing capsular and hilar vascularity (mixed) on Doppler evaluation**



**Figure 4: 19-year-old male, known case of lymphoma on ultrasound-guided there is enlarged level II round lymph node with absent hilum, sharp borders and heterogeneous echo texture proved on fine needle aspiration cytology**

### Ultrasound Correlation with FNAC/Histopathology

In a study done by Danninger *et al.*,<sup>5</sup> ultrasonography sensitivity and specificity for detecting malignant nodes was 96% and 69%, respectively.

Ahuja and Ying,<sup>6</sup> concluded that ultrasound was 95% sensitive and 83% specific for classifying metastatic/non-metastatic lymph nodes (Table 2).

In our study on USG out of 80 lymph nodes, 35 were malignant, 21 were tubercular and 24 were reactive lymph nodes. On FNAC/histopathology out of 80 lymph nodes, 29 lymph nodes were malignant, 21 were tubercular, and 30 were reactive lymph nodes (Table 3).

In our study, the ultrasonography sensitivity, specificity, positive and negative predictive values are 90%, 74%, 77%



**Table 10: No perfusion on USG diagnosis with no perfusion on FNAC**

Category	Present (%)	Absent (%)	Total
Malignant	2 (6.8)	27 (93.10)	29
Tubercular	3 (14)	18 (85.70)	21
Reactive	4 (13)	26 (86)	30
Total	9 (11.2)	71 (88.7)	80

USG: Ultrasound-guided, FNAC: Fine needle aspiration cytology

and 92%, respectively, for differentiating neoplastic from non-neoplastic cervical lymphadenopathy.

Thus, our study confirmed the reliability of ultrasound sensitivity and specificity in evaluating cervical lymph nodes on ultrasound as reported in literature.

### Lymph Node Border

Sharp and unsharp Border: Sharp borders in malignancy are due to the infiltrating tumor cells which replace normal lymphoid tissues and it causes an increasing acoustic impedance difference between lymph nodes and surrounding tissues whereas unsharp borders in malignant nodes indicate invasion into adjacent structures. But in benign because of edema or active inflammation of the surrounding tissues, they will have unsharp borders. In a study by Ahuja and Ying,<sup>1</sup> they concluded that border sharpness is not helpful in diagnosis.

In our study, out of 29 malignant nodes, 19 shows sharp border, out of 30 reactive 18 shows unsharp border, out of 21 tubercular 13 shows unsharp border. In this study, the *P* value for the border was 0.09, which showed the association to be not significant (Table 6).

### Lymph Node Hilum

Widened, narrow and absent: In malignancy/metastases infiltration of the malignant tissue result in early distortion of internal nodal architecture with invasion of hilum, resulting in narrowing or absence of hilum (Figure 3). In case of reactive nodes, pathogen reaches nodal cortex in early stages induces lymphocyte proliferation and if inflammatory stimulus still persists, causes formation of new germinal center resulting in widening of hilum.

In one study done by Vasallo *et al.*,<sup>4</sup> 26 of benign nodes 58% showed a wide central hilum, 35% showed a narrow hilum and 8% no hilum. Of 68 malignant nodes, only 6% of nodal metastasis exhibited a wide central hilum, 48% exhibited no hilum, and 46% showed narrow hilum.

In our study, 83% of malignant nodes showed absent hilum, 13% of malignant nodes showed narrow hilum. 65% of tubercular nodes showed absent hilum and 23%

with narrow hilum. 46% of reactive nodes showed wide hilum. The *P* < 0.01 shows significant association.

### Echotexture of the Lymph Nodes

Homogeneous and heterogeneous: In one study done by Toriyabe *et al.*,<sup>7</sup> 17 of 19 nodes which showed heterogeneous echotexture were proved as malignant and 30 out of 33 lymph nodes which are homogenous echotexture were proved benign/reactive by histopathology study.

Our study shows 23 of reactive lymph nodes are homogeneous and 19 of the malignant lymph nodes are heterogeneous correlating with the previous study (Table 7).

The *P* value for this criterion was 0.0015, which showed the association to be significant.

### Matting

Ahuja and Ying<sup>1</sup> stated that matting is the important criteria to diagnose tubercular lymph nodes. Because of the soft tissue edema surrounding the affected lymph nodes results in matting of the lymph nodes.

Ahuja *et al.*<sup>8</sup> stated that matting and adjacent soft tissue edema is common in tuberculous nodes; however, they are rarely seen in malignancy.

In our study, out of 80 nodes, 28 showed matting all of which are tubercular (100%). Reactive and malignant lymph nodes show no matting.

### Vascular Pattern

#### Hilar vascular pattern

Benign/reactive nodes tend to have a prominent hilar vascularity due to increase in the vessel diameter and blood flow as the infection progresses (Figure 4).

In a study done by Na *et al.*,<sup>9</sup> 97% of benign/reactive and 18% of malignant lymph nodes showed hilar vessels.

In our study of 80 lymph nodes: Malignant 7, tubercular 3, and reactive 21 showed hilar vessels. The *P* value for this criterion was <0.01, which showed the association to be very significant (Table 8).

### Capsular (Peripheral) Flow

In a study done by Na *et al.*,<sup>9</sup> there is peripheral vascularity with the loss of central nodal vascularity is tubercular nodes 24 and metastatic.<sup>8</sup>

Our study shows tubercular 7 and malignant 3 lymph nodes showed only capsular vascularity which was statistically not significant (Table 9).

### Mixed vascular pattern

In our study of 100 lymph nodes: Malignant 80%, reactive 10%, and tubercular 62% showed mixed vascularity. The *P* value for this criterion was <0.001 showed the association to be statically significant.

In a study done Na *et al.*,<sup>9</sup> 85% of malignant and 76% of tubercular nodes showed mixed vascular pattern.

This mixed vascularity flow is seen in tubercular, however, more commonly in malignant nodes.

### Limitations of Doppler

According to Na *et al.*,<sup>9</sup> it is very difficult to detect superficially located, slow flow signals, It is difficult to obtain Doppler spectral wave forms in non-cooperative patients.

## CONCLUSION

### This Study Concludes that

1. High resolution sonographic and color Doppler examination proved as a valuable primary investigation to identify lymph nodes and helps to differentiate neoplastic (malignant) from non-neoplastic (reactive and tubercular) lymph nodes.
2. Ultrasound evaluation is very sensitive in differentiating between cystic/necrotic foci and solid swellings.
3. Ultrasound helps in identifying abnormal nodes and useful for guided FNAC.
4. Finally, all ultrasound diagnosis must be correlated with FNAC/histopathology study not only to determine whether the nodes are malignant, reactive, tubercular,

nodes but also to determine the histology of the neoplasm.

### At the End of Our Study, We Present Evaluation Criteria that Help in Differentiating Non-neoplastic from Neoplastic Cervical Lymph Nodes

1. Gray scale findings of size, shape, long axis/short axis ratio, nodal echogenic hilum, lymph node echogenicity, matting, and nodal necrosis.
2. Color Doppler findings of focal absence of perfusion, capsular vessels, hilar vascularity and mixed vascularity.

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# Hydatid Cysts in Unusual Sites: A Retrospective Imaging Study in Assam

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## Abstract

**Background:** Hydatid disease is a worldwide zoonosis produced by the larval stage of the *Echinococcus* tapeworm. It can reach any organ or tissue in the body and develops into small hydatid cysts (HCs). Most commonly, it occurs in the liver and lungs.

**Aim:** To study the cases of HCs in unusual sites.

**Materials and Methods:** A retrospective radiological study of HCs other than liver and pulmonary HCs for 1 year in a tertiary care hospital in Assam.

**Results:** Altogether, 11 cases of HCs in unusual sites were included in the study, and different imaging findings were noted.

**Conclusion:** With this study, effort was made to bring some light over the rare HC cases in this part of North-East India.

**Key words:** *Echinococcus*, Hydatid cyst, North-East, Unusual sites

## INTRODUCTION

Hydatid disease (HD) is one of the most frequent parasitosis, caused by the larval stage of *Echinococcus granulosus*, especially in countries with a warm climate such as India, African countries, Turkey, South American countries, and Middle Eastern countries.<sup>1</sup> In India, the highest prevalence is reported in Andhra Pradesh, Tamil Nadu, and Jammu and Kashmir.<sup>2</sup>

Infestation by *E. granulosus* in humans most commonly occurs in the liver (55-70%) followed by the lung (18-35%). Incidence of unusual sites is about 8-10%.<sup>2</sup> There are two types of *Echinococcus* infections. *E. granulosus* is the more common type, whereas *Echinococcus multilocularis* is less common but more invasive, mimicking a malignancy. Dogs or other carnivores are definitive hosts, whereas

sheep or other ruminants are intermediate hosts. Humans are accidental intermediate host infected by the ingestion of food or water that has been contaminated by feces of definitive hosts containing the eggs of the parasite. After the outer capsule of the egg has been ingested, the freed embryo (oncosphere) enters a branch of the portal vein by passing through the duodenal mucosa. Most of these embryos become lodged in the hepatic capillaries, where they either die or to grow into hydatid cysts (HCs).<sup>3,4</sup>

Here, a study was conducted on HCs occurring in unusual sites in human in a tertiary care hospital in Assam, and to the best of our knowledge, very few such studies in human have been published from this part of the country.

## MATERIALS AND METHODS

This is a retrospective study based on reports, films and digital pictures of X-rays, ultrasonography (USG), computed tomography (CT), and magnetic resonance imaging (MRI) of the patients with suspected HC attending the Department of Radiology, Gauhati Medical College and Hospital, Guwahati. The study was conducted for 1 year from June 2015 to May 2016. Ethical clearance

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was obtained from the Ethical Committee of the Medical College. Some of the patients were followed up and post-operative HC was confirmed histopathologically. In some cases, Gadolinium-based contrast was used for imaging. Siemens (800 MA) for X-ray, Siemens Acuson Antares machine for ultrasound, 16 slice Philips MX16 machine for CT scan, and 1.5 T Siemens Somatom Tim Avanto machine for MRI were used in the study.

### Inclusion Criteria

Patients with radiologically diagnosed HC other than liver and pulmonary HC.

### Exclusion Criteria

1. Patients with radiologically diagnosed liver and pulmonary HC
2. Patients with HC other than liver and pulmonary HC but refused to take part in the study.

## RESULTS AND OBSERVATIONS

Altogether, 11 cases with HC in unusual sites were included in the study.

### Case 1 - Splenic HC

A 30-year-old male patient referred to Radiology Department with abdominal pain. USG images revealed hydatid matrix filling the cyst, dependent hydatid sand and floating membrane, and detached laminated membrane (Figure 1a and b). Contrast enhanced CT (CECT) revealed unilocular cyst arising from splenic parenchyma with small pericyst calcification (green arrow - c). Non-contrast CT shows increase in calcification after 3 months of albendazole therapy (blue arrow - d and e).

small pericyst calcification (Figure 1c). Noncontrast CT (NCCT) showed increase in calcification after 3 months of albendazole therapy (Figure 1d and e).

### Case 2 - Retroperitoneal HC

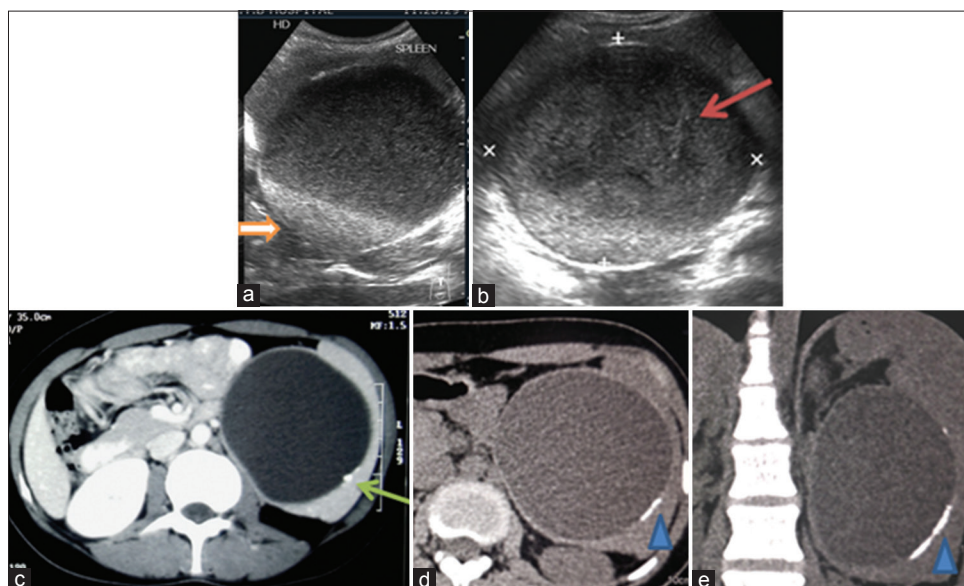
A 31-year-old male patient came with intermittent dull aching abdominal pain with vague abdominal symptoms. Axial, coronal, and sagittal CT (Figure 2a-d) sections revealed a well-defined, unilocular, homogeneous, spherical cyst in retroperitoneum, and arising from right psoas muscle. The lesion showed typical hyperdense wall on NCCT (Figure 2a) with no enhancement on CECT (Figure 2b-d).

### Case 3 - Intramuscular HC

A 35-year-old male patient came with chief complain of swelling on the right thigh since 3 years. USG image shows linear serpentine structures and daughter cyst within the lesion (Figure 3a and b). Axial T1, T2W and short tau inversion recovery coronal MRI revealed multivesicular cyst in the right quadriceps femoris, with multiple daughter cysts appearing more hypointense on T1, with coiled floating membranes in cyst (Figure 3c-g).

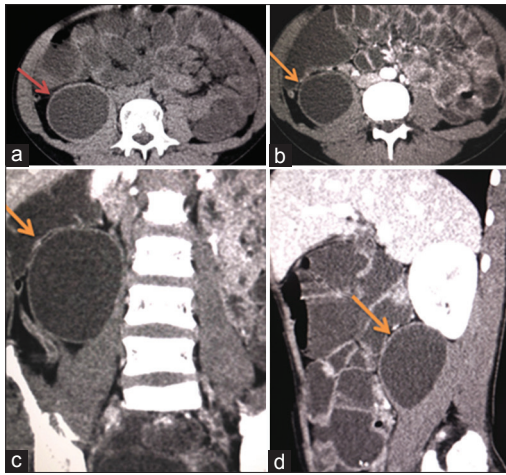
### Case 4 - Intramuscular HC

A 70-year-old male patient came with chief complaints of swelling in the left thigh since 10 years (Figure 4a). X-ray left thigh showed soft tissue swelling with no involvement of underlying bone (Figure 4b). USG revealed large heterogeneous lesion with multiple anechoic cysts within (Figure 4c). MRI revealed mixed signal intensity lesion with multiple small intralesional cysts, hypointense

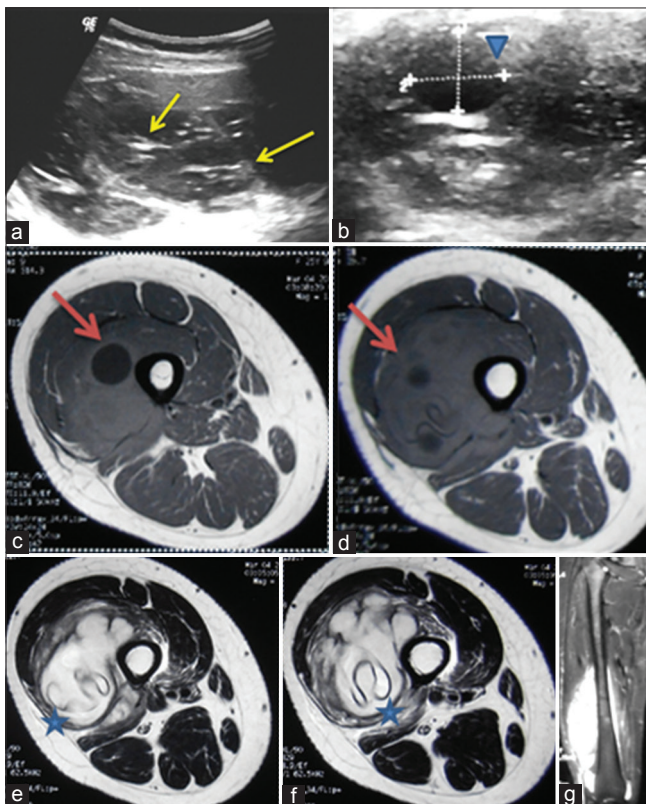


**Figure 1:** Ultrasonography images show hydatid matrix filling the cyst, dependent hydatid sand (bold arrow - a) and floating membrane, detached laminated membrane (red arrow - b). Contrast enhanced computed tomography (CT) shows unilocular cyst arising from Splenic parenchyma with small pericyst calcification (green arrow - c). Non-contrast CT shows increase in calcification after 3 months of albendazole therapy (blue arrow - d and e)





**Figure 2:** Axial, coronal, and sagittal computed tomography (CT) (a-d) sections reveal a well-defined, unilocular, homogeneous, spherical cyst in retroperitoneum, arising from right psoas muscle. The lesion exhibits typical hyperdense wall on non-contrast CT (red arrow - a) with no enhancement on contrast enhanced CT (orange arrow - b-d)



**Figure 3:** Ultrasonography image shows linear serpentine structures (yellow arrow) and daughter cyst (blue arrow head) (a and b) within the lesion. Axial T1, T2W and short tau inversion recovery coronal magnetic resonance imaging show multivesicular cyst in right quadriceps femoris, with multiple daughter cysts (red arrow) appearing more hypointense on T1, with coiled floating membranes in cyst (blue star) (c-g)

on T1 (Figure 4e), and hyperintense on T2 (Figure 4d). Mild enhancement was present along walls of the cyst

(Figure 4g). The patient was operated (Figure 4f), and HC was confirmed histopathologically.

#### Case 5 - Breast HC

A 35-year-old woman came with gradually progressive, painless lump in the left breast since 1½ year. USG of left breast revealed a solid appearing lesion with diffuse echoes. Posterior acoustic enhancement (Figure 5a) and floating echogenic membrane (Figure 5b) were clues to correct diagnosis. “Contained rupture” of lesion was noted from its posterior wall, with intact pericyst and focal breach in ectocyst (Figure 5c). Right breast was normal.

#### Case 6 - Intracranial HC

A 40-year-old male patient came with chief complain of a severe headache and giddiness since 6 months. MRI revealed well-defined lesion in the right parietal region appears homogeneously hypointense on T1W (Figure 6a) and hyperintense on T2W (Figure 6b) sequences. MRI showing neither any enhancement (Figure 6c) nor blooming on susceptibility-weighted imaging and diffusion restriction (Figure 6d and e). The patient was operated (Figure 6f), and HC was removed.

#### Case 7 - Right Myocardial HC with Splenic Hydatid

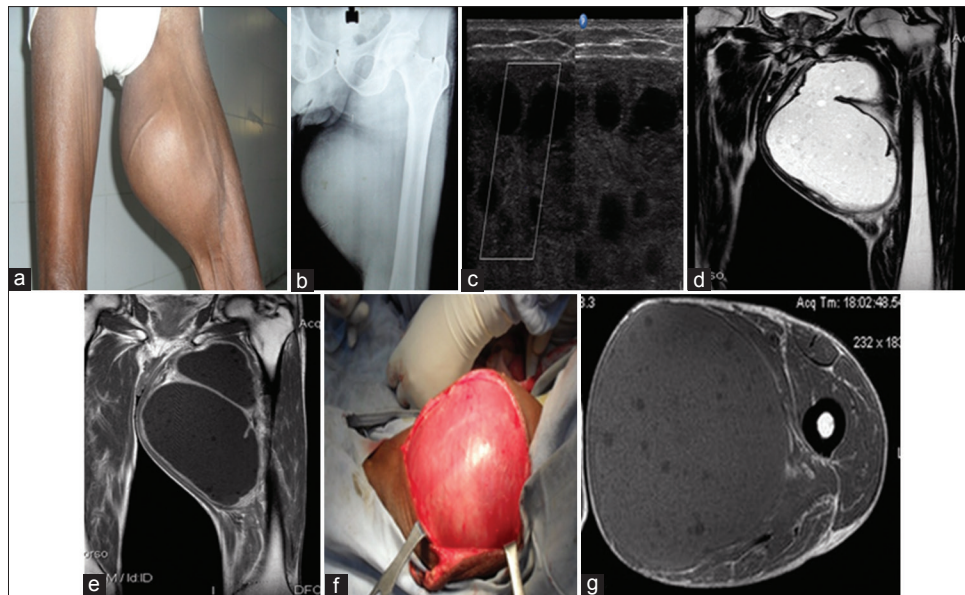
A 44-year-old female came with chief complain of chest pain and breathlessness. Cardiac CT and MRI revealed well-defined multiloculated non-enhancing cystic lesion in the right myocardium. Similar cystic lesion was present in spleen (Figure 7a-d). Coronal image showed cardiac and splenic cystic lesions (Figure 7e). Patient underwent surgical extirpation of cardiac HC followed by splenic cystectomy after 6 weeks (Figure 7f).

#### Case 8 - Subcutaneous HC

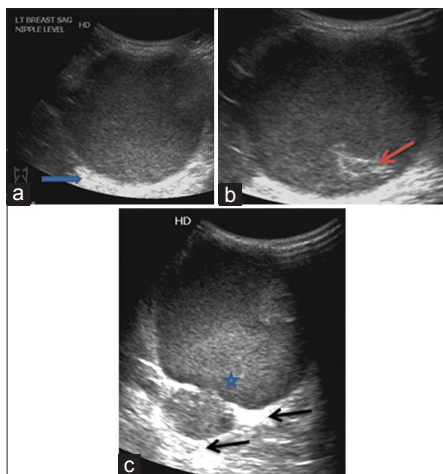
A 50-year-old female came with chief complain of swelling over upper third of the right arm since 7 years (Figure 8a). X-ray of right shoulder showed soft tissue density lesion in upper 1/3<sup>rd</sup> of the right upper limb (Figure 8b). USG revealed heterogeneous lesion in subcutaneous plane with multiple rounded anechoic cysts within surrounded by double membrane (Figure 8c). MRI showed mixed signal intensity lesion with multiple intralesional cysts in subcutaneous plane (Figure 8d-g).

#### Case 9 - Renal HC

A 35-year-old female came with lump in abdomen on the left side and hematuria. USG revealed enlarged and multicystic left kidney. Cysts showed double wall with membranous structures within (Figure 9a). CT revealed large cystic lesion with multiple daughter cysts and peripheral wall calcifications and enhancement (Figure 9b and c). MRI abdomen confirmed HCs (Figure 9d-g).



**Figure 4:** 70 years patient with left thigh swelling (a). X-ray left thigh shows soft tissue swelling with no involvement of underlying bone (b). Ultrasonography show large heterogeneous lesion with multiple anechoic cysts within (c). Magnetic resonance imaging shows mixed signal intensity lesion with multiple small intralesional cysts. Hypointense on T1 (e) and hyperintense on T2 (d). Mild enhancement along walls of the cyst (g). Intraoperative hydatid cyst (f)



**Figure 5:** Ultrasonography of left breast revealed a solid appearing lesion with diffuse echoes. Posterior acoustic enhancement (blue arrow - a) and floating echogenic membrane (red arrow - b) were clues to correct diagnosis. "Contained rupture" of lesion is noted from its posterior wall, with intact pericyst (black arrows) and focal breach in ectocyst (blue star - c)

### Case 10 - Intraperitoneal HC

A 65-year-old female came with distension of abdomen since 2 years. USG revealed multiple large well-defined intraperitoneal anechoic cystic lesions with crumpled membranes and small daughter cysts within walls of lesions (Figure 10a-c). CECT revealed multiple large ill-defined cystic lesions involving the peritoneal cavity and the right lobe of liver with peripherally arranged daughter cysts and calcifications in few lesions (Figure 10d-g).

### Case 11 - Spinal HC

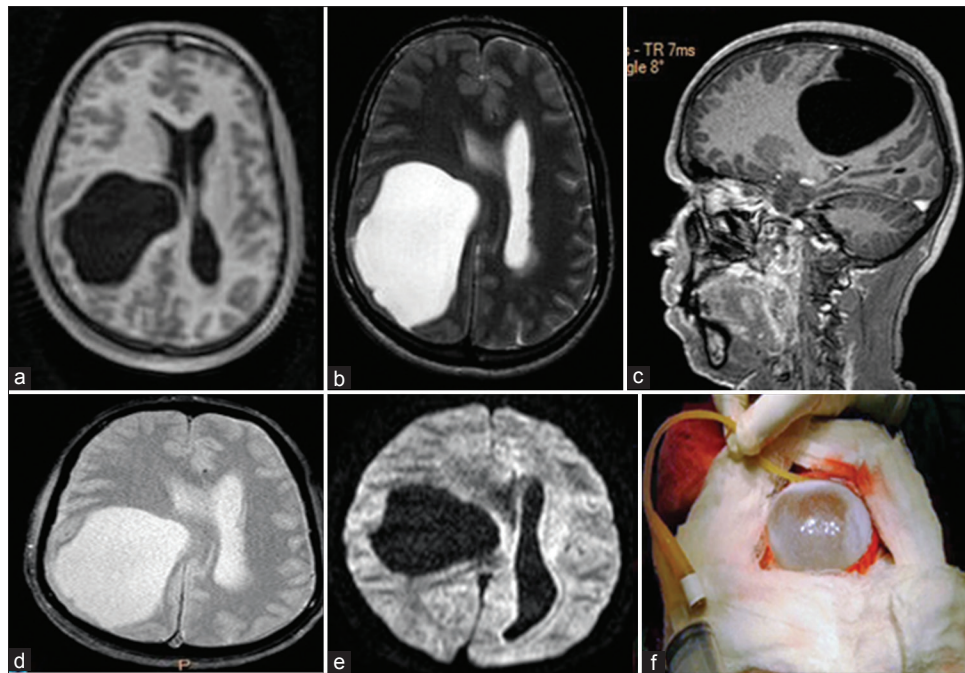
A 32-year-old male patient came with a history of back pain radiating to the right lower limb since 3 months. There was no history of trauma, fever, or any other last operative history. T1W plain and post contrast images showed evidence of well-defined multiloculated hypointense lesion seen involving the left hemipelvis with extension into the spinal canal and compressing the cauda equina. The lesion showed minimal peripheral enhancement on post contrast images (Figure 11a-c). T2W sagittal, axial, and coronal images revealed evidence of well-defined multiloculated hyperintense cystic lesions involving the left hemipelvis in presacral region. The lesion was extending into spinal canal and compressing the cauda equine (Figure 11d-f).

## DISCUSSION

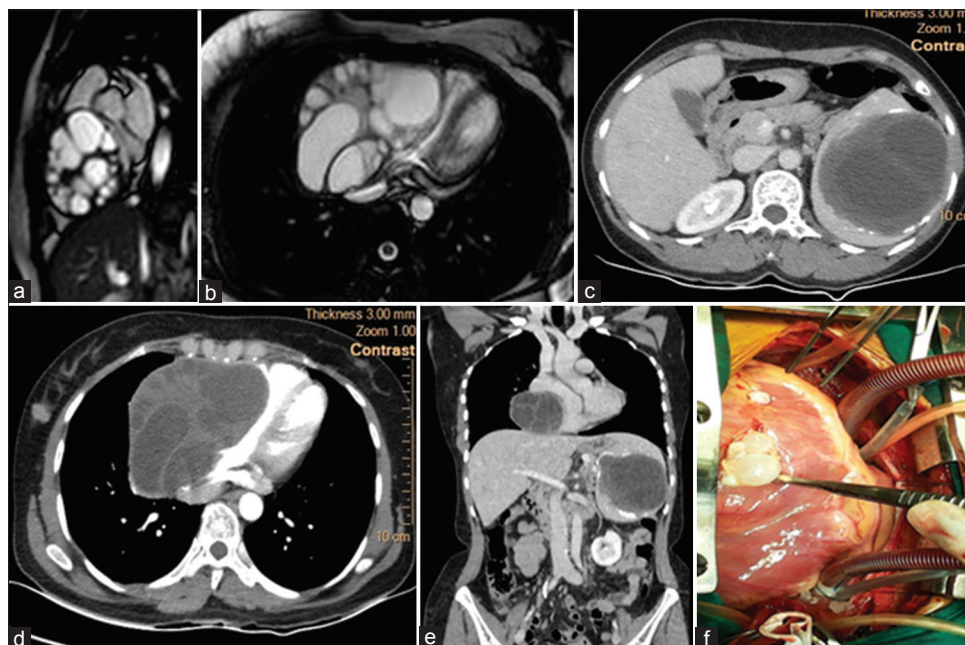
HD is endemic in India. The annual incidence of HD per 100,000 persons varies from 1 to 200.<sup>5</sup> HC has been reported from every part of the human body such as liver, lungs, peritoneum, bones, ovaries, breast, and brain.<sup>6</sup> Although portal blood stream remains the main pathway of parasite spread, normally existing portocaval shunts, lymphatic invasion by the parasite, and retrograde migration from vena cava to subclavian vein have been documented and explain some of these rare sites.<sup>7</sup>

Spleen is the third most common site for *Echinococcus*.<sup>8</sup> Sonography is helpful, especially in the early stages, when the lesion is cystic, in detecting daughter cysts, hydatid





**Figure 6:** Well-defined lesion, in right parietal region, appears homogenously hypointense on T1W (a) and hyperintense on T2W (b) sequences. Magnetic resonance imaging showing neither any enhancement (c - Sagittal T1 post-gadolinium contrast) nor blooming on susceptibility-weighted imaging and diffusion restriction (d - axial DW1 and e - axial SW1). Intra-operative intracranial HC (f)



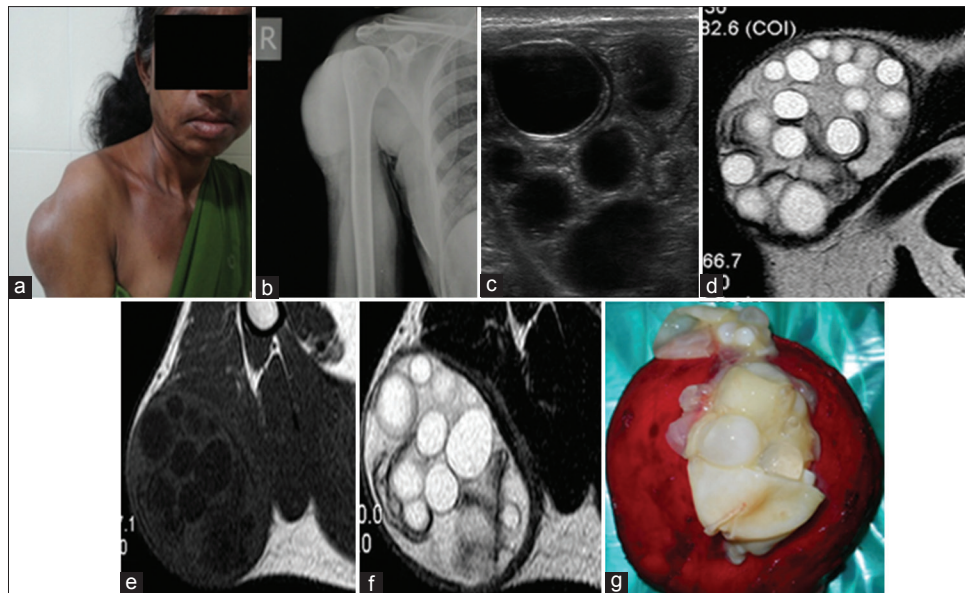
**Figure 7:** Cardiac computed tomography and magnetic resonance imaging showing well-defined multiloculated non-enhancing cystic lesion in right myocardium. Similar cystic lesion is present in spleen (a-d). Coronal image showing cardiac and splenic cystic lesions (e). Cardiac hydatid cyst intraoperatively (f)

membranes, and hydatid sand.<sup>9,10</sup> When ultrasound reveals infoldings of the inner cyst wall, separation of the hydatid membrane from the wall of the cyst, or hydatid sand, a diagnosis of HD is probable.<sup>11</sup>

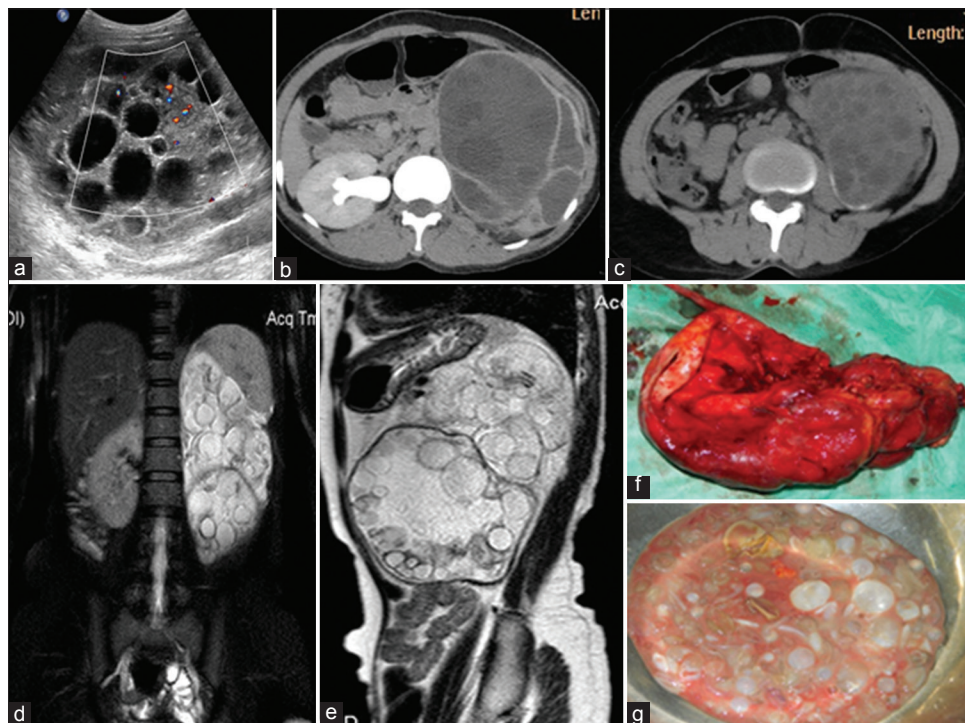
CT is the best mode for determining the number, size, and anatomic location of the cysts. CT may also be

used for monitoring lesions during therapy and to detect recurrences.<sup>12</sup> Calcification is usually curvilinear or ring-like and involves the pericyst.<sup>13</sup>

Isolated retroperitoneal HC is very rare as mentioned by various literatures. Ghonge *et al.* reported a case with retroperitoneal cystic lesion in the posterior pararenal



**Figure 8:** Female patient with swelling over upper third of right arm (a). X-ray of right shoulder shows soft tissue density lesion in upper 1/3<sup>rd</sup> of right upper limb (b). Ultrasonography shows heterogeneous lesion in subcutaneous plane with multiple rounded anechoic cysts within surrounded by double membrane (c). Magnetic resonance imaging shows mixed signal intensity lesion with multiple intralesional cysts in subcutaneous plane (d - T2W sagittal, e - T1W coronal, f - T2W coronal). Cut section of operative specimen showing hydatid membranes (g)

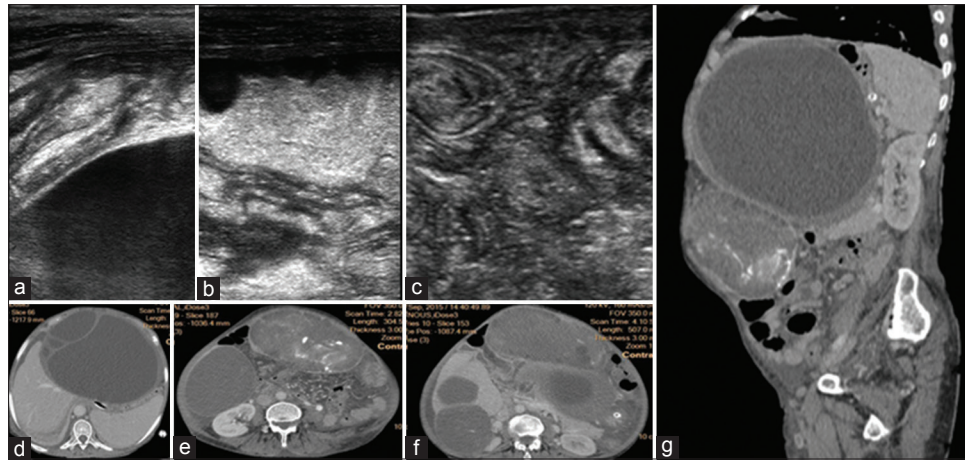


**Figure 9:** Ultrasonography reveals enlarged and multicystic left kidney. Cysts showed double wall with membranous structures within (a). Computed tomography shows large cystic lesion with multiple daughter cysts and peripheral wall calcifications and enhancement (b and c). Magnetic resonance imaging abdomen confirmed hydatid cysts (HCs) (d and e). Post-operative specimens showing multiple HCs (f and g)

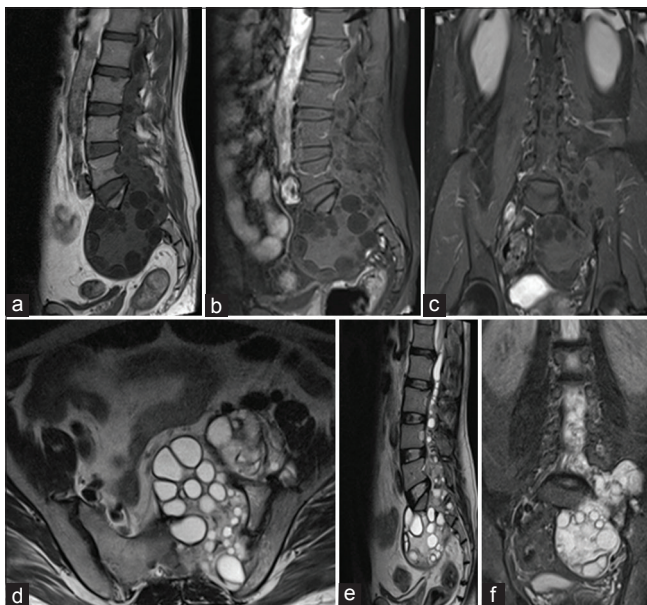
space with splenomegaly. CT scan was done for further characterization of the lesion and showed a large cystic mass lesion with multiple septations posterior to the left kidney.<sup>14</sup>

Primary muscle involvement located in the skeletal muscle is very rare.<sup>15</sup> Sipahioglu *et al.* reported a case with primary HC located in the medial thigh. A multilocular cystic mass was detected in the MRI.<sup>15</sup>





**Figure 10: Ultrasonography shows multiple large well defined intraperitoneal anechoic cystic lesions with crumpled membranes and small daughter cysts within walls of lesions (a-c). Contrast enhanced computed tomography shows multiple large ill-defined cystic lesions involving the peritoneal cavity and right lobe of liver with peripherally arranged daughter cysts and calcifications in few lesions (d-g)**



**Figure 11: T1W plain and post contrast images show evidence of well-defined multiloculated hypointense lesion seen involving left hemipelvis with extension in to the spinal canal and compressing the cauda equina. The lesion shows minimal peripheral enhancement on post contrast images (a-c). T2W sagittal, axial, and coronal images show evidence of well-defined multiloculated hyperintense cystic lesions involving the left hemipelvis in presacral region. The lesion is seen extending in to spinal canal and compressing the cauda equine (d-f)**

HD of the breast is extremely rare even in endemic areas, its only accounts for 0.27% of all cases.<sup>16</sup> Recently, Kumar *et al.* reported a case of isolated HC of the breast with USG study of the breasts revealed a thick walled cystic lesion with floating membranes and internal echoes in the subareolar region of the breast.<sup>17</sup>

HD affects the central nervous system in <2% of cases.<sup>18</sup> Although in other organs they are multiple, they are usually

solitary in brain.<sup>19</sup> Although HD may be located anywhere in the brain, it is most frequently located in the middle cerebral artery territory.<sup>20</sup> MRI shows a well-defined oval or cystic mass with signal intensities similar to cerebrospinal fluid (CSF), sometimes with a low-intensity rim. MRI may also show pericyst as a halo of high signal intensity on T2-weighted images, and in some cases, perifocal edema may be detected.<sup>20</sup>

Cardiac echinococcosis is scarcely encountered with a frequency of 0.01-2%.<sup>21</sup> The most commonly affected cardiac chambers are the left ventricle (50-60% cases).<sup>22</sup> Cardiac HCs have low signal intensity on T1-weighted MRI and high signal intensity on T2-weighted images.<sup>9</sup>

Primary HD of the soft tissue is extremely rare, even in endemic areas, and accounts for 0.5-5.4% of all HD cases, with very little data on the incidence of subcutaneous echinococcosis.<sup>23</sup> Vecchio *et al.* reported a case with growing mass in the deltoid region with USG and MRI strongly suggested HC.<sup>24</sup>

Renal HC involvement is rare and constitutes only 2-3% of all patients.<sup>25</sup> Kidney involvement is usually single and located in cortex. USG shows multicystic mass and CT shows uni or multilocular cyst with well-defined walls.<sup>26</sup>

Primary peritoneal hydatidosis accounts for <2% of intra-abdominal hydatidosis.<sup>27</sup> A case of peritoneal hydatidosis was reported by Hegde and Hiremath and on the USG of the abdomen and pelvis, there was evidence of a large multicystic space-occupying lesion in the left hypochondrium and the left lumbar region. The cyst showed a central echogenic area and CECT showed a large lobulated cystic lesion in the left hypochondrium.<sup>27</sup>

Skeletal involvement with the primary HC is found in 0.5-4%. The vertebra, long bone epiphyses, ileum, skull, and ribs are affected in descending order.<sup>28</sup> HC usually begins in the vertebral body. Extension into the spinal canal results in spinal cord compression. The imaging appearance of the HC usually comprises a single spherical lesion with | clearly defined borders containing fluid with the intensity similar to that of CSF on both CT and MRI.<sup>29</sup>

## CONCLUSION

These 11 numbers of cases of HCs in unusual sites within a span of 1 year, automatically raises a finger that this North-East state is not lagging behind than other states of India in occurrence of HD even in rare sites. Moreover, radiologists should keep HCs in their mind as differential diagnosis while dealing patients with cystic lesions of this part of the country.

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# Knowledge of Asthma in Mothers of Children Suffering from Wheezing Disorder

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## Abstract

**Background:** Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation

**Materials and Methods:** This double-blind, randomized, prospective study was performed in the mothers, 300 in number, having children aged 6 months to 18 years were enrolled as sample.

**Results:** Maximum number of mothers (79.3%) reported change in weather as the most important precipitating factor for their child's illness. Dust (47.3%), food/drinks (42.7%), and cold air (37.3%) were other commonly reported precipitating factors. Mothers had poor knowledge about home management of an acute attack of asthma. Only 34% of mothers give aerosol therapy during an acute attack. Although the majority of mothers knew about aerosol therapy, they were not using it because of various false beliefs like addictive nature of therapy, fear of social stigma associated with its use and its side effects.

**Conclusion:** In conclusion, information about asthma is inadequate among parents of asthmatic children in our setting. Misconceptions about the disease and paucity of information about current trends about management among parents are a significant finding.

**Key words:** Addictive, Aerosol, Asthma, Paucity

## INTRODUCTION

Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness, and cough that vary over time and in intensity, together with variable expiratory airflow limitation. The GINA Science Committee crafted this definition to portray the characteristics that are typical of asthma and highlight the features that distinguish it from other lung diseases.<sup>1</sup>

The definition means that asthma is:

Characterized by recurrent respiratory symptoms - especially wheezing, shortness of breath, chest tightness, and coughing.

- Heterogeneous - its symptoms and their intensity are different from person to person. Most people with asthma have signs of inflammation in the airways of their lungs.
- Variable - the symptoms wax and wane over time for each individual with asthma. Measurements of lung function also vary over time.

Asthma is a chronic inflammatory disorder of the airways. Chronically inflamed airways are hyper-responsive; they become obstructed and airflow is limited (by bronchoconstriction, mucus plugs, and increased inflammation) when airways are exposed to various risk factors. Asthma affects an estimated 300 million individuals worldwide. The prevalence of asthma is increasing, especially in children. Annually, the World Health Organization has estimated that 15 million disability-adjusted life years are lost and 250,000 asthma deaths are reported worldwide. The clinician should establish whether the patient has any of the following symptoms such as, wheezing, cough, cough at night or with exercise, shortness of breath, chest tightness, and sputum production.

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The clinician should determine the pattern of symptoms as perennial, seasonal or both, continuous or intermittent, daytime or nighttime, onset and duration. The clinician should ask whether any of the following precipitate and/or aggravate symptoms such as viral infections, environmental allergens, irritants (e.g., smoke exposure, chemicals, vapors, and dust), exercise, emotions, home environment (e.g., carpets, pets, and mold), stress, drugs (e.g., aspirin and beta blockers), foods, changes in weather.

## MATERIALS AND METHODS

This is a prospective study. Mothers total 300 in number, having children aged 6 months to 18 years were enrolled as sample. The sampling for the study was done randomly among the mothers of children visiting the outdoor department and indoor department. The following inclusion and exclusion criteria were adopted for the purpose to study.

### Inclusion Criteria

- Mothers accompanied by children aged 6 months to 18 years, having not <2 episodes of wheezing in the preceding 6 months.
- Mothers of children diagnosed as asthma.

### Exclusion Criteria

- Mothers of children aged <6 months.
- Mothers of children having congenital abnormalities.
- Mothers who were not willing to give consent voluntarily.
- Mothers who could not converse in Punjabi or Hindi.
- Mothers with adopted child/children.
- Mothers belonging to medical or paramedical profession.

The method adopted for the collection for the data was of structured interview questionnaire type, after obtaining a prior written informed consent from the participating mothers. The questions translated in vernacular language from the questionnaire were asked in a face to face interaction session, and the responses were recorded in the proforma attached to the plan. Mothers were asked about their qualification. Those who could not read and write were labeled illiterate. Those who had studied up to 10<sup>th</sup> standard were labeled less than high school, and those who had studied more than 10<sup>th</sup> standard were labeled more than high school. Questions were asked regarding the type of household. To label a house overcrowded following criteria of persons per room was used:

- 1 room: 2 persons
- 2 rooms: 3 persons
- 3 rooms: 5 persons

4 rooms: 7 persons

5 or more rooms: 10 persons (additional 2 for each further room).

A baby under 12 months is not counted and children 1-10 years were counted as half a unit. Socioeconomic status was assessed by modified Kuppuswamy scale. The estimated time taken to fill one questionnaire was 20-25 min. The data collected in the study was statistically analyzed using SPSS software to reach conclusions.

## RESULTS

As per the inclusion criteria mentioned in the plan to the thesis, a sample size of 300 mothers was selected for the study. They were asked questions pertaining to the study in a structured questionnaire having both open- and closed-ended responses.

Out of total number of 300 mothers, who participated in the study 54% ( $n = 162$ ) had children within age group of 6 months - 3 years, 25% ( $n = 75$ ) in 3-6 years, 13% ( $n = 39$ ) in 6-10 years and 8% ( $n = 24$ ) above 10 years (Tables 1 and 2).

Table 3 shows that of the total 300 participant mothers 81% ( $n = 243$ ) were residing in adequately ventilated houses and rest of them, i.e., 19% ( $n = 57$ ) were residing in inadequately ventilated houses.

Table 4 shows that of the total 300 participant mothers 46% ( $n = 138$ ) were having smoker(s) in the house and rest

**Table 1: Age group**

Age	Count <i>n</i> (%)
6 months - 3 years	162 (54)
3-6 years	75 (25)
6-10 years	39 (13)
10-18 years	24 (8)
Total	300 (100)

**Table 2: Sex distribution**

Sex	Count <i>n</i> (%)
Male	183 (61)
Female	117 (39)
Total	300 (100)

**Table 3: Ventilation**

Ventilation	Count <i>n</i> (%)
Adequate	243 (81)
Not adequate	57 (19)
Total	300 (100)



of them, i.e., 54% ( $n = 162$ ) were not having any smoker in the house.

Table 5 shows that of the total 300 participant mothers maximum, i.e., 27.7% ( $n = 83$ ) belonged to lower middle socioeconomic status while minimum, i.e., 10.3% ( $n = 31$ ) belonged to lower socioeconomic status.

Table 6 shows that of the total 300 children, maximum, i.e., 61% ( $n = 183$ ) had age of onset of wheeze between 6 months and 3 years followed by 31.3% ( $n = 94$ ) between 3 and 6 years while minimum, i.e., 1% ( $n = 3$ ) had onset between 10 and 18 years.

Table 7 shows that of the total 300 participant mothers, 53% ( $n = 159$ ) gave history of asthma or similar illness in family members while 47% ( $n = 141$ ) had no such family history.

Table 8 shows that of the total 300 participant mothers 32.3% ( $n = 97$ ) knew that their child had asthma while 67.7% ( $n = 203$ ) denied that their child had asthma.

Table 9 shows that of the total 97 participant mothers who knew that their child has asthma, maximum, i.e., 84.5% ( $n = 82$ ) had come to know this from medical staff.

Table 10 shows that of the total 300 participant mothers only 12.7% ( $n = 38$ ) considered their child's illness a Hereditary disease.

**Table 4: Any smoker in the house**

Any smoker in the house	Count $n$ (%)
Yes	138 (46)
No	162 (54)
Total	300 (100)

**Table 5: Socioeconomic status (By Kuppaswamy scale)**

Socioeconomic status	Count $n$ (%)
Upper	38 (12.7)
Upper middle	73 (24.3)
Lower middle	83 (27.7)
Upper lower	75 (25.0)
Lower	31 (10.3)
Total	300 (100)

**Table 6: Age of onset of wheeze**

Age	$n$ (%)
<6 months	12 (4)
6 months - 3 years	183 (61)
3-6 years	94 (31.3)
6-10 years	8 (2.7)
10-18 years	3 (1.0)
Total	300 (100)

Table 11 shows that of the total 300 participant mothers only 29.3% ( $n = 88$ ) considered their child's illness a Contagious disease.

Table 12 shows that of the total 300 participant mothers, maximum, i.e., 70.3% ( $n = 211$ ) were getting their child from medical practitioner while only 2% ( $n = 6$ ) were getting treatment for their child from quacks.

Table 13 shows that maximum number of mothers, i.e., 79.3% ( $n = 238$ ) reported change in weather as a precipitating factor for their child illness. Dust (47.3%), food/drinks (42.7%) and cold air (37.3%) were other common precipitating factors.

Table 14 shows that out of 300 participating mothers, maximum number of mothers, i.e., 68.3% ( $n = 205$ ) preferred to give oral medications in case of an acute attack at home. Only 34.9% ( $n = 104$ ) were in favor of giving aerosol therapy.

Table 15 shows that out of 300 participating mothers, maximum number of mothers, i.e., 63% ( $n = 189$ ) were

**Table 7: Family history of asthma or similar illness**

Family history	Count $n$ (%)
Siblings	49 (16.3)
Parents	56 (18.7)
Grandparents	35 (11.7)
Others	19 (6.3)
No history	141 (47.0)
Total	300 (100)

**Table 8: Does your child has asthma?**

Does your child has asthma?	Count $n$ (%)
Yes	97 (32.3)
No	203 (67.7)
Total	300 (100)

**Table 9: If yes, how did you come to know that your child has asthma?**

How did you come to know?	Count $n$ (%)
Medical staff	82 (84.5)
Paramedical staff	8 (8.2)
Quacks	5 (5.1)
Relatives/friends	2 (2)
Total	97 (100)

**Table 10: Is asthma/your child's illness a hereditary disease?**

Is asthma/your child's illness a hereditary disease?	Count $n$ (%)
Yes	38 (12.7)
No	262 (87.3)
Total	300 (100)

having anti-Histamines at home for this illness. Only 38% ( $n = 114$ ) had beta agonists at their home for use in their child's illness.

Table 16 shows that of the total 300 participant mothers 93.3% ( $n = 280$ ) knew about aerosol therapy.

Table 17 shows that of the total 300 participant mothers, only 26% ( $n = 78$ ) were regularly using aerosol therapy.

**Table 11: Is asthma/your child's illness a contagious disease?**

Is asthma/your child's illness a contagious disease?	Count $n$ (%)
Yes	88 (29.3)
No	212 (70.7)
Total	300 (100)

**Table 12: Who is regularly treating your child for asthma/your child's illness?**

Mother's answer	Count $n$ (%)
Medical practitioner (s)	211 (70.3)
Paramedical	50 (16.7)
Homeopathic/ayurvedic	15 (5.0)
Quacks	6 (2.0)
No treatment	18 (6.0)
Total	300 (100)

**Table 13: Which of these factors precipitate asthma/your child's illness?**

Factors	Number of mothers (%)
Change in weather	238 (79.3)
Tobacco smoke	31 (10.3)
Dust	142 (47.3)
Animal dander	0 (0)
Cockroach	0 (0)
Strong odor/other smells	22 (7.3)
Exercise/sports	25 (8.3)
Cold air	112 (37.3)
Medicines	10 (3.3)
Swimming	6 (2)
Food/drinks	128 (42.7)
Indoor mould	0 (0)

**Table 14: What will you do if your child develops acute wheezing/breathlessness/cough at home?**

Mothers answer	$n$ (%)
Give oral medications	205 (68.3)
Steam inhalation	51 (17)
Aerosol therapy	104 (34.9)
Immediately take child to doctor without doing anything at home	30 (10)
Others	6 (2)

Table 18 shows that of the 78 participant mothers, who were regularly using aerosol therapy for their child majority 61.5% ( $n = 48$ ) were using metered dose inhaler with spacer and only 7.6% ( $n = 6$ ) were using Rota halers.

Table 19 shows that of the 78 participant mothers, who were using aerosol therapy for their child, maximum, i.e., 57.6% ( $n = 45$ ) were using both beta agonists and steroids as aerosol therapy for their child. 14.1% ( $n = 11$ ) were not aware of the nature of the drug being given to their children.

Table 20 shows that of the total 300 participant mothers, only 12.7% ( $n = 38$ ) were giving regular oral medication to their child.

Table 21 shows that of the 38 participant mothers, who were giving regular oral medication to their children, maximum, i.e., 31.6% ( $n = 12$ ) were using anti-Histamines.

**Table 15: What medicines do you have at home for this illness?**

Nature of medication (oral)	Count $n$ (%)
Beta agonists	114 (38)
Steroids	19 (6.3)
Antihistaminics	189 (63)
Leukotriene modifiers	30 (10)
Desi medication	21 (7)
Homeopathic	16 (5.3)
Nature not known	32 (10.7)

**Table 16: Do you know about aerosol therapy?**

Do you know about aerosol therapy?	Count $n$ (%)
Yes	280 (93.3)
No	20 (6.7)
Total	300 (100)

**Table 17: Do you regularly use aerosol therapy for your child?**

Do you regularly use aerosol therapy for your child?	Count $n$ (%)
Yes	78 (26)
No	222 (74)
Total	300 (100)

**Table 18: If yes, which one do you preferably use?**

Mother's answer	Count $n$ (%)
Nebulizer	14 (17.9)
MDI with spacer	48 (61.5)
MDI without spacer	10 (12.8)
Rotahalers	6 (7.6)
Total	78 (100)

MDI: Metered dose inhaler

**Table 19: What aerosol drug is your child being given?**

Nature of drug	Count n (%)
Beta agonist	12 (15.3)
Steroids	10 (12.8)
Both	45 (57.6)
Don't know	11 (14.1)
Total	78 (100)

**Table 20: Is your child receiving any regular oral medication?**

Mother's answer	Count n (%)
Yes	38 (12.7)
No	262 (87.3)
Total	300 (100)

**Table 21: If yes, what medication?**

Nature of medication	Count n (%)
Beta agonist	6 (15.8)
Steroids	5 (13.2)
Antihistaminics	12 (31.6)
Leukotriene modifiers	7 (18.4)
Desi medication	3 (7.9)
Homeopathic	3 (7.9)
Nature not known	2 (5.3)
Total	38 (100)

## DISCUSSION

Out of the total 300 mothers, 54% had children in the age group 6 months - 3 years, 25% in 3-6 years, 13% in 6-10 years and 8% had children above 10 years. 61% were having male and 39% were having female wards. Of the mothers who participated in the study, only 15% were illiterate, 53.3% had studied less than high school and 31.7% more than high school.<sup>2-4</sup>

About 59% of them belonged to rural areas whereas 41% were residing in urban areas. Only 13% of them were living in kutcha houses, and 87% were residing in pucca houses. Overcrowding was present in 62.3% of houses. 67% of mothers were using liquid petroleum gas as fuel in their houses while rest was using other fuels such as firewood, cow dung, and kerosene. 39% were having pet(s) in their houses. 46% mothers reported to have smoker(s) in their houses.<sup>5-7</sup>

Out of the 300 mothers, 12.7% belonged to upper class, 24.3% to upper middle class, 27.7% to lower middle class, 25% to upper lower and minimum, i.e., 10.3% to lower socioeconomic class as assessed by modified Kuppaswamy scale.

Mahdi *et al.* in their study on asthmatic patients have shown that family history of asthma was present in 44.5% cases of

asthma.<sup>8</sup> Zhao *et al.* in their study on parents of asthmatic children in 29 cities of China had reported family history of asthma in 29.7% cases. In our study, family history of asthma is given by 53% participating mothers.<sup>7</sup>

Asthma is a global problem due to ignorance or distorted information/knowledge of patients about their disease.<sup>9</sup> Ignorance about the disease is not only a problem in rural areas and it is equally affecting asthma management in urban areas. Lai *et al.* in their study had found that 48.2% parents of asthmatic children hesitated in referring to their child's illness as asthma.<sup>2</sup> Shivbalan *et al.*, in their study, had shown that only 39% parents of asthmatic children accepted their child's illness as asthma. The physician was the only source of information regarding the diagnosis and disease related scientific knowledge to these parents. Out of rest of the parents 46% attributed their child's illness as wheeze, 8% as recurrent respiratory infections, 3% as eosinophilia, 2% as primary complex, 1% as allergy, and 1% as respiratory distress.<sup>6</sup> In this study, 32.3% mothers accepted their child's illness as asthma. Of the mothers who accepted their child as suffering from asthma, 84.5% had come to know this from their physician. Out of 110 parents who refused their child's disease as Asthma, 43% attributed it to allergies, 17.3% to recurrent respiratory tract infections and 0.006% to pulmonary tuberculosis. There were 0.06% mothers who had no opinion about their child's illness.

Lai *et al.* in their study showed that 34.1% of parents had believed asthma to be contagious.<sup>2</sup> Rodríguez *et al.* in their study have shown that 53.1% of parents considered asthma an emotional illness and 52.5% believed that the way that parents raised their children caused asthma.<sup>3</sup> Mavale-Manuel *et al.* in their study had found that 11% of parents considered asthma to be contagious.<sup>5</sup> Prasad *et al.* in their study had found that 11.1% ascribed heredity as the underlying cause of asthma. About 50% patients believed this disease to be infectious, 12.6% due to curse of god and 5.2% to be associated with TB.<sup>4</sup> Shivbalan *et al.* in their study found that 35% of parents believed asthma as hereditary and 26% as contagious.<sup>6</sup> In our study, 12.7% mothers believed it to be hereditary and 29.3% as contagious.

Our study found that the majority of participating mothers (70.3%) were getting their child treated from a Registered Medical Practitioner.

As found in other chronic ailments, parents of asthmatic children also have a tendency to seek alternative systems of medicine for treatment of their child's illness. Lai *et al.* found that 65% parents in their study had attempted other systems of medicine. Homeopathy was the most common alternative.<sup>2</sup> Prasad in their study concluded that alternative

modes of treatment were sought by 46.7% participating patients.<sup>4</sup> In this study, 18% mothers had sought alternative modes of treatment. Desi medication was the most common alternative attempted.

Parents have diverse views regarding the prognosis and treatment of asthma. Lai *et al.* in their study found that only 30.6% parents believed that treatment from the hospital would cure their child.<sup>2</sup> In the study by Shivbalan *et al.*, 34% parents thought that disease would wane off with increasing age. 19% of them were not aware of the prognosis.<sup>9</sup> In a study by Mavel-Manuel *et al.*, 50% parents answered that asthma is curable.<sup>5</sup> In this study, 26% mothers thought it to be curable and a large number (54%) was unaware about the prognosis of their child's illness.

## CONCLUSIONS

Asthma management programs are incomplete without good parents' and patients' education program. Such programs would augment awareness, eliminate social stigma and misconceptions in the community regarding asthma. Knowledge about the prevailing perception about asthma

in the community would be the first step in achieving it. This study is a step toward it.

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# Serum Uric Acid Level in Patients with Chronic Kidney Disease: A Prospective Study

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## Abstract

**Background:** Chronic kidney disease (CKD) is a serious condition associated with premature mortality, decreased quality of life, and increased health-care expenditures. Chronic kidney disease occurs when one suffers from gradual and usually permanent loss of kidney function over time.

**Material and Method:** This is a prospective observational study. In this study, one hundred forty six ckd patients were studied with detailed clinical and laboratory examination and divided (and then compared) into two age groups: one group included 56 ckd patients with raised serum uric acid and another group containing 90 ckd patients with normal serum uric acid. Both groups were age matched.

**Results:** In our study, prevalence of raised serum uric acid in ckd patients was found to be 38.4%. It is observed that, CKD patients with raised serum uric acid were predominantly male and presented mainly in later part of life. There is statistically significant ( $p < 0.05$ ) positive correlation is found between serum uric acid and stages and severity of ckd, hypertension, diabetes mellitus, dyslipidemia, smoking, alcoholism, serum BUN, serum creatinine, CRP, N/L Ratio, urine albuminuria, anaemia, cardiovascular disease, mortality and negative correlation with eGFR and creatinine clearance.

**Conclusion:** In ckd patients, higher serum uric acid levels were associated with higher degree of renal dysfunction, hypertension, diabetes, dyslipidemia, smoking, alcoholism, CRP, N/L Ratio, urine albuminuria, anaemia, cardiovascular disease/events and mortality. It is found that most common cause of mortality in ckd patients with raised serum uric acid was cardiovascular disease/events.

**Key words:** Chronic Kidney Disease, Patients, Uric Acid

## INTRODUCTION

Chronic kidney disease (CKD) is a serious condition associated with premature mortality, decreased quality of life, and increased health-care expenditures. Chronic kidney disease occurs when one suffers from gradual and usually permanent loss of kidney function over time. This happens gradually, usually over months to years.<sup>1</sup>

The lineage of kidney disease as a subject of study generally is traced to 1827, when Richard Bright (1789-1858) described his eponymous disease of the kidneys in albuminuric dropsical

patients who died in kidney failure.<sup>2</sup> By middle of 19<sup>th</sup> century, kidney disease was defined, its diagnosis by urinalysis was established, and its structural changes were characterized, but speciality of nephrology went unborn and patients continued to seek urologic care for their hematuria, proteinuria and uremia.<sup>3</sup> It was a return to the roots of nephrology at the turn of the 21<sup>st</sup> century that refocused attention on kidney disease not as a fatal condition requiring replacement therapy, but as a clinical entity that is common, harmful, early to diagnosed and potentially treatable.<sup>4</sup>

It was to meet this need that the initial set of clinical practice guidelines for dialysis care was published in 1997 by the DOQI (Dialysis Outcome Quality Initiative) which was changed to KDOQI (Kidney Disease Outcome Quality Initiative) at the turn of the millennium.<sup>2</sup>

KDOQI (Kidney Disease Outcome Quality Initiative), in 2002, published the Clinical Practice Guidelines for Chronic kidney disease.<sup>5,6</sup>

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Chronic kidney disease (CKD) prevalence is increasing world-wide and the prevalence of end-stage renal disease (ESRD) is expected to rise by 44% from 2000 to 2015.<sup>7</sup>

The pattern of disease morbidity and mortality throughout the world is changing both in the developed and the emerging world. The major cause of end-stage renal failure in most countries worldwide is now diabetes. Countries throughout Asia also have large percentages of their incident end-stage renal failure patients due to diabetes: Pakistan, 42%, Taiwan, 35%, Philippines, 25% and Japan, 37%.<sup>8</sup> India has the largest number of people with diabetes in the world, with the projected figures of 57.2 million cases in 2025. This will make India the reservoir of CKD.<sup>9</sup>

The annual incidence of ESRD differs between developed and developing countries, 34 — 240 per million population (pmp) to 98 — 198 per million populations, respectively.<sup>10</sup>

Agarwal SK, *et al*, (2005), in All India Institute of Medical Sciences New- Delhi, India carried out the first community-based epidemiological study to determine the prevalence of chronic renal failure in India. A total 4,972 subjects were evaluated from whom samples for testing were available in 4,712 cases. CRF was detected in 37 patients (0.785%). CRF prevalence was calculated to be 7,852 per million populations. Hypertension and diabetes were found in 22.8% and 11.1%, respectively. Diabetic nephropathy was possibly the common etiological factor, found in 41% of patients with CRF.<sup>11</sup>

The K/DOQI definition (2002) of CKD was accepted worldwide and given as follows:<sup>5</sup>

#### Criteria for the Definition of Chronic Kidney Disease(CKD)

Kidney damage for ≥ 3 months as defined by structural or functional abnormalities of the kidney, with or without decreased GFR, that can lead to decreased GFR, manifest by either:

- Pathological abnormalities; or
- Markers of kidney damage, including abnormalities in imaging tests
- GFR <60ml/min/1.73m<sup>2</sup> for 3 months, with or without kidney damage

#### Classification of CKD

The K/DOQI guidelines (2002) for classification of ckd by severity are given in the following table.

Classification of ckd<sup>5</sup>

## MATERIALS AND METHODS

The present study is a prospective study carried out on 146 CKD patients in ICU and medicine ward. Ethical

Clearance was obtained from the ethical committee for the study. Patients satisfying the inclusion and exclusion criteria were enrolled into the study. Detailed clinical, biochemical, haematological examinations were conducted to establish the diagnosis and stage of CKD.

The present study was carried out on 146 adult patient of CKD (Chronic Kidney Disease). Out of which 56 ckd patients with raised serum uric acid were placed in study group and also 90 CKD patients with normal serum uric acid with age matched were placed in comparison group.

#### Inclusion Criteria

- 1) All the patients of both the sexes >18 years of age
- 2) All the diagnosed cases of chronic kidney disease.

#### Exclusion Criteria

- 1) All the patients <18 years of age.
- 2) All HIV positive individuals.
- 3) All the patients having history of gout and/or Hyperuricemia.
- 4) Patients who are taking anti tubercular drugs and thiazide diuretics.

#### Diagnostic Criteria

All the patients were evaluated for chronic kidney disease (ckd) as per the K/DOQI criteria (2002) by National Kidney Foundation for diagnosis of ckd.<sup>5</sup>

After confirmation of diagnosis from the above parameters, blood samples are drawn from these patients for the estimation of serum uric acid by Trivedi and Kabasakalian with a modified Trinder peroxidase method using TBHB(2,4,6-Tribromo-3- hydroxybenzoic acid).

The study was designed to include the Demographic, clinical data, biochemical and haematological changes observed in CKD patients. The data was entered into a structured proforma separately. Management was done as per standard guidelines. Patients were discharged after significant improvement in clinical as well as haematological and biochemical parameters.

Detailed clinical examination was done in all CKD patients. All these CKD patients were evaluated clinically for history of fever, easy fatigability, facial puffiness, swelling over extremities, nausea and vomiting, generalized bodyache, breathlessness, altered sensorium, convulsions, decreased urine output, haematuria, haematemesis/melaena, pallor, pedal oedema, blood pressure and other vitals.

The laboratory investigations done in all CKD patients included a complete haemogram, neutrophil-lymphocytic ratio (N/L Ratio), fasting and postprandial blood sugar level, serum BUN, creatinine, eGFR, creatinine

clearance, serum electrolytes (sodium, potassium, calcium, phosphorus), serum uric acid, liver function test, lipid profile (Total cholesterol, HDL, LDL, Triglycerides), C- reactive proteins(CRP), 24hrs urine albuminuria, HIV, Hepatitis B and C.

Detailed ultrasonography of abdomen and pelvis was done to check the size, shape and echo texture of the kidney. Formal approval of hospital ethical committee and written consent of the CKD patients were obtained for this study.

### Statistical Analysis

Data was analyzed by statistical Product for social service sciences Version-16 (SPSS 16) statistical software. Data was presented in frequency and percent distribution form. Association in between the parameters was tested using Pearson's chi square test or Fishers exact test. Mean values of parameters were compared between normal and raised uric acid levels in ckd patients using unpaired t-test. Mean comparisons of values of parameters in between patients with 5 stages of ckd were done by using ANOVA (Analysis Of Variance Test). The significance level was set at  $p < 0.05$ . P less than 0.05 was considered as significant

## RESULTS

146 patients of documented CKD were taken and divided into 2 groups of which study group included 56 ckd patients with raised serum uric acid levels and comparison group included 90 ckd patients with normal serum uric acid levels. Statistical analysis showing study's result is given as follow:

### Sex

Of 90 CKD patients with normal uric acid level, 58.9% were male and 41.1% were female. Of Raised uric acid CKD patients, 78.6% were males and 23.2% were females. There was statistically significant ( $p < 0.05$ ) difference of male predominance over female in CKD patients with raised uric acid level.

### 3) Prevalence of serum uric acid in CKD

Serum uric acid was raised in 38.4% CKD patients and CRP was raised in 51.4% patients out of 146 having CKD.

### 4) Stages of CKD

In those with raised uric acid level, Maximum i.e. 53.6% CKD patients had stage 5 CKD, 30.4% had Stage 4 and 8.9% had Stage 3 CKD, 5.4% had Stage 2 and 1.8% has Stage 1 CKD. Of Normal uric acid level patients 26.7% were in stage 5, 25.6% were in stage 4 and 16.7% in Stage 3 while 15.6% in Stage 2 and Stage 1. There was

statistically highly significant ( $p < 0.01$ ) difference with higher proportion of patients in higher Stage of CKD in raised uric acid group compared to normal uric acid group.

### 5) Complications of CKD (Anaemia and Cardiovascular Disease)

61.1% raised uric acid CKD patients had cardiovascular disease compared to 38.9% normal uric acid patients. All 56 i.e. 100% patients with raised uric acid level had anemia compared to 76.7% of normal uric acid. There was statistically very highly significant ( $p < 0.001$ ) difference with higher percentage of patient in raised uric acid having cardiovascular disease and anemia in CKD patients.

### 7) Relation With Severity Of CKD:

There was statistically significant ( $p < 0.01$ ) difference with increasing stages severity of duration of illness, BUN, Serum Creatinine, uric acid concentration, potassium, phosphorus, estimated GFR, creatinine clearance and CRP.

### 8) Mortality:

10) Relation of serum uric acid with different biochemical parameters (Tables 1-8).

## DISCUSSION

Previous studies have shown that serum uric acid is having independent role in progression of ckd and is also cause and predictor of associated morbidities in ckd.

Blood samples for measurement of serum uric acid level and other biochemical assessments were obtained immediately after admission. Uric acid concentration expressed in milligrams per deciliters (mg/dl). Male patients with uric acid concentration  $> 7$  mg/dl and female patients with  $> 6$  mg/dl were considered as having raised serum Uric acid. Furthermore for studying correlations of serum Uric acid with other clinical and investigational findings, all ckd patients were divided into two groups out of which one group included all ckd patients with raised uric acid and other group included all ckd patients with normal uric acid. Both groups were age matched.

There were 90 ckd patients studied in ckd with normal UA group and 56 patients were studied in ckd with raised UA group.

Serum UA level of ckd patients done on day of admission in both age matched groups were compared by t-test where its value  $p < 0.05$  is considered as statistically significant. Thus patients who were having raised serum UA level was because

**Table 1: Classification on severity of CKD**

Stage	Description	GFR ml/min/1.73m <sup>2</sup>	Related items	Classification by treatment
1	Kidney damage with normal or i GFR	90	Albuminuria, proteinuria, hematuria	T if kidney Transplant Recipient
2	Kidney damage with mild 1, GFR	60-89	Albuminuria, proteinuria, hematuria	
3	Moderate 1 GFR	30-59	Chronic renal insufficiency or early renal insufficiency	
4	Severe GFR	15-29	Chronic renal insufficiency or late renal insufficiency or pre ESRD	D if dialysis (hemodialysis or peritoneal dialysis)
5	Kidney failure	<15 or dialysis	Renal failure, uremia, ESRD	

of ckd and in both ckd groups derangement of other clinical and biochemical profiles were due to raised serum UA.

The findings which we got in our study are discussed as follows:

### Age

In our study, we found that out of 146 ckd patients maximum that is 53.4% were within age group of 51-70 yrs. and 39.7% ckd patients were in age group of 31-50 yrs. This finding is consistent with findings of the study by Punamyadav *et al*, (2014), Madero *et al*, (2009) and George S. *et al*, (2013). It is observed that incidence of ckd reaches its maximum strength in later part of life.<sup>12-14</sup>

### Sex

In our study, (from Table 2), it is found that 78.6% males and 21.2% females were in ckd with raised UA group which shows statistically significant ( $P < 0.027$ ) difference of male predominance over females in ckd patients with raised UA level. This finding in our study is consistent with findings in the studies by Nacak *et al*, (2014) & Madero *et al*, (2009)

## SERUM URIC ACID LEVELS IN RELATION WITH SEVERITY OF CKD

In our study, (from Table 4, 6 & 9), it is found that, there was statistically significant ( $p < 0.01$ ) correlation of raised serum uric acid with increasing stages of ckd, and it's severity. Serum uric acid was statistically significantly ( $p < 0.001$ ) positively correlated with serum BUN, serum creatinine, and negatively correlated with eGFR, and creatinine clearance. In our study, ANOVA study also showed the statistically significant positive correlation between raised serum uric acid and progressively declining renal functions and severity of ckd. This finding in our study is consistent with the findings of studies by Chen *et al*, (2014), Mostafa Kamel *et al*, (2013)<sup>16</sup>, Nermina Babic *et al*, (2014), J. T. Park *et al*, (2009), where it is found that, there was statistically highly significant positive correlation of serum uric acid with stages and severity of ckd, duration of illness and markers

**Table 2: Sex distribution according to Serum uric acid status of patients with chronic kidney disease**

Sex	Serum uric acid		Total
	Normal	Raised	
Female	37 41.1%	13 23.2%	51 34.2%
Male	53 58.9%	43 78.6%	95 65.8%
Total	90 100.0%	56 100.0%	146 100.0%

Chi-Square tests	Value	Df	P value
Pearson Chi-Square	4.910	1	0.027

**Table 3: Serum uric acid and CRP level of patients with chronic kidney disease**

Parameters	Frequency	Percent (%)
Serum uric acid		
Normal	90	61.6
Raised	56	38.4
CRP		
Normal	71	48.6
Raised	75	51.4
Total	146	100.0

**Table 4: Stage of CKD according to Serum uric acid status of patients**

Stage of CKD	Serum uric acid		Total
	Normal	Raised	
1	14 15.6%	1 1.8%	15 10.3%
2	14 15.6%	3 5.4%	17 11.6%
3	15 16.7%	5 8.9%	20 13.7%
4	23 25.6%	17 30.4%	40 27.4%
5	24 26.7%	30 53.6%	54 37%
Total	90 100.0%	56 100.0%	146 100.0%

Chi-Square tests	Value	Df	P value
Pearson Chi-Square	18.01	4	0.001



of reduced renal functions like serum BUN and serum creatinine and negatively correlate with eGFR.

## HYPERTENSION

In our study, (from Table 10), it is found that, significant proportion of hypertensive patients had come in ckd with raised UA group i.e., 85.7%, and showing

statistically significant positive correlation ( $p=0.031$ ) of UA with hypertension, this finding is consistently matched with the findings of studies by J. T. Park *et al*, (2009), Paul *et al*, (2012) and Liu WC *et al*, (2012). It is found that, there is statistically significant higher systolic BP ( $P<0.001$ ) and diastolic BP ( $P<0.001$ ), in raised UA ckd patients than normal UA ckd patients. This findings are consistently matched with findings of studies by B. Satirapoj *et al*, (2010) and Mostafa Kamel *et al*, (2013).

**Table 5: Associated disorders according to Serum uric acid status of patients with chronic kidney disease**

Parameters	Serum uric acid		Total	X2	P value
	Normal	Raised			
CKD with cardiovascular diseases					
No	69 75%	23 25%	92 100%	18.767	<0.001
Yes	21 38.9%	33 61.1%	54 100%		
CKD with anemia					
No	21 23.3%		21 14.4%	15.262	<0.001
Yes	69 76.7%	56 100.0%	125 85.6%		

## Diabetes Mellitus

In our study, (from Table 10), it is found that, there was statistically significant positive difference of diabetes ( $p=0.011$ ) in ckd patients with raised uric acid level (44.6%) than normal uric acid level (24.4%) in CKD patients. Also, serum uric acid has statistically significant positive correlation ( $p<0.001$ ) with both fasting and post prandial blood sugar level. This finding in our study is consistently matched with the findings of studies by J. T. Park *et al*, (2009), Adel Gouri *et al*, (2013) and Liu WC *et al*, (2012).<sup>15-30</sup>

## CONCLUSION

In ckd patients, higher serum uric acid levels were associated with higher degree of renal dysfunction, hypertension,

**Table 6: Comparison of mean findings according to severity of CKD. ANOVA**

Parameters	CKD					F	P value
	Stage 1 (n=15)	Stage 2 (n=17)	Stage 3 (n=20)	Stage 4 (n=40)	Stage 5 (n=54)		
Age (yrs)	51.6	51.53	53.0	55.85	57.15	1.279	0.281
Duration of illness	7.00	8.00	7.95	11.18	12.69	11.432	<0.001
BMI (kg/m2)	22.20	22.79	22.07	22.01	21.23	1.895	0.115
Sr.BUN (mg/dl)	43.67	47.65	48.68	57.87	60.78	4.149	0.003
Sr. Creatinine (mg/dl)	0.90	1.141	1.975	3.845	5.543	220.14	<0.001
Sr. uric acid (mg/dl)	4.46	4.81	5.35	7.29	7.68	35.545	<0.001
SR.SODIUM (mEq/1)	145.8	145.0	145.15	144.59	143.16	1.180	0.322
SR.POTASSIUM (mEq/1)	4.83	4.39	5.03	4.75	5.27	3.568	0.008
Sr. Calcium (mg/dl)	8.27	8.39	7.29	7.28	7.16	1.826	0.127
Sr. phosphorus (mg/dl)	5.16	5.08	5.50	5.79	6.37	4.395	0.002
eGFR (ml/min/1.73m2)	94.95	72.61	40.79	17.68	11.86	813.95	<0.001
Creatinine clearance (ml/min)	74.73	59.06	35.61	16.62	11.37	375.13	<0.001
CRP (mg/l)	4.79	4.88	5.22	6.75	7.33	17.634	<0.001

**Table 7: Outcome according to Serum uric acid status of patients with chronic kidney disease**

Outcome	Serum uric acid		Total
	Normal	Raised	
Alive	90 65.2%	48 34.8%	138 100%
Dead		8 100%	8 100%
Total	90 61.6%	56 38.4%	146 100.0%
<b>Chi-Square tests</b>			
	Value	Df	P value
Pearson Chi-Square	13.602	1	<0.001

**Table 8: Comparison of different parameters in ckd patients with raised and normal serum uric acid**

Parameter	Uric acid		Total	P value
	Normal	Raised		
Age (yrs)	52.97	54.07	55.0	0.604
Sex(% Male)	58.9%	78.6%	65.8%	0.027
SBP on admission (mmHg)	141.76	162.14	149.58	<0.001
DBP on admission (mmHg)	87.8	95.7	90.84	<0.001
HT	70%	85.7%	76%	0.031
Fasting BSL (mg/dl)	102.4	131.46	113.55	<0.001
Postprandial BSL (mg/dl)	170.52	202.9	182.96	<0.001
HbA1C	5.47	7.25	6.15	<0.001
DM	24.4%	44.6%	32.2%	0.011
Smoking	10%	60.7%	29.5%	<0.001
Dyslipidemia	51.1%	69.6%	58.2%	0.027
Urine albuminuria (mg/d)	389.94	1112.32	667.02	<0.001
CRP (mg/l)	5.92	6.98	6.33	<0.001
N/L ratio	2.26	2.81	2.47	<0.001
S BUN (mg/dl)	44.42	72.11	55.04	<0.001
Creatinine (mg/dl)	2.774	4.93	3.59	<0.001
eGFR (ml/min/1.73m2)	44.16	15.15	33.03	<0.001
Anemia risk	76.7%	100%	85.6%	<0.001
Cardiovascular risk	23.3%	58.9%	37%	<0.001
Death	0	14.3%	5.5%	<0.001

diabetes, dyslipidemia, smoking, alcoholism, CRP, N/L Ratio, urine albuminuria, anaemia, cardiovascular disease/events and mortality. It is found that most common cause of mortality in ckd patients with raised serum uric acid was cardiovascular disease/events.

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# Tuberculosis Airway Disease and Bronchiectasis- A Prospective Study

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## Abstract

**Background:** Tuberculosis is very rampant in India accounting for 20% of the global burden. Patient of Pulmonary Tuberculosis inspite having completed the complete course of anti tuberculosis therapy many a time has to continue treatment for post tubercular complications like restrictive and obstructive lung disease and bronchiectasis leading to increased cost of treatment, hospital admissions and increased morbidity and mortality.

**Materials & Methods:** We studied 100 patients of Chronic obstructive Pulmonary disease above 20 years of age with FEV1/ FVC of 0.7 or less with associated symptoms of cough with expectoration and breathlessness and studied the history of Tuberculosis. Studied 50 cases of bronchiectasis with history of Pulmonary Tuberculosis. We looked bronchiectasis by HRCT among patients admitted for moderate to severe COPD.

**Results:** In this study we found that 57% of patients diagnosed to have chronic obstructive pulmonary disease by clinical examination and spirometry were found to have a history of tuberculosis treatment. Post tubercular obstructive airway disease was more common in males (Male: female ratio 48:9). Among sixty patients of posttubercular bronchiectasis Male: Female ratio was 58:42. More than 50% of these patients were smokers. Among these cases of post tubercular bronchiectasis 28% had chronic obstructive pulmonary disease as co-morbidity. In our analysis of 50 cases of moderate to severe chronic obstructive airway disease we found 60% of them had associated bronchiectasis by HRCT. Mean age of these patients of bronchiectasis associated with COPD was 63±7 with male preponderance of 9:1. This combination of patients had more exacerbations, less serum albumin levels and more mortality.

**Conclusion:** Tuberculosis causes bronchiectasis and chronic obstructive and restrictive lung disease similar to COPD. Chronic obstructive pulmonary disease and Tuberculosis can coexist. Chronic obstructive pulmonary disease is associated with bronchiectasis in a significant number of patients. Chronic obstructive pulmonary disease patients are prone to develop secondary bacterial infections including tuberculosis. Bronchiectasis is associated with airway disease. The triad increases the complications, morbidity and mortality.

**Key words:** Bronchiectasis, COPD, Exacerbations, Morbidity, Mortality

## INTRODUCTION

The triad of Pulmonary Tuberculosis, obstructive airways disease and bronchiectasis is responsible for considerable morbidity and mortality in India. The speciality with this triad is Tuberculosis disease of the lungs leads to fibrosis and reactive airways and leads to crippling obstructive

and restrictive lung disease similar to chronic obstructive pulmonary disease.<sup>1-3</sup> Chronic obstructive pulmonary disease is common in smokers and so is tuberculosis. Both Chronic obstructive lung disease and pulmonary tuberculosis may coexist. COPD patients are prone to secondary bacterial infections including mycobacterial disease. Pulmonary Tuberculosis leads to bronchiectasis. Bronchiectasis causes secondary infections and associated with airway disease. Chronic obstructive lung disease patients have associated bronchiectasis. The triad leads to crippling secondary infections, increased morbidity and mortality and increase in hospital expenditure. The problem is magnified if there is coexisting diabetes mellitus and or HIV disease which increases the suffering further.<sup>4-6</sup>

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## MATERIALS & METHODS

The protocol was approved by the local ethics committee and written informed consent was obtained from each patient.

We have included the summary of three studies done in our tertiary care centre. Study one is the enumeration of patients of COPD with history of Tuberculosis. Second study is the study of post tubercular bronchiectasis and third a study of association of bronchiectasis in moderate to severe COPD patients. We analysed our results and compared with authenticated studies.

### Study I

We have studied 100 cases of COPD diagnosed with FEV1/FVC 0.7 or less presenting with symptoms of cough with expectoration and breathlessness in our tertiary care centre.

Among them 57 (57%) gave the history of tuberculosis. 48 were male and 9 were females.

### Study II

Post Tubercular Bronchiectasis: We did a 2 year study on the prevalence and clinical profile of post tubercular bronchiectasis in our tertiary care centre.

We included the following patients

1. Those who completed successful Anti-TB Treatment (ATT)
2. Symptomatology included
  - (a) Cough with expectoration-recurrent
  - (b) Dyspnoea
  - (c) Fever
  - (d) Hemoptysis
3. Thorough clinical examination eliciting the signs of bronchiectasis, cystic fibrosis, consolidation and coarse crepitations.
4. Sputum for acid fast bacilli (AFB) -spot and overnight specimen done and only sputum AFB negative cases were included.

### Exclusion Criteria

1. Sputum positive for AFB status
2. Extremely moribund conditions
3. Unwilling and non-cooperative clientele.

## RESULTS

Sample size was 60 subjects (n=60) with male–female ratio of 35:25 (58%:42%), with in the age range of 17–69 years, of which majority were in the 31–50 years group (43.3%). Initial presenting symptoms were productive cough

(95%), dyspnoea (90%) and hemoptysis (35%). History of smoking was noted in 53% of total sample. It is worth noting that minority of the females were also smokers.

Chronic obstructive pulmonary disease (COPD) (28%) is the major co morbid condition associated with PTBX followed by hypertension (12%), type 2 diabetes (5%) and coronary artery disease (5%).

Majority of patients had bronchiectatic changes which were identifiable on chest X-ray (53%). One-fourth patients had fibrosis (25%). Features of destroyed lung were evident in 9 cases (15%). Fungal ball was seen in 4 cases (7%). Bilateral involvement was seen in 25 cases (42%) followed by right predominance (33%).

HRCT Thorax revealed the following types

1. Traction bronchiectasis: 25 cases (42%)
2. Mixed bronchiectasis: 15 cases (25%)
3. Saccular bronchiectasis: 9 cases (15%)
4. Cystic bronchiectasis: 7 cases (12%)
5. Central bronchiectasis: 4 cases (6%).

Secondary bacterial infections in our study included staphylococcal, klebsiella and pseudomonas species.

Our study of Post tubercular bronchiectasis has associated COPD in 28% of patients. Two patients in our study of sixty patients showed active tuberculosis in the bronchial washings.

## BRONCHIECTASIS IN COPD PATIENTS

In our own study of association of bronchiectasis in COPD patients. 50 patients of COPD having moderate to severe COPD were analysed with clinical, chest x-ray, CT scan, serum c reactive protein and albumin levels and microbiological study by sputum microscopy for culture and sensitivity and gram stain. Mean age of the patients was  $63 \pm 7.87$  years. Out of 50 Patients 45 were men (90%) and the remaining were women (10%). Bronchiectasis was present in 30 patients (60%). H. influenza was the commonest organism isolated from sputum. Patients with bronchiectasis had significantly more exacerbations ( $p=0.0001$ ), severe airway obstruction ( $p=0.037$ ), higher CRP levels ( $p=0.0001$ ) and low albumin levels ( $p=0.007$ ). Nine patients (30%) died in bronchiectasis group and only one patient (3.33%) died in patients without bronchiectasis. Our study showed an elevated prevalence of bronchiectasis in patients with moderate to severe COPD and was associated with severe airway obstruction. Increased exacerbations, inflammation, malnutrition and mortality in Indian patients.



## DISCUSSION

China is a country of high population. The prevalence of tuberculosis in terms of absolute number is high in China. Adult patients who diagnosed as bronchiectasis at the hospital between 1995 and 2011 were recruited to this study. The amount of hospitalized patients with bronchiectasis in 2011 was 9.3 fold of that in 1995. The number was increase very fast during the seventeen years. The data tallied with the situation of pulmonary TB in China. 69.21% (4892 in 6977) patients were original from countryside. The main causes of bronchiectasis were pulmonary TB (31.17%), bacterial infection and pertussis. The peak age ranges of post-TB bronchiectasis were 30 to 39 and 60 to 69. Patients with post-TB bronchiectasis prone to have haemoptysis but less sputum. The chest radiography of patients with post-TB bronchiectasis represented upper lobes injury of the lung. Less pseudomonas aeruginosa culture positive and less acute exacerbation were recorded in post-TB bronchiectasis patients from the data of available follow-up patients.<sup>7-8</sup>

They concluded that the main cause of bronchiectasis in China was pulmonary TB, possibly because of the grim pulmonary TB epidemic situation. Post-TB bronchiectasis patients have marked different clinical features and prognosis, compared with non-TB bronchiectasis.

Tuberculosis of the bronchi and bronchioles can cause destruction of the airways. Endobronchial and peribronchial obstruction of airways because of lymph nodes can cause obstruction and pooling of secretions with secondary infection and further destruction of the airways and can cause bronchiectasis. Bronchiectasis is associated with reactive airways because of secondary infection leading to obstructive and restrictive airway disease. Bronchiectasis patients are prone to secondary infections including mycobacterial disease. An association between chronic obstructive pulmonary disease (COPD) and tuberculosis (TB) has been described, mainly due to smoking and corticosteroid use. Whether inhaled corticosteroid (ICS) therapy is associated with an increased risk of TB remains unclear.<sup>9-15</sup>

Tuberculosis (TB) is a major cause of death worldwide. The World Health Organization estimated that there were 9 million new cases of TB in 2013.<sup>2</sup> The risk factors for TB included age, male gender, low socioeconomic status, malnutrition, substance abuse, silicosis, human immunodeficiency virus infection, malignancy, diabetes, renal disease, celiac disease, gastrectomy, transplant, and receiving corticosteroids and tumor necrosis factor inhibitors. In addition, an association between obstructive pulmonary disorders (i.e. chronic obstructive pulmonary

disease [COPD] and asthma) and active TB has been described, mainly due to smoking and corticosteroid use. Keeping a high suspicion and regularly monitoring for the development of pulmonary TB in COPD patients are necessary, especially for those receiving higher doses of oral corticosteroids and other COPD medications. Although ICS therapy has been shown to predispose COPD patients to pneumonia in large randomized clinical trials, it does not increase the risk of TB in real world practice.

COPD patients are at high risk of developing pulmonary TB, especially those frequently receiving oral corticosteroids and oral  $\beta$ -agonists. Although ICS therapy has been shown to predispose COPD patients to pneumonia in large randomized clinical trials, it does not increase the risk of TB in real world practice.

The study done by chih-Hsin Lee et al showed that COPD patients were more likely to develop pulmonary TB than non-COPD subjects under a wide variety of diagnostic scenarios for COPD. ICS was not a risk factor for developing active pulmonary TB among COPD patients after considering important clinical characteristics and other prescriptions. COPD patients who received higher doses of oral corticosteroids and oral  $\beta$ -agonists were more likely to develop active pulmonary TB.<sup>1</sup> Age, male gender, diabetes, and receiving oral corticosteroids were risk factors for TB.<sup>3</sup> Use of Inhalation corticosteroid ICS does not lead to increased risk of developing TB.<sup>1</sup> COPD patients are at risk of serious bacterial infections including tuberculosis<sup>12</sup>

In the executivesummary of the 2006 update of the Global initiative forchronic obstructive lung disease (GOLD) guidelines,the role of tuberculosis in the development of chronic airways obstruction has been recognized. According to the GOLD Workshop summary, chronic bronchitis or bronchiolitis and emphysema can occur as complications of pulmonary tuberculosis.<sup>4,5</sup>

A Pakistani study found that 55.3% of treated pulmonary tuberculosis patients presenting with dyspnoea, had an obstructive ventilatory defect.<sup>6</sup> Previous studies had also revealed that an obstructive pattern of pulmonary functional impairment following treated pulmonary tuberculosis was more common. Post tubercular impairment can manifest as reversible or irreversible obstructive airway disease, mixed defect or as pure restrictive defects. Immunological mechanisms have been postulated as a cause of Post tubercular asthma. Cavitation, extensive fibrosis, bulla formation and bronchiectasis implicated in the genesis of COPD caused by the destroyed lung due to pulmonary tuberculosis. Only a few studies have been done to identify this entity, but all the studies have definitely concluded that such an entity exists. However, the exact abnormality that

results from tuberculosis infection has to be considered in detail with future studies and a better understanding of the pathophysiology of airflow limitation may point the way to therapeutic strategies for control of symptoms in these patients.<sup>8</sup>

Pulmonary tuberculosis can lead to obstructive and restrictive lung disease resembling COPD. It can result in both reversible and irreversible airway obstruction. It is unclear whether there is a similarity in the pathology but clinically we see a post tubercular disease which is more or less similar to COPD.

The overall prevalence of airflow obstruction (forced expiratory volume in one second/forced vital capacity post-bronchodilator <0.7) was 30.7% among those with a history of tuberculosis, compared with 13.9% among those without a history. Males with a medical history of tuberculosis were 4.1 times more likely to present airflow obstruction than those without such a diagnosis. This remained unchanged after adjustment for confounding by age, sex, schooling, ethnicity, smoking, exposure to dust and smoke, respiratory morbidity in childhood and current morbidity. Among females, the unadjusted and adjusted odds ratios were 2.3 and 1.7, respectively.<sup>14</sup>

#### **Mycobacterium Tuberculosis and Opportunist Mycobacteria**

Bronchiectasis may result from pulmonary Mycobacterium tuberculosis infection, with the incidence reflecting the prevalence of tuberculosis in the population. It is also increasingly recognised that opportunist mycobacteria are associated with localised or widespread bronchiectasis. Bronchiectasis, like other forms of lung damage, makes patients prone to picking up environmental mycobacterial species and bronchial damage may occur as a result of opportunist mycobacterial infection. Opportunist mycobacteria have been isolated in 2% and 10% of random sputum specimens from patients with bronchiectasis, but the clinical significance is unclear. Patients with Mycobacterium avium complex infection may develop bronchiectasis over years.<sup>10</sup>

The scenario can be different in a populous country like India where tuberculosis is rampant. Tuberculosis can be a secondary complication in a case of post tuberculosis bronchiectasis patient because of endogenous reactivation secondary to poor nutrition and destroyed lung or exogenous reinfection.

Airway diseases, bronchiectasis and bronchial asthma present with similar symptoms. The differentiation between asthma, chronic obstructive pulmonary disease and bronchiectasis in the early stage of disease is extremely important for the adoption of appropriate therapeutic measures. Because

of the high prevalence of these diseases and the common pathophysiological pathways, some patients with different diseases may present with similar symptoms.<sup>11</sup>

Bronchiectasis is often accompanied by airway disease. In our study of post tubercular bronchiectasis was seen 28% of patient showed symptoms of COPD. Bronchiectasis is often accompanied by obstructive disease

## **CONCLUSION**

Tuberculosis can cause bronchiectasis and airway disease. Smoking is an aetiological factor for both Tuberculosis and COPD. Bronchiectasis patients have susceptibility to bacterial infections including Mycobacterium tuberculosis and M. avium-intracellulare. Bronchiectasis is associated with airway disease and COPD patients have high prevalence of Bronchiectasis in nearly 60% of our patients. COPD patients can have secondary infections and mycobacterial disease.

Tuberculosis, Bronchiectasis and COPD is a deadly triad responsible for increase in hospital admissions, increased health care expenditure and financial burden for the individual families.

The problem becomes much complicated in the event of coexistent Diabetes mellitus and or HIV disease both of which can be facilitating factors for development of Pulmonary Tuberculosis and complications thereon.

High degree of awareness on the part of the physician, early treatment of Tuberculosis with proper drugs, implementation of RNTCP programme, prevention of smoking and explanation of the hazards of smoking at an early age by means of awareness programmes can decrease this problem of third world countries

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# Amniotic Membrane in Periodontics: An Insight

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## Abstract

Periodontal diseases leading to deterioration of tooth supporting structures are a serious concern for clinicians. The clinical application of amniotic membrane for guided tissue regeneration (GTR) while fulfilling the current mechanical concept of GTR, amends it with the modern concept of biological GTR. Amniotic membrane not only maintains the structural and anatomical configuration of regenerated tissues but also contribute to enhancement of healing.

**Key words:** Amniotic, Guided tissue regeneration, Periodontics, Stem cell

## INTRODUCTION

Periodontal disease is a chronic inflammatory condition that occurs in response to predominantly Gram-negative bacterial infection originating from dental plaque.<sup>1</sup>

Prior to the 1950s, periodontitis was treated mostly by tooth exfoliation or extraction, and that is still the predominant treatment for most of the world's populations today. Until the 1980s, the most commonly used treatment consisted of scaling and root planing, followed by resective surgery aimed at achieving zero pocket depth. During the 1980s, data were obtained demonstrating that the thoroughness of root debridement and subgingival infection control, not the presence or absence of periodontal pockets, is the major determinant of successful periodontal therapy, and non-surgical therapy became a commonly used treatment. Neither resective surgery nor non-surgical therapy results in significant regeneration of periodontal attachment. Recent data clearly show that regeneration of the previously destroyed periodontal attachment tissues is biologically possible, and regeneration has become the goal of therapy for the 1990s.<sup>2</sup>

Regeneration by grafting may be further enhanced by the use of barrier membranes that exclude gingival fibroblasts and epithelium from the healing site. Still further enhancement seems to be possible by local application of various growth factors although studies in this important area are now only in their infancy. The future of periodontal therapy is exceedingly bright.<sup>1</sup>

However, the current regenerative procedures have limitations in attaining complete and predictable regeneration, especially in advanced periodontal defects.<sup>3</sup>

For successful periodontal regeneration, formation of a functional epithelial seal, insertion of new connective tissue fibers into the root, reformation of a new acellular cementum on the tooth surface and restoration of alveolar bone height are required. The complex events associated with periodontal regeneration involve recruitment of locally-derived progenitor cells that can differentiate into periodontal ligament cells, mineral-forming cementoblasts, or bone-forming osteoblasts.<sup>4,5</sup>

Advances in stem cell biology and regenerative medicine have presented opportunities for tissue engineering and gene-based approaches in periodontal therapy.<sup>6,7</sup> These new approaches offers interesting alternatives to existing therapies for the repair and regeneration of the periodontium.

Applications of amnion membrane include chemical or thermal burns, correction of corneal epithelial defects,

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neurotrophic corneal ulcers, leaking blebs after glaucoma surgery, reconstruction of conjunctival and ocular surfaces, ocular cicatricial pemphigoid or Stevens-Johnson syndrome, and bullous keratopathy. These membranes have also been used in furcation defects, intrabony defects, and gingival recession coverage.<sup>8</sup>

Periodontal plastic surgical procedures aimed at coverage of exposed root surface. Owing to the second surgical donor site and difficulty in procuring a sufficient graft for the treatment of root coverage procedures, various alternative additive membranes have been used. A recent resorbable amniotic membrane not only maintains the structural and anatomical configuration of regenerated tissues but also enhances gingival wound healing, provides a rich source of stem cells. Therefore, amniotic membrane is choice of material these days in augmenting the better results in various periodontal procedures.

Diño *et al.*<sup>9</sup> demonstrated for the first time that amniotic membrane could be separated, sterilized and safely used at a later date. Amnion-derived cells with multipotent differentiation ability have attracted a lot of attention in the regeneration of periodontal tissues.

Amnion lines the innermost portion of the amniotic sac of the placenta. Its structure consists of a single layer of epithelium cells, thin reticular fibers, a thick compact layer, and a fibroblast layer. The basement membrane contains collagen Types III-V and cell-adhesion bioactive factors including fibronectin and laminins.<sup>10</sup> Data suggest the amnion basement membrane closely mimics the basement membrane of human oral mucosa.<sup>11</sup>

Despite the introduction of allograft dermis tissue products and biologic mediators, autograft tissue remains the “gold standard” of periodontal plastic surgery as it provides excellent predictability, improved long-term root coverage, and superior esthetics over other treatment options.<sup>12</sup> Despite these clinical outcomes, the use of autograft tissue has drawbacks. Autogenous graft tissue is limited in supply and its procurement significantly increases patient morbidity while also lengthening the duration of surgery.<sup>13</sup>

The utilization of amniotic membrane diminished in the early 1980's because of increase in the communicable diseases such as HIV, hepatitis, etc. Amnion re-appeared in the cryopreserved form for the treatment of ophthalmic wounds in the late 1990's and early 2000's.<sup>4</sup> Lawson in 1985 was the first who studied the use of amniotic membrane along with pectoralis major muscle for oral cavity reconstruction. He concluded that placement of amnion over the deep aspect of the muscle that is exposed to the oral cavity resulted in a more rapid development of mucosa.

When muscle was used without amniotic membrane, the healing process usually took twice as long. Furthermore, when amnion was not used, it showed a significant amount of wound contracture.<sup>14</sup>

## AMNION – STRUCTURE AND FUNCTION

The amniotic membrane encases the amniotic fluid and fetus and is highly flexible because of which it is easily be separated from the chorion.<sup>1</sup> Amniotic membrane has two types of cells-epithelial cells derived from embryonic ectoderm and amnion mesenchymal cells from embryonic mesoderm. At ultra-structural level it is a thin, transparent, avascular composite membrane composed of three major layers, which is a single epithelial layer, a thick basement membrane, and an avascular mesenchyme consisting mainly of collagen, respectively. Amniotic membrane has no blood vessels or nerves; instead, the nutrients it requires are supplied directly by diffusion out of the amniotic fluid and/or from the underlining decidua. The amniotic epithelial cell (AEC) layer is a single layer of flat, cuboidal and columnar cells that are in direct contact with the amniotic fluid. It is from this layer that amniotic mesenchymal stem cells are isolated and stored for further regenerative use.<sup>15</sup>

## EXTRACELLULAR MATRIX

Extracellular matrix materials form the structural components of the architecture of the membrane and contain a variety of specialized proteins including fibronectin, proteoglycans, glycosaminoglycan, laminin, and other similar materials. The basal lamina contains a large amount of proteoglycans like heparin sulfate that is one of the major proteoglycans in the gingiva. The spongy layer on the stromal portion of the amnion has an abundance of hydrated proteoglycans and glycoproteins that form a non-fibrillar network along with collagen.<sup>16</sup>

The matrix of human amniotic membrane contains abundant growth factors like keratinocyte growth factor, basic fibroblast growth factor, transforming growth factor-beta (TGF-β), nidogen growth factor, and epidermal derived growth factor which promote periodontal regeneration. These growth factors provide a natural healing environment, accelerate healing and mimic the stem cell niche for ex vivo growth.<sup>17</sup>

## BENEFITS

### Epithelialization

Amniotic membrane facilitates migration of epithelial cells, reinforces basal cell adhesion, promotes epithelial

differentiation, prevents epithelial apoptosis, and promotes epithelialization in healing of wounds. The basement membrane of amniotic membrane serves as a safe and suitable bed for the growth of epithelial cells. Sufficient oxygenation for epithelial cells is provided by its good permeability in contrast to other synthetic materials. Thus, amniotic membrane is an ideal tissue which facilitates the growth of epithelial cells, helping in their migration and differentiation.<sup>8</sup>

## ANTI-INFLAMMATORY

The mesenchymal stem cells in the amniotic membrane decrease the secretion of proinflammatory cytokines like tumor necrosis factor alpha and interferon while increasing the production of anti-inflammatory cytokines interleukin-10 and interleukin-4.<sup>1</sup> The proinflammatory mediators, interleukin-1 $\alpha$  and interleukin-1  $\beta$ , are also suppressed by matrix of stroma of amniotic membrane. The inhibitors of matrix metalloproteinases (MMPs) found in the amniotic membrane decreases matrix MMPs released by infiltrating neutrophils and macrophages.<sup>1,8</sup> Various tissue inhibitors of MMPs 1, 2, 3, and 4, interleukin-10, and interleukin-1 receptor antagonists and endostatin which inhibit endothelial cell proliferation, angiogenesis, and tumor growth are also expressed by human amniotic epithelial and mesenchymal cells.<sup>8</sup> It also reduces the recruitment of various other inflammatory cells including polymorphonuclear cells, CD3 cells, CD4 T cells and CD11b cells to the injured site thereby reducing the inflammation.<sup>1,8</sup>

## ANTIVIRAL AND ANTIMICROBIAL

Amniotic membrane firmly adheres with the wound via fibrin and elastin linkages that seals the wound and prevent contamination.<sup>1</sup> This tight adherence helps in restoring lymphatic integrity, protects circulating phagocytes from exposure and allows faster removal of surface debris and bacteria from the wound.<sup>18</sup> Its antiviral properties are exhibited by the presence of a powerful antiviral agent, cystatin E which is an analog of cysteine proteinase inhibitors.<sup>8,15</sup>

## ANTI-SCARRING

Amniotic membrane secretes vascular endothelial growth factor (VEGF), hepatocyte growth factor that maintains a proper balance between TGF-1 and TGF-3 that prevents scarring.<sup>1</sup>

## ANGIOGENESIS

The cells of the amniotic membrane enhance the production of VEGF by activating the VEGF receptors

1 and 2. Extensive neovascularization after the application of Amniotic membrane is due to the release of angiogenic factor like insulin derived growth factor that promotes granulation tissue formation and epithelialization.<sup>15</sup>

## IMMUNOMODULATORY

The unique molecular surface architecture and biochemical properties of Amniotic membrane that is derived from the layer of trophoblast cells renders it unsusceptible to maternal immune attack.<sup>1</sup> The native AECs express the non-polymorphic, non-classical human leukocyte antigen (HLA-G) but lack the polymorphic antigens HLA-A, B (Class IA) and HLA-DR (Class II) on their surfaces. The Class I antigen is seen in almost all cells of the amniotic membrane unlike the Class II antigen which is only present in some fibroblasts. These mesenchymal stem cells are different from other nucleated mammalian cells as they show little allogenic reactivity when administered to major histocompatibility complex unmatched adult immune competent recipients.<sup>15</sup>

## PROCESSING OF AMNIOTIC MEMBRANE

For clinical use, amniotic membrane can be prepared in the following forms:<sup>1</sup>

- Fresh membrane
- Dried membrane
- Frozen membrane
- Stabilized amniotic membrane
- Cryopreserved membrane
- Freeze derived irradiated membrane

## AMNIOTIC MEMBRANE IN DENTISTRY

The use of amniotic membrane has recently increased clinically as an allograft material for chronic and acute wound care management, for scar tissue reduction, as a barrier membrane, and as a soft tissue regeneration graft.<sup>19</sup> The graft of amniotic membrane is a viable and reliable method to cover the exposed periosteum as they serve as a good alternative to mucosal and skin grafts.<sup>20</sup> Amnion allograft might be a suitable alternative to connective tissue graft in procedures to cover denuded root surfaces and can reduce recession depth.<sup>21,22</sup>

It is easily available and preserved and is a cost-effective material.<sup>23</sup>

## LIMITATIONS OF AMNIOTIC MEMBRANE

The use of amniotic membranes requires immense skill; thus, doctor's inexperience is a limitation. There is always

an associated risk of infection transmissions. Amniotic membranes are fragile membranes, so they need to be dealt with very carefully. Cryopreserved membranes are expensive. The procedure associated with the use of these membranes is technique-sensitive and also depends on morphology of the defect.<sup>8</sup>

## CONCLUSION

Human amniotic membrane is a uniquely suited material for use as an allograft in wound management and is rising in various fields of tissue engineering, medicine, regeneration biology, and stem cell research. The clinical application of amniotic membrane not only maintains the structural and anatomical configuration of regenerated tissues but also contributes to the enhancement of healing through reduction of post-operative scarring and subsequent loss of function and providing a rich source of stem cells. To conclude, amnion from discarded placenta can be an interesting source of cells for regenerative medicine.

However, further research and long-term clinical trials are required for exploring the full potential of this stem cell reservoir.

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# A Case Report of Low Cerebrospinal Fluid Pressure Headache Due to Cerebrospinal Fluid Leak

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## Abstract

We, here, present a case of 24-year-old female, who was admitted to our hospital with history of headache off and on since last 1 month that was aggravated by rising from bed in the morning and on standing posture. With this scenario, she was started nonsteroidal anti-inflammatory drugs and antimigraine regimen. Since there was no relief, she was investigated and found to have low cerebrospinal fluid pressure headache. Who improved on treatment with epidural blood patch.

**Key words:** Cerebrospinal fluid, Computerized tomography, Intracranial hypotension, Nonsteroidal anti-inflammatory drugs, Spontaneous intracranial hypotension

## INTRODUCTION

The most common cause of intracranial hypotension (ICH), or low cerebrospinal fluid (CSF) pressure in the brain, is CSF leak. Low CSF pressure headache is caused by an internal spinal fluid leak and may range from obvious and disabling to subtle and nagging.

The syndrome of ICH is a single pathophysiological entity of diverse origin. Usually, it is characterized by an orthostatic headache, that is, one that occurs or worsens with upright posture, although patients with chronic headaches or even no headache have been described.<sup>1</sup>

The nature and location of the headache vary greatly from patient to patient, but consistently the pain is exacerbated by laughing, coughing, jugular venous compression, and Valsalva maneuver, and is resistant to treatment with analgesic agents.<sup>2,3</sup>

In addition to headache, patients may experience nausea, vomiting, anorexia, neck pain, dizziness, horizontal

diplopia, changes in hearing, galactorrhea, facial numbness or weakness, or radicular symptoms involving the upper limb, all of which are orthostatic in nature.<sup>4</sup> The ICH generally is considered to be a benign condition and most cases resolve with conservative management.

## CASE REPORT

A 24-year-old female patient admitted with c/o recurrent type headache since 1 month, nausea, vomiting, and neck pain intermittently since last 1 month.

The patient was alright before 1 month to start with then later started with continuous type of headache, located to occipital, frontal and temporal region, gradually progressive in nature, relieved on lying down and after taking tea/coffee, and aggravated by sitting and standing position.

Later, she also started c/o intermittent type nausea, vomiting, and neck pain. For all these complaints she use to prescribed nonsteroidal anti-inflammatory drugs (NSAIDS) and migraine medications by local practitioners and over counter medication.

Initially, she use to get relief with same but had many repeated episodes and now admitted for same because headache becomes unbearable to her.

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On examination, BP/PR/TEMP found to be normal, B/L pupils equally reacting to light. There was no postural drop in BP. There was no neurodeficit and neck rigidity. Rest systemic examination was found to be normal.

On laboratory examination, she was having HB=11.9, TLC=5200, PLATELETS = 2.39 lakh, Sr. creatinine = 0.81, PT/INR = 12.5/1.03, HIV/HBS Ag = Negative.

Magnetic resonance imaging (MRI) cervicodorsal spine shows mild cerebellar tonsillar herniation through foramen magnum, tonsil appears pear shaped.

CSF intensity signal in anterior epidural region extending from upper border of D1 vertebra to midlevel of D3 vertebral body s/o possibility of CSF leak in anterior epidural space.

For confirmation computerized tomography (CT) myelogram done, which was s/o extravasation of contrast in above mentioned area so our diagnosis was confirmed to have low CSF pressure headache secondary to CSF leak.

Initially, patient was treated with NSAIDS, head low position, coffee, and bed rest. Later on planned for epidural blood patch (EBP), after giving EBP, patient was significantly improved symptomatically.

No second setting required. Patient came to follow-up asymptomatic after 15 days.

## DISCUSSION

In 1939,<sup>5</sup> Georg Schaltenbrand, a German neurologist, using the term “aliquorrhea” described spontaneous occurrence of a syndrome of orthostatic headache and a few other symptoms associated with low CSF opening pressure (OP).<sup>6</sup> This later came to be known as spontaneous ICH (SIH).<sup>7,8</sup> Modern neuroimaging has revolutionized our understanding of this entity. The original theory of Schaltenbrand that the disorder was due to decreased CSF production has never been substantiated. It is now recognized that almost all cases of SIH result from spontaneous CSF leaks. The overwhelming majority of these spontaneous leaks occur at the spinal level and only rarely from the skull base.<sup>9</sup> Although the triad of orthostatic headaches, low CSF pressures, and diffuse pachymeningeal enhancement is the classic hallmark of this disorder, the variability is indeed substantial.<sup>10</sup> The core factor in pathogenesis, and the independent variable is loss of CSF volume; while CSF pressures, clinical manifestations, and MRI abnormalities are variables dependent on the loss of CSF volume. The term “SIH” no longer appears broad enough to embrace all these variations. Therefore, terms

such as “CSF hypovolemia” or “CSF volume depletion” as well as “spontaneous CSF leaks” have appeared in the literature and have been used interchangeably.<sup>8,11,12</sup>

## Etiology

The etiologies of CSF volume depletion are listed in Table 1.

## Clinical Features and Related Mechanisms

### Headaches

Headache is the most common clinical manifestation. This is often orthostatic (present when upright and relieved in recumbency). The latency of headache onset or resolution from change in posture classically should be only a few minutes, but in reality, the variability is substantial, and with chronicity, this latency may become even further prolonged. The headache may be throbbing, but more commonly it is not, and is described as a pressure sensation of variable intensity, sometimes quite intense. It is typically, although not invariably, bilateral.<sup>13</sup> It may be bifrontal, occipital, bifrontal-occipital, or holocephalic. Occasionally, it may start as a focal or unilateral headache and evolve into a holocephalic headache if the patient continues to be up and about. The headaches are often aggravated by Valsalva-type maneuvers and occasionally are even triggered by such maneuvers. At this point, it should be emphasized that not all orthostatic headaches are due to ICH or CSF leaks (this will be discussed later in this communication), and not all headaches in CSF leaks are orthostatic.

Sinking of the brain and the resultant traction on pain-sensitive suspending structures of the brain is thought to be the main cause of the orthostatic headaches in CSF

**Table 1: The etiologies of CSF volume depletion are listed**

True hypovolemic state (reduced total body water)
Traumatic CSF leaks
Definite trauma (MVs, sports injuries, etc.)
Thecal holes and rents from LPs and epidural catheterizations
Spinal and cranial surgeries including skull base and some sinus surgeries
Proximal brachial plexus avulsion injuries, nerve root avulsions
CSF shunt overdrainage
Spontaneous CSF leaks
Undetermined cause
Preexisting weakness of the dural sac, surgical anatomical observations
Meningeal diverticula
Disorders of connective tissue matrix
Marfan syndrome, Marfanoid features
Joint hypermobility
Retinal detachment at young age
Abnormalities of elastin and fibrillin in cultured dermal fibroblasts
Trivial trauma in the setting of preexisting dural weakness
Spondylotic spurs, herniated discs

leaks. Dilatation of the cerebral veins and venous sinuses may also be a participatory mechanism and in some situations perhaps even the dominant mechanism.

Some patients with stubborn orthostatic headaches, in recumbency, may report an earlier and a more effective relief in certain positions or postures, such as Trendelenburg position,<sup>14</sup> or by lying prone with the head dropped somewhat at the edge of the bed. It has been demonstrated that CSF OP is significantly higher in prone than in lateral decubitus position.<sup>15</sup>

### Clinical Features Other Than Headaches

- Spinal pain (neck, interscapular, and less commonly lower back), sometimes orthostatic
- Nausea with or without emesis (often orthostatic)
- Diplopia
- Cochleovestibular manifestations (tinnitus, change in hearing, and dizziness)
- Photophobia, visual blurring
- Upper limb numbness, paresthesias
- Gait unsteadiness<sup>16</sup>
- Facial numb feeling
- Change in level of consciousness (i.e., encephalopathy,<sup>17</sup> lethargy, stupor,<sup>18</sup> coma<sup>19</sup>)
- Personality change, memory decline, apathy, frontotemporal dementia-like picture<sup>20,21</sup>
- Meniere-like syndrome<sup>22</sup>
- Upper limb radiculopathy<sup>23</sup>
- Trouble with bowel or bladder control.<sup>24</sup>

### Diagnosis

#### LP and CSF analysis

In search of inflammatory, infectious or neoplastic disease, CSF OP is low in the large majority; but in a significant minority, perhaps in about one fourth of patients, it is within normal limits. The OP is uncommonly atmospheric and rarely is even negative (Table 2).

#### Radioisotope cisternography

Indium-111 is the radioisotope of choice. It is introduced intrathecally (IT) via an LP and its dynamics are followed by sequential scanning at various intervals of up to 24 or even 48 h. Normally, after 24 h, though often earlier, ample radioactivity can be detected over the cerebral convexities while no activity outside the dural sac is noted, unless there has been inadvertent injection of part of the radioisotope extradurally or if some of the IT-injected radioisotope has extravasated through the dural puncture site or CSF leaks.

#### MRI abnormalities of head and spine and their related mechanisms

Head and spine MRI abnormalities of CSF leaks and CSF hypovolemia are listed.

**Table 2: CSF analysis**

Color	Clear/xanthochromic
Protein concentration	Normal/high
Leukocyte count	Normal/lymphocytic pleocytosis
Erythrocyte count	Normal/high
	Glucose concentration, cytology, and bacteriology should all be normal

#### Head MRI abnormalities in CSF leaks

- The most common and most reliable head MRI abnormality in spontaneous CSF leaks is cephalad opening of aqueduct of sylvius as seen in midline sagittal views
- Diffuse pachymeningeal enhancement: Uninterrupted, nonnodular, can be thick or thin, no leptomeningeal abnormality
- Descent (“sagging” or “sinking”) of the brain
  1. Descent of cerebellar tonsils at or below the foramen magnum (may mimic type I Chiari)<sup>25</sup>
  2. Descent of the brainstem and mesencephalon, occasionally without descent of cerebellar tonsils to or below foramen magnum
  3. Increase in anteroposterior diameter brainstem resulting from distortion of the brainstem
  4. Descent of iter<sup>‡</sup> below the incisural line 10<sup>13</sup>
  5. Obliteration of prepontine or perichiasmatic cisterns
  6. Crowding of the posterior fossa
  7. Flattening of the optic chiasm
  8. Flattening of the anterior pons
- Subdural fluid collections, typically hygromas, infrequently hematomas
- Enlargement of the pituitary (may mimic pituitary tumor or hyperplasia)<sup>26</sup>
- Engorged cerebral venous sinuses
- Decrease in size of the ventricles (“ventricular collapse”).

#### Spine MRI abnormalities in spontaneous CSF leaks

- May or may not be the actual site of leak, even when the diverticulum is large, although larger diverticula may be more prone to be the site of the leak
  1. Extra-arachnoid fluid collections (often extending along several spinal levels)<sup>27-29</sup>
  2. Extradural extravasation of fluid (extending to paraspinal soft tissues)
    - a. May identify the level of the leak (i.e., cervical, thoracic or lumbar), not uncommon
    - b. May identify the actual site of the leak, uncommon<sup>30</sup>
  3. Meningeal diverticula, a single or multiple, various sizes, any level of spine
  4. Spinal dural enhancement<sup>31</sup>
- Engorgement of spinal epidural venous plexus.

### CT myelography (CTM)

CTM thus far is the most accurate study for demonstrating the exact site of the spinal CSF leakage.<sup>1</sup> Similar to radioisotope cisternography, it also provides an opportunity to measure the CSF OP at the time of dural puncture. In addition to its accuracy in revealing the site of the leak, it can show meningeal diverticula, dilated nerve root sleeves, extra-arachnoid fluid collections, and extradural egress of contrast into the paraspinal tissues.

### Treatment

For spontaneous spinal CSF leak, a variety of treatment modalities have been tried as follows:

1. Conservative measures
  - a. Bed rest (those with substantial orthostatic headaches remain reclined much of the time anyway)
  - b. Coffee
  - c. Hydration (actually overhydration since most patients are not dehydrated)
  - d. Time
2. Medications
  - a. Analgesics
  - b. Caffeine
  - c. Theophylline
  - d. Corticosteroids
3. Abdominal binder
4. Epidural injections of:
  - a. Homologous blood ("EBP")
    - i. Targeted
    - ii. Distant at lumbar level or bilevel, "blind EBP"
  - b. Fibrin glue
  - c. Fibrin glue and blood
5. Surgical repair of the leak
6. Other measures in special situations
  - a. Intrathecal fluid injection (volume replacement)
  - b. Epidural saline infusion
  - c. Intravenous saline infusions
  - d. Epidural infusion of dextran.

EBP is now recognized as the treatment of choice in those patients who have not responded to the initial trial of conservative management.<sup>32</sup> EBP works via two separate mechanisms: (1) The immediate effect related to volume replacement by compression of the dural sac (decreasing the volume of the container); (2) sealing of the dural defect, which may be delayed from the first one. Therefore, it is not uncommon to note an initial quick response in connection with the first mechanism, recurrence of symptoms within merely a day or two, and then, a gradual and often variable improvement after several days. Variability is, however, substantial. The efficacy of each EBP is about 30%.<sup>1</sup> A previous EBP failure should not be taken as a signal that a subsequent EBP will fail. Indeed, many patients

may require more than one EBP and some have required several. At times, a cumulative effect from multiple EBPs may be noted. Similarly, a previous success will not guarantee success of a future EBP. The site of the leak in spontaneous CSF leaks is mostly at levels above the lumbar spine where most of the epidural block patches are placed. Therefore, the odds are that many of these will be nontargeted and distant from the site of the leak. (3) The dural defect in spontaneous CSF leaks, as opposed to post-lumbar puncture leak, often is not a simple hole or rent instead it is frequently a preexisting zone of attenuated dura with or without associated diverticula where an unsupported arachnoid may finally give way and ooze CSF from one or more sites. Surgical anatomical observations<sup>33</sup> have clearly identified such defects in many patients who have ended up with surgery.

Surgery in well-thought-of cases is effective and can be tried when less invasive measures (such as EBP) fail.

Furthermore, some patients may have CSF leaks from more than one site and at different levels. It is strongly emphasized that thorough pre-operative neurodiagnostic studies should be conducted to identify the actual site of the leak before surgery is undertaken.

The fundamental purpose of the surgery in the treatment of CSF leaks is to stop the leak.

### Complications of Spontaneous CSF Leaks

1. Subdural hematoma
2. Rebound intracranial hypertension
3. Cerebral venous sinus thrombosis
4. Bibrachial amyotrophy
5. Superficial siderosis
6. Natural history and outcome
7. Recurrence of CSF leaks.

### CONCLUSION

A 24-year-old case of spontaneous CSF leak treated with EBP significantly improved symptomatically and clinically.

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# Extraskelatal Ewing's Sarcoma of Floor of Mouth: A 1-year follow-up of the Rare Disease in a Rare Location

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## Abstract

Extraskelatal Ewing's sarcoma (EES) are very rare soft tissue neoplasms, especially in the head and neck region. Only very few cases of extraskelatal ES in this site is reported in literature. A soft tissue swelling in the floor of mouth in a 15-year-old boy, which was diagnosed as extraskelatal ES of the sublingual gland after extensive investigations is reported. To the best of our knowledge, this is the first report of a case of extraskelatal ES of the sublingual gland. This case highlights the importance of considering this tumor in the differential diagnosis of soft tissue mass in the oral cavity.

**Key words:** Extraskelatal Ewing's sarcoma, Ewing's sarcoma, Ewing sarcoma family of tumors, Peripheral neuroectodermal tumor

## INTRODUCTION

Ewing's sarcoma (ES) is a highly malignant bone tumor of long bones occurring in children and young adults and was first described by James Ewing in 1921. However, there have been reported cases of malignant soft tissue tumors which are indistinguishable from ES.<sup>1</sup> Extraskelatal ES (EES) is a rare round cell malignant neoplasm with rapid growth and an uncharacterized mesenchymal cell origin, and it is histologically similar to ES arising from bone.<sup>2</sup> The ES family of tumors (ESFT) represents a group of high-grade small round cell tumors, including ES of bone, EES, peripheral primitive neuroectodermal tumor (PNET), and Askin tumor (thoracopulmonary PNET). These tumors originate from the neuroectoderm and are composed of undifferentiated neuroepithelial cells that

have the capacity to differentiate into neuronal, neuroglial, or other mesenchymal cell types.<sup>3</sup> Differentiation is based on cellular characteristics or anatomic location or both. ES is poorly differentiated and may arise in bones or soft tissues; PNET arises in the soft tissues and shows neuroectodermal differentiation. Fusion of the ES gene on 22p12 with one of a number of related transcription factors, the most common (90%) being FLI1 on 11q24, unites all ESFTs. The result is a protein able to interact with a number of regulators of cellular proliferation.<sup>4</sup> The annual incidence and mortality rates are 0.1/100,000 and 0.05/100,000, respectively.<sup>3</sup>

Primary ESFT can present virtually anywhere in the body.<sup>4</sup> Patients present with painless mass.<sup>4</sup> EES rarely occurs in the head and neck region, with only five cases reported in a series of 118 patients in the four largest series in English literature.<sup>5</sup> Another report indicated that only 5% to 11% of EES cases occur in the head and neck region, and the nose, eyelid, nasopharynx, parotid gland, scalp, and parapharyngeal space have been described.<sup>6</sup> We herein present a case of EES arising from sublingual gland. To the best of our knowledge, EES of sublingual gland has not been described previously.

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## CASE REPORT

A 15-year-old patient came to Oral Medicine and Radiology Department with swelling under surface of tongue for 1 year and pain for 2 days (Figure 1). Swelling was gradually increasing in size and was painless. A history of difficulty in tongue protrusion and speaking started 1 month back. Pain started 2 days back due to trauma to swelling by near teeth and patient consulted for the same.

On examination, swelling of size 5×4 cm extending from left side of floor of mouth extending from 31 regions till 38 regions involving left ventral aspect of tongue noted. Mucosa overlying the swelling appeared stretched. Ulcer of size 1×1 cm noted in floor of mouth opposite to 36, 37 with irregular margins, whitish halo, necrotic slough on base. On palpation, the swelling was non-tender, firm, immobile (Figure 2). A provisional diagnosis of malignant salivary gland neoplasm was made based on clinical examination.

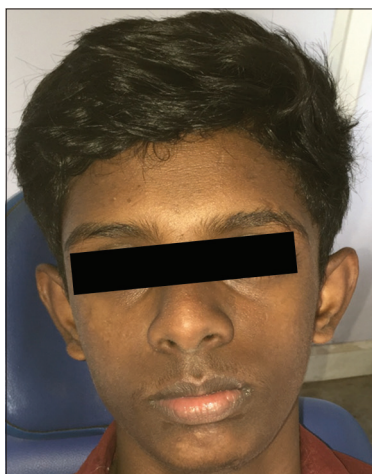


Figure 1: Extraoral view of the patient



Figure 2: Intraoral photograph showing swelling left floor of mouth causing tongue deviation and traumatic ulcer lingual to 46

Ultrasonographic examination of swelling was done with 8-12 MHz transducer. Sonographically, a well-defined ovoid heterogenous predominantly hypoechoic solid lesion with infiltrating margins noted in floor of mouth, extending just left of midline without significant cystic components noted (Figure 3).

Fine-needle aspiration cytology report revealed a round cell lesion with atypical features. Computed tomography (CT) features were that of a large ill-defined soft tissue mass lesion in the region of floor of mouth on left side, occupying the region of sublingual gland. The lesion was causing mass effect, displacing tongue to left side. In post contrast CT image, mild, relatively homogenous enhancement of lesion noted to a density of about 70-90 HU. The lingual artery was displaced posteromedially and stretched by the lesion. Furthermore, there was mild narrowing of oropharynx on left side. Mildly enlarged bilateral submandibular lymph nodes also noted (Figure 4). In magnetic resonance imaging (MRI), the lesion was heterogeneously hyperintense, compared to the musculature of the tongue, showed few markedly hyperintense areas, possibly cystic areas. The submandibular gland was seen separate from the lesion. A tongue-like extension was noted posterosuperiorly to

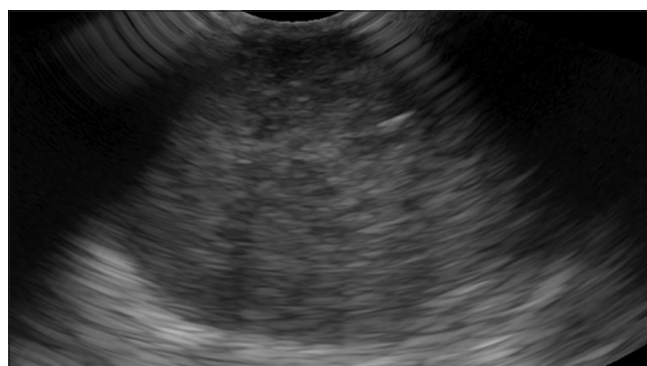


Figure 3: Ultrasonogram-Heterogenous architecture with internal hypoechoic foci

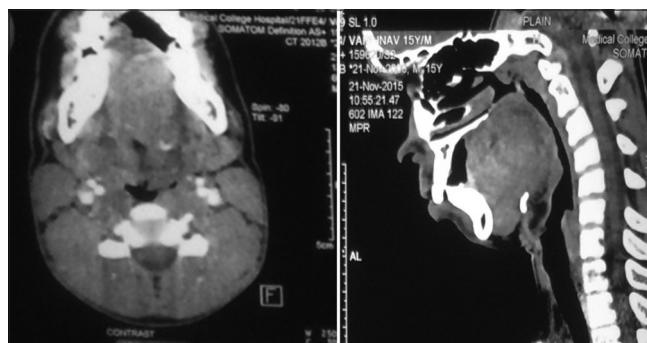


Figure 4: Postcontrast computed tomography showing large lobulated soft tissue mass lesion in floor of mouth on left side, possibly infiltrating the intrinsic and extrinsic muscles of tongue with mild enhancement

retromolar trigone and perineural extension of lesion suspected. Hence, a differential diagnosis of adenoid cystic carcinoma/schwannoma was given.

Incisional biopsy was done. Histopathology was consistent with malignant round cell neoplasm possibly PNET/ES. Immunohistochemistry showed CD99 (MIC 2) diffuse strong membrane positivity. Tumor cells were negative for LCA, desmin, and synaptophysin (Figure 5).

To assess disease status, high definition whole-body positron emission tomography (PET)/CT scan was taken. As per PET/CT, no evidence of any abnormal metabolism noted elsewhere in body. The patient responded well to chemotherapy consisting vincristine, adriamycin, and cyclophosphamide. After 12 cycles of chemotherapy, repeat PET scan was taken and no evidence of metastasis noted. After 1-year follow-up, repeat PET scan was taken and no evidence of metastasis was detected (Figures 6 and 7).

## DISCUSSION

Extraosseous ES of the sublingual gland is an extremely rare soft tissue swelling. It was first described by Tefft *et al* in 1969 in four patients who had paravertebral soft tissue tumors with a histologic appearance resembling ES.<sup>7</sup> EES is usually seen in the second or third decades.<sup>7</sup> EES has equal frequency in both males and females as contrasted with ES of bone, where the male to female ratio is 2:1.<sup>7</sup> The sites commonly involved are soft tissues of the trunk (particularly paravertebral region) or lower extremities.<sup>7</sup>

Clinically, about 75% of the patients with EES present with a rapidly enlarging swelling which is usually less painful than its skeletal counterpart. It has a high propensity to spread locally, infiltrating fascial planes, and invading muscles and bone.<sup>5</sup> Lymphadenopathy indicating nodal metastasis is rare, reported in 0-12% of cases. In our case, there was metastatic change in level 2c lymph node.

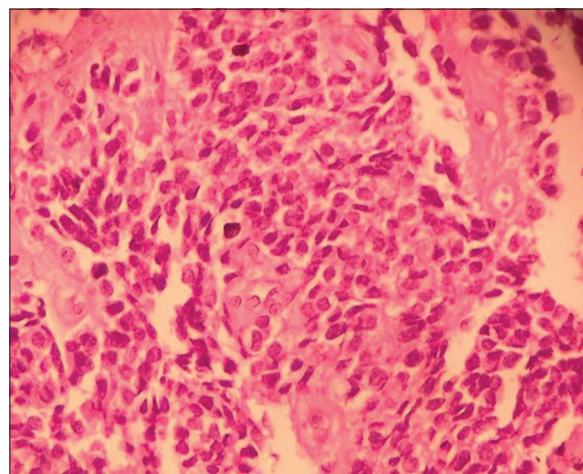
High-resolution CT and MRI scans are useful in the diagnosis and surgical planning although the features are not specific for EES. On MRI, the tumor is usually isointense to the muscles on T1W and hyperintense on T2W images, with enhancement on postcontrast scans. In this case, the tumor was hyperintense. Although generally valuable in head and neck surgery, fine-needle aspiration cytology has limited diagnostic accuracy for the definitive diagnosis.

The classical histopathological features of ESFT consist of uniform round cells, with irregularly shaped chromatic nuclei surrounded by scanty cytoplasm. Mitotic figures may be seen. Special cellular arrangements, such as rosettes or

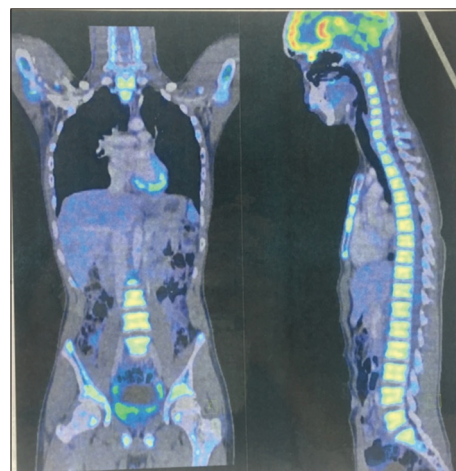
differentiations, are not often seen. The cells often show immunohistochemical positivity for various neurofilaments, CD-99, and S-100. In our case, CD-99 was positive.

ES/PNET arising from the sublingual gland is only rarely reported, so there is a need to differentiate it from other tumors arising in this region. Schwannomas (Neurilemmoma/neurinoma) are well-encapsulated, slow-growing benign nerve sheath neoplasms are seen as central low-signal foci with an enhancing periphery on postcontrast T1W images.<sup>7</sup>

There are significant differences in clinical presentation, treatment strategy, and outcomes for EES compared to skeletal ES. EES may require different treatment strategies. Depending on the site of the tumor and its extension, treatment can be with surgery, chemotherapy, and



**Figure 5: Histopathology-Infiltrative neoplasm composed of cells arranged in diffuse sheets and cords. Cells have moderate scanty eosinophilic clear cytoplasm. Irregular round oval hyperchromatic nuclei. Immunohistochemistry shows CD99 [MIC 2] diffuse strong membrane positivity**



**Figure 6: positron emission tomography scan showing no evidence of metastasis**





**Figure 7: Post treatment follow-up after 1 year showing regression of lesion**

radiotherapy used separately or in various combinations. Our patient responded favorably to chemotherapy.

### Treatment

Neoadjuvant chemotherapy is the standard of care before definitive radiation or surgery for localized disease. ESS is unique among sarcoma in that primary and metastatic diseases can respond dramatically to initial therapy with robust initial responses predicting a better outcome. PET/CT can play an important role in treatment response assessment because patients can show metabolically inactive tumor with reduced bulk.

### CONCLUSION

In conclusion, the present case highlights a rare case of EES/PNET in the second decade of life and presented

as swelling floor of mouth. The mass was seen to involve sublingual gland. Multiple imaging modalities such as US, CT, MRI, and PET-CT were used for diagnosis, and the definitive diagnosis was made by histopathological and IHC examination. MRI and PET-CT played a complimentary role in assessing local tumor resectability and presence of metastatic disease. Diagnosis could be established only after a biopsy. The complaints resolved following chemotherapy.

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# Closure of Oroantral Communication Using Buccal Advancement Flap: A Case Report

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## Abstract

The term oroantral communication (OAC) is an abnormal communication between the oral cavity and the maxillary sinus, which mostly occurs as a result of extraction of upper premolars and molars. This may, subsequently, lead to the formation of oroantral fistula if left untreated at an early stage. The fistula may close spontaneously due to swelling of the gingival tissue but in very rare cases. The maxillary sinus occupies an important place in oral and maxillofacial surgery owing to its anatomical proximity to the teeth. The hard palate and the alveolar process form the floor of the maxillary sinus. Passage of microflora from the oral cavity into the maxillary sinus occurs with the presence of fistula. In children and adolescents, the risk of OAC is less, due to smaller volume of the maxillary sinus. Surgical treatment to close the communication should be done at an early stage after thorough evaluation and planning.

**Key words:** Buccal flap, Maxillary sinus, Oroantral communication

## INTRODUCTION

The largest part of the upper jaw is taken up by the maxillary sinus, which is also known as antrum of Highmore after the name of anatomist Nathaniel Highmore who first defined the sinus as a space in the bone and called it as antrum.<sup>1</sup> Oroantral communication (OAC) is a common complication seen after the extraction of maxillary premolars and molars, where the sinus floor is close to the root apices and the maxillary sinus is separated by a thin bony lamella.<sup>2,3</sup>

Normal sinus mucosa thickness ranges in between 1 and 7 mm.<sup>4</sup> Periapical infections and cysts lead to resorption of the bony floor of the sinus which increases the risk of OAC. It can also occur due to trauma and iatrogenically while performing sinus lift procedures and placing dental implants, etc., epithelialization of this pathological communication leads to the formation of oroantral

fistula (OAF). Openings which are <2 mm may heal spontaneously whereas larger openings require surgical intervention. In 1957, Martensson considered that there is minimal possibility of spontaneous healing when the OAF is persistent for 3-4 weeks or fistulae with diameter >5 mm.<sup>5</sup> There are many techniques for the closure of OAC including buccal or palatal alveolar flaps and their modifications. The preferred technique depends on surgeons past experience and expertise.

## CASE REPORT

A 40-year-old<sup>6</sup> male reported with the chief complaint of aspiration of oral fluids into the nasal cavity and halitosis. Past dental history revealed extraction of maxillary premolar tooth 12 days back. Clinical and radiographic investigation revealed oroantral communication (Figure 1). Patient was briefly explained about the treatment plan, and pre-operative medications were advised. Surgery was done on the next day under local anesthesia; two vertical releasing incisions having a trapezoidal shape were placed, and buccal flap was raised. The palatal flap was also elevated. Socket lining was debrided; curettage was done to remove any epithelial lining or infected tissue, and fresh bleeding was induced in the socket. The buccal flap was placed over the socket and sutured to palatal flap

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using interrupted 3-0 silk sutures (Figure 2). Releasing incisions in the buccal flap were also sutured. Post-operative instructions and medications including nasal decongestant spray were advised. Periodic follow-up was done. Healing

was uneventful with no aspiration of fluids in the nasal cavity after 4 months of follow-up (Figure 3).

## DISCUSSION

In choosing the surgical approach for closure of OAC, different parameters must be considered, including location, size of the defect as well as height of the alveolar ridge, persistence, sinus inflammation and patient's general condition. Most of the surgical techniques to close the OAC and OAF rely on mobilizing the tissue and advancing the resultant flap into the defect. The advantage of the buccal flap to close the OAC is its possible utilization when the fistula is located in more mesial area as in our case.<sup>7</sup> The loss of buccal vestibule may require an additional vestibuloplasty indenture wearing patients. In addition to the use of various flaps for closure, the use of some alloplastic materials has also been documented. Zide and Karas used blocks of hydroxyapatite to close the communication by filling the bone defect in the alveoli.<sup>8</sup> Infection of the maxillary sinus if any must be treated before surgical intervention, as the infection may cause delayed healing and bone graft failure. Due to patient's economic status, the option of using autogenous bone graft to fill the defect was kept for the 2<sup>nd</sup> surgery (if required); in case of failure of the flap alone to close the defect satisfactorily. However, the patient was fully satisfied and there were no symptoms of OAC present on 4<sup>th</sup> month's follow-up. This technique of buccal flap closure was innovative and successful for treating mild OAC.

## CONCLUSION

Treatment options for OAC include various local and free soft tissue flaps with or without bone grafting, and the best method should be emphasized upon to achieve proper closure. Strict instructions should be given to the patient to avoid creation of negative pressure in the oral cavity and nasal decongestants/steroidal anti-inflammatory spray should be prescribed to avoid any infection in the nasal cavity; which delays healing. While suturing the flaps, only non-cutting needle should be used to avoid tearing of the flap.

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**Figure 1: Intraoperative picture showing oroantral communication**



**Figure 2: Intraoperative picture showing the sutured flap over the defect**



**Figure 3: Follow-up picture on 4<sup>th</sup> month showing completely closed defect and healed tissue**

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# Odontoameloblastoma of Maxilla - A Rare Odontogenic Entity Mimicking Fibro-osseous Lesion: A Case Report

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## Abstract

Odontoameloblastoma (OA) is an exceedingly uncommon odontogenic tumor that contains an ameloblastomatous component and odontoma like elements. It is characterized by slow-growing lesion with growth pattern similar to solid multicystic ameloblastoma. The majority of the tumors are associated with unerupted teeth and commonly seen in males. It is usually asymptomatic and may occur in either maxilla or mandible but shows a slight predilection for the mandible. As this tumor is extremely rare, there exists controversy regarding its development and treatment. Here, we present a case of OA in 20-year-old male patient resembling a fibro-osseous lesion and a brief review of the related literature.

**Key words:** Maxilla, Odontoameloblastoma, Odontogenic tumor, Odontoma

## INTRODUCTION

The odontoameloblastoma (OA) is an extremely rare neoplasm, which is defined in the current WHO histological classification of odontogenic tumors as a tumor that “includes odontogenic ectomesenchyme in addition to odontogenic epithelium that resembles an ameloblastoma both in structure and behavior.”<sup>1</sup>

It usually occurs between 6 months and 40 years predominantly involving mandible with a predilection for molar-premolar region.<sup>2,3</sup> It is an expansile centrally destructive lesion exhibiting slow growing characteristics like ameloblastoma and if left untreated may cause substantial facial deformity. Symptoms include a slowly progressive swelling of the alveolar plates, dull pain, an altered occlusion, delayed eruption, or impacted teeth.

Radiologically the tumor presents as a well-defined unilocular or multilocular radiolucent cavity containing varying amounts of radiopaque material, which may or may not bear resemblance to formed teeth. It may also be in the form of small, dense particles or as a large central mass leading to divergence of adjacent tooth roots.<sup>2,4</sup>

We are presenting a case of OA in the posterior region of the right maxilla of a 20-year-old male.

## CASE REPORT

A 20-year-old male reported with a chief complaint of a slow growing swelling in his right mid face region for 1 year (Figure 1a). The swelling was asymptomatic but was causing discomfort while speaking and eating. The swelling was gradually increased in size and reached to present size. Intraoral examination revealed a diffuse swelling on palate extending from 11 tooth region to the right maxillary tuberosity obliterating the vestibule. There was the absence of 13, 15, 16, 17 teeth for last 6 months. The swelling was firm, nontender, nonfluctuant, nonpulsatile, and smooth on palpation. The overlying mucosa overlying mucosa was normal in color and texture.

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Computed tomography scan showed a diffuse lesion that produced marked destruction of bone and contained abundant dense and irregular foci of mineralized tissue surrounded by radiolucent areas. The tumor extended upwards to involve the floor of the orbit. Displacement of the lateral nasal wall with obliteration of maxillary sinus (Figure 1b).

The patient was advised for biopsy, and the histopathological feature revealed multiple ameloblastic islands arranged in follicles in a scanty fibro-connective tissue stroma containing numerous small and large areas of calcified mass resembling dental hard tissues such as dentine, osteodentin, cementum with a variable amount of primitive mesenchymal tissue (Figure 2). A histological diagnosis of

OA was given. Then, the patient was operated at a later date, and the tumor was excised. The gross specimen (Figure 1c) was showing multiple grayish white hard and soft tissue specimen (m) about 6 cm × 3 cm. On microscopic examination of excised tumor showed the features of OA same as in incisional biopsy specimen. Hence, the final diagnosis confirmed as OA of right maxilla. The post-operative recovery was uneventful, and after 1 year follow-up, the patient was normal with no evidence of recurrence.

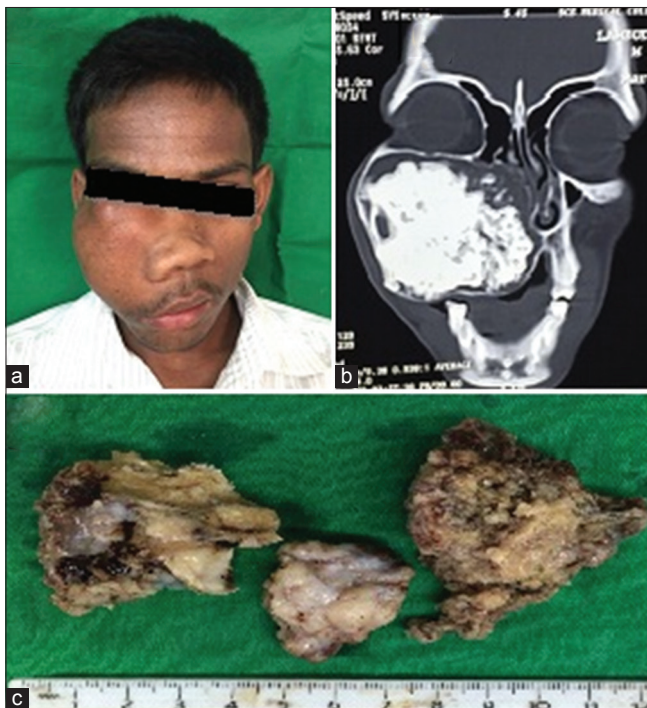
## DISCUSSION

The OA, also known by some authors as ameloblastic odontoma,<sup>5,6</sup> is a very rare mixed odontogenic neoplasm, characterized by the simultaneous occurrence of an ameloblastoma and a compound or complex odontoma in the same tumor mass.<sup>1,4</sup> The epithelial proliferation forms ameloblastic islands in follicular or plexiform patterns typical of ameloblastoma but, unlike conventional ameloblastoma, these induce the production of mineralized dental tissues on the adjacent mesenchymal cells and may respond to this changes with the production of enamel.

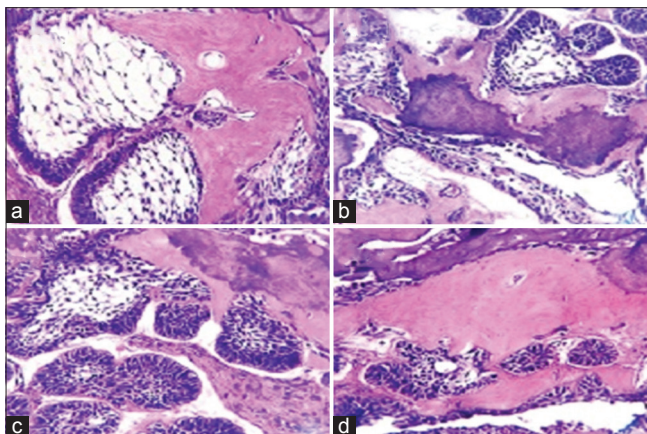
Although there are various case reports of this condition, several authors agree that only a few of them met the histologic and clinical criteria to be classified as OA,<sup>4,5,7,8</sup> which is supported by the present study. The histopathological features of the OA are complex. There is a proliferating odontogenic epithelium portion similar to that of an ameloblastoma, generally presenting a plexiform or follicular pattern. This epithelial portion appears intermingled with dental tissues of variable degrees of maturity in the form of developing rudimentary teeth, resembling a compound odontoma or conglomerate masses of enamel, dentin and cementum, as seen in a complex odontoma.<sup>9</sup> Kaugars and Zussmann<sup>5</sup> have suggested following criteria for the histological diagnosis of OA - (a) unequivocal ameloblastoma, (b) connective tissue with a mature homogenous appearance, and (c) fragments of malformed calcified dental structures.

The case presented here exhibited all the histopathological features of OAs. In this case, the dental tissue was represented by masses of dentin and cementum. Enamel matrix, however, was not observed.

From a clinical and radiographic point of view, the differential diagnosis includes several odontogenic and non-odontogenic well-defined unilocular or multilocular radiolucencies with varying amounts of radiopaque material within them. These include developing compound or complex odontomas, ameloblastic fibro-odontoma, calcifying epithelial odontogenic tumor, calcifying odontogenic cyst, adenomatoid odontogenic tumor, and cemento-ossifying fibroma. OA radiologically mimicking



**Figure 1: (a) Clinical picture. (b) Computed tomography scan axial view showing extension of the lesion. (c) Excised gross specimen**



**Figure 2: (a-d)-Histopathology (H and E, x400)**

**Table 1: Clinico-pathological comparison between odontameloblastoma and ossifying fibroma**

Odontameloblastoma	Ossifying fibroma
1. Age - 6 month-40 years	1. 30-40 years
2. Sex - Male>Female	2. Female>Male
3. Site - Mandible>maxilla	3. Mandible>maxillaoma
4. C/F-painless mass associated with a delayed eruption	4. Asymptomatic expansile slow growing
5. Biological behavior-locally aggressive	5. Benign behavior
6. Radiographic-well-defined unilocular/multilocular radiolucency having varying amounts of radiopaque material resembling dental hard structures with the features of a complex odontoma	6. Well-defined circumscribed border, expanded cortex, heterogeneous calcification medullary pattern
7. Histopathology-ameloblastoma with odontoma like features	7. Cellular fibrous stroma, islands of new bone formation, relatively homogenous pattern
8. Treatment-enucleation and resection	8. Curettage/excision
9. Prognosis-high rate of recurrence	9. Recurrence – rare
10. Source-odontogenic origin	10. Non-odontogenic

with fibro-osseous lesion like ossifying fibroma, but here, we try to speak out some clinico-radiological feature to differentiate OA from ossifying fibroma (Table 1).

The pathogenesis of OA is unknown. One possible explanation is that the mineralized dental tissues are formed as a hamartomatous proliferation in response to inductive stimuli produced by the proliferating epithelium over the mesenchymal tissue.<sup>4</sup>

Wächter *et al.*<sup>10</sup> compared four cases of OA with 14 cases of ameloblastic fibro-odontoma and found that there are no clear cut histological criteria to separate these two lesions. However, solid/multicystic ameloblastoma like structures was more characteristic for the OA, whereas ectomesenchymal component was more pronounced in the ameloblastic fibro-odontoma.

The potential for OA to recur is well known. In fact, Yamamoto *et al.*<sup>11</sup> demonstrated a high proliferation potential of the OA based on the expression of tenascin in the basement membrane of the odontogenic epithelium of this tumor and on the results obtained with proliferating cell nuclear antigen staining indicate that this tumor may have the same biologic potential as that of an ameloblastoma and should, therefore, be treated and followed-up in a similar fashion.<sup>9,12</sup> In the review by Mosqueda-Taylor *et al.*,<sup>12</sup> 3 of 14 cases recurred (21.4%), which was a similar figure to that found by Reichart *et al.*<sup>13</sup> for ameloblastoma.

## CONCLUSION

OA may be clearly recognized and distinguished from other mixed odontogenic tumors. Although it tends to occur at

a prior age than conventional ameloblastoma, it has the same potential to produce bone expansion, root resorption, and recurrence. Pre-operative clinico-radiological diagnosis is more challenging than histopathological diagnosis for suitable treatment planning. OA should be treated as locally aggressive lesions with periodic follow-up.

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# Management of Facial Laceration in a Child Resulting from Animal Conflict

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Animal conflict wounds or bite wounds are commonly located on face, owing to its prominence. Emergency centers around the world attend around eleven million cases of skin lacerations yearly. Out of this 1-2 million cases involve conflict with domestic animals including cats, dogs, bulls, etc. Although exact numbers are not clear due to lack of compulsory reporting of such injuries, their repercussion and importance should not be underestimated.<sup>1,2</sup> Bacteriology of these wounds and lacerations includes broad spectrum of microorganisms. Initial management of facial laceration includes proper irrigation and debridement to avoid any infection. These facial lacerations have disfiguring effect with depressing psychological repercussion to the patient. Children are frequently involved in animal conflicts due to their provocative behavior or short stature, which exposes their face closer to animal's reach.<sup>3</sup>

This article presents a case of facial laceration and its management; which would be of interest to all the professionals including dentists, maxillofacial surgeons who deal with facial tissues.

A 10-year-old male child was referred to our center from a primary health center in a remote hamlet with a wide facial laceration extending from the right body of mandible extraorally to lower lip (Figure 1). Treatment of lacerations due to animal conflicts or bite consists mainly of proper wound cleaning to diminish the chances of life-threatening infections as well as administration of adequate antibiotics. Parents of the child reported the cause of laceration to be a conflict of the child with



Figure 1: The extent of laceration in the right cheek region



Figure 2: The sutured laceration under local anesthesia

their domestic bull; whose horns caused a deep laceration on child's right cheek. The patient was administered tetanus prophylaxis at primary hospital. In a child who follows immunization calendar, tetanus injection may not be necessary as compared to adults who should get the vaccine administered if there is 5 years gap. Primary evaluation of patient was carried out and was found to

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be hemodynamically stable. Facial examination revealed a laceration involving skin and mucosa in the right cheek and labial region, with no signs of arterial bleed. Facial artery which runs in close approximation to the present laceration was found to be intact. No bony or dental fracture was present. Closure of the laceration was planned under local anesthesia, as the patient was young. Wound was copiously irrigated using saline, hydrogen peroxide, and povidone-iodine solution. Wound debridement was done which significantly reduces the chances of infection.<sup>4</sup> Wound closure was done in layers using 3-0 vicryl and 4-0 ethicon for skin closure (Figure 2). Systemic antibiotics, analgesics, and topical ointments were advised. The patient was followed up periodically, and healing was uneventful (Figure 3). Sutures were removed on the 8<sup>th</sup> post-operative day. Patient and his parents were very much satisfied with the results and minimal pain while operating.

#### Points to Ponder

- Brisk irrigation and elimination of foreign material are of vital importance as the human animal conflicts involve dirt, grass, etc., which may cause severe infections.
- Topical antibacterial ointments help in maintaining moist environment which inhibits the formation of scab; which impairs epithelization.
- Possible care should be taken to minimise post-operative disfiguration and an ugly scar and if



**Figure 3: Post-operative follow up picture after suture removal with topical ointment**

required secondary correction surgery should be performed.

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