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# Bangladesh Medical College Journal

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# Recent worst Dengue outbreak in Bangladesh

B Nilufar

Dengue is among the most important human diseases caused by mosquito-borne viruses. The global prevalence of dengue has grown dramatically in recent decades. The disease is now endemic in more than 100 countries in Africa, the Americas, the Eastern Mediterranean, the Western Pacific and particularly in Southeast Asia. The World Health Organization (WHO) estimates that more than 2.5 billion people are at risk of dengue virus infections with 50 to 100 million cases occurring annually. Among these infections, approximately 500,000 cases are dengue hemorrhagic fever (DHF), with 24,000 deaths which mostly occur in children. More than 40% of the world's population lives in dengue endemic areas. A vast majority of cases are asymptomatic and hence the actual numbers of dengue cases are under reported and many cases are misclassified. Dengue is found in tropical and sub-tropical climates worldwide, mostly in urban and semi-urban areas. Local variations are influenced by rainfall, temperature and unplanned rapid urbanization.

Today, severe dengue affects most Asian countries and has become a leading cause of hospitalization and death among children and adults in these regions. Children contribute to a large proportion of the severe disease cases. There is no specific treatment for dengue/ severe dengue, but early detection and access to proper medical care lowers fatality rates below 1%. The seasonal prevalence is during the monsoon season which runs from June to September. Typically, an epidemic of one serotype is followed a few years later by an epidemic with one of the others. Once humans are infected, humans become the main carriers and multipliers of the virus & serve as a source of the virus for uninfected mosquitoes.

Dengue fever was first observed in Bangladesh in 2000, claimed 93 deaths in that year. However it struck again in 2018, killed 26 and affected 10,148 people. The 2019 dengue outbreak in Bangladesh is a worst & severe outbreak of dengue fever that began at April and is still ongoing. This year, dengue fever outbreak was alarming in Bangladesh. On a single day in August, nearly 2,500 patients tested positive of dengue and were admitted in hospitals. The number of dengue patients identified across Bangladesh this year so far is nearly double of the total diagnosed with the mosquito-borne disease recorded in the past 19 years. DGHS has also confirmed, a total 91,866 people were hospitalized throughout the country (Till 13.10.19). Besides, although being an urban disease, dengue had a strong presence in the rural areas of the country as well this year.

There are 4 serotype of Dengue virus designated as DEN-1, DEN-2, DEN-3 and DEN-4. All 4 serotypes have single stranded RNA as genome. The RNA genome contains 3

structural genes and 7 non-structural genes. Non-structural gene codes for non-structural proteins which helps in viral replication. One of the nonstructural protein NS1 is the only protein that is continuously secreted by infected host cells & plays an important role in disease pathogenesis & diagnosis.

The first infection cause mostly minor disease, but secondary infections has been reported to cause severe diseases (DHF or DSS) in both children and adults. This phenomenon is called Antibody-Dependent Enhancement. Dengue virus infection causes aberrant immune responses which not only impair the immune response to clear the virus, result in overproduction of cytokines, as well as abnormal production of autoantibodies. Serotype cross-reactive antibodies from the previous infection bind to virions without neutralization and enhance the entry of virus into monocytes. As a result, the level of dengue virus-specific T cell activation is markedly enhanced which produce a storm of cytokines such as IFN- $\gamma$ , IL-2 and TNF- $\alpha$ . The simultaneous circulation of anamnestic IgG dengue antibodies and dengue viral antigens activates complement cascade which increase vascular permeability. The aberrant generation of anti-NS1 antibodies cross-react with platelet or endothelial cells is also thought to be responsible for thrombocytopenia & vascular leakage.

The *Aedes aegypti* mosquito is the primary vector of Dengue, though *Aedes. Albopictus* is also found to be involved in virus transmission. The distribution of dengue vectors, is affected by climatic factors. Since their life cycles are well adapted to the human environment, environmental changes resulting from human activity such as urbanization exert a great impact on vector distribution. Thus, the species is usually abundant in the indoors and urban areas in tropical countries and the close association with humans contributes largely to the effective transmission of dengue viruses.

Diagnosis involve both clinical evaluation & laboratory methods. Confirming dengue virus infection may involve detection of the virus, viral nucleic acid, antigens or antibodies, or a combination of these techniques. During the early stages of the disease, virus isolation, nucleic acid or antigen detection can be used to diagnose the infection. At the end of the acute phase of infection, serology is the method of choice for diagnosis. It is imperative to diagnose the disease during the early phase. Recently, the World Health Organization (WHO) has recommended the use of a rapid test to detect dengue NS1 antigen as it is simple to use and can provide results within 30 minutes. The accuracy of the NS1 antigen rapid test is considered high with sensitivity 55%-82% and specificity 97%-100%. It should be performed within 5 days of onset of fever. Anti-

Dengue IgM specific antibodies can be detected after 5 days of onset of fever & highest level achieved after 7 days. In primary Dengue Infection IgM will be more than IgG. In secondary Dengue infection, higher elevation of Anti Dengue Specific IgG antibodies & lower levels of IgM. To distinguish primary and secondary dengue infections, IgM/IgG antibody ratios are now more commonly used. Detection of nucleic acid by RT-PCR confirm diagnosis in less than <5 days of illness. Its sensitivity & specificity is 100%. This test is expensive & available only in referral centers. In addition some indirect tests are useful in management of patients like complete blood count, Haematocrit, other biochemical tests specially liver function tests. In Dengue shock syndrome coagulation profile is assessed.

The prevention or reduction of transmission of DENV is dependent on the control of mosquito vectors and limiting of human-mosquito contact. Personal protection and the environmental management of mosquitoes are important in preventing illness. Dengue vaccine is a vaccine used to prevent dengue fever in humans. As of 2019, one version is commercially available, known as CYD-TDV and sold under the brand name Dengvaxia. The vaccine is only recommended for use in individuals 9-45 years of age living in endemic areas & those who have previously had dengue fever or populations in which most people have been previously infected. The value of the vaccine is limited by the fact that it may worsen outcomes in those who have not previously been infected. Dengvaxia is a live, attenuated vaccine that is administered as three separate injections, with the initial dose followed by two additional shots given six and twelve months later.

In conclusion we can say that the outbreak of dengue occurred recently in Bangladesh is a manmade situation. Preparedness to prevent and control occurrence of dengue fever needs integrated and timely intervention by the concerned authority. Efficacy of vaccine is recommended to be tested by further investigation.

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# Isolation and Sensitivity Pattern of Blood Stream Organisms in a Selected Tertiary Care Hospital in Dhaka

Sharmin S<sup>a</sup>, Alamgir F<sup>b</sup>, Nahar A<sup>c</sup>, Hasnat S<sup>d</sup>, Begum N<sup>e</sup>

## Abstract

**Background:** There is wide variation of predominant organisms in blood cultures among different health care facilities. Bacterial aetiology and its resistance patterns vary from place to place. It is mandatory to know the local aetiological agent and its sensitivity pattern for better outcome of the patient.

**Objective:** To determine the prevalence of various microbes isolates in the blood & their antibiogram in Bangladesh Medical College Hospital.

**Methods:** This retrospective cross-sectional study was done by evaluating the results of blood samples sent for culture and sensitivity to the dept. of Microbiology of BMCH from January to June 2017. Samples were collected in BD BACTEC plus Aerobic/F and BD BACTEC peds plus /F bottle irrespective to antibiotics administration. They were incubated in the automated BACTEC 9120 for five days. Culture positive samples were accomplished by sub culture on Blood agar, Chocolate agar and MacConkeys agar media (OXOID CO.UK). Antimicrobial susceptibility tests were carried out by the Kirby-Bauer disc diffusion method using Muller Hinton agar media and antibiotic disc from OXOID CO. UK. Standard panel of antibiotic disc were tested for each organism.

**Results:** Total 2695 blood samples were analyzed; out of these 221 (8.2%) were bacteriologically positive. Among them Gram negative bacilli were 217 (98.1%). *Salmonella typhi* (72%) and *Salmonella paratyphi* (17.6%) were the predominant Gm negative bacilli. *Salmonella typhi* and *paratyphi* showed higher susceptibility to Ceftriaxone (97%), Amoxiclavate (98%), Ciprofloxacin (95%) and showed lower sensitivity to Azithromycin which were 42% and 23% respectively. *Escherecia coli* showed low sensitivity to Ciprofloxacin (45%) and Ceftriaxone (36%).

**Conclusion:** Isolation rate of blood culture was 8.2%, among the isolated organism *S.typhi* (72%) & *S.paratyphi* (17.6%) were predominant. *S.typhi* and *S.paratyphi* were almost resistant to Azithromycin.

**Keywords:** Isolation, Sensitivity, Blood stream organism, Blood culture, Antibiogram.

## Introduction:

Bacteremia & septicemia are one of the most significant serious infections which cause morbidity & mortality among hospitalized patients worldwide.<sup>1</sup> Diagnosis of these infections is concerned with the isolation & identification of

aetiological agent. Blood culture is the gold standard method to detect above conditions. Blood culture provides valuable information for the management of febrile, acutely ill patient with or without localizing signs and symptoms.

There is wide variation of predominant organisms in blood cultures among different health care facilities. Gram negative bacteremia can result septic shock and the mortality is even greater with high-grade bacteremia and polymicrobial infections.<sup>2</sup> Gram positive is also seen to be on the rise, especially in children.<sup>2</sup> The bacteremia which is caused by the Enterobacteriaceae family is associated with an increased mortality as compared to the Blood Stream Infection (BSI) caused by Gram positive bacteria.<sup>3</sup>

Bacterial aetiology and its resistance pattern vary from place to place. It is mandatory to know the local aetiological agent and sensitivity pattern for better outcome of the patient. Antimicrobial susceptibility test assists a great deal in precise identification of the most appropriate choice of drug administration in decreasing morbidity and mortality. The choice of antimicrobial therapy for blood stream infections is often empirical & based on the knowledge of local antimicrobial activity profile of the most common bacteria causing such infection.

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Therefore, the aim of the present study was to determine the prevalence of various microbes isolates in the blood & their antibiogram in Bangladesh Medical College Hospital.

## Material and Methods:

This retrospective study was carried out in the Department of Microbiology, BMCH from January to June 2017. All the blood samples sent for culture and sensitivity were evaluated. Data regarding the age, sex, pathogens, sensitivity were recorded. All samples were collected in BD BACTEC plus Aerobic/F and BD BACTEC peds plus /F bottle irrespective to antibiotics administration. Five to ten ml & one to five ml of blood from adult & children were collected respectively with all aseptic precautions describe in the manual of the manufacturer. Samples were incubated in the automated BACTEC 9120 for five days.

The preliminary signal of bacterial growth in BD BACTEC bottle was detected and displayed on the LED monitor of BACTEC 9120 system. Specific identification of all culture positive samples were accomplished by sub culture on Blood agar, Chocolate agar and MacConkeys agar media (OXOID CO.UK). Inoculated Blood agar and MacConkeys agar plates were incubated aerobically at 37°C. The Chocolate agar plates were incubated at 37°C under 5-10% CO<sub>2</sub> condition (candle jar) and examined after 18-24 hours of incubation. Gram's stain biochemical and serological test were done for final identification.

Antimicrobial susceptibility test was carried out by the Kirby-Bauer disc diffusion method using Muller Hinton agar media and antibiotic disc from OXOID CO. UK. Standard panel of antibiotic disc were tested for each organism. For quality control ATCC strains of *Staphylococcus aureus* (ATCC 25923) and *Escherichia coli* (ATCC25922) were used side by side. The zone sizes were measured and interpreted according to the CLSI standard.

## Results:

**Table 1:** Rate of culture positive and negative sample (n=2695)

Results of culture	Number	Percentage
Positive Growth of bacteria	221	8.2
No growth	2474	91.8
<b>Total</b>	<b>2695</b>	<b>100</b>

Of the 2695 blood samples which were sent for culture and sensitivity, 221(8.2%) were bacteriologically positive (Table-1).

**Table 2:** Distribution of positive specimen according to the age (n = 221)

Age	Number	Percentage
Adult	154	69.68
Children	67	30.32
<b>Total</b>	<b>221</b>	<b>100</b>

Among the isolated pathogens 217(98.1%) were Gram negative bacilli and 4(1.8%) were Gram positive. Out of these 2695, Children of less than 12 years were 30.31% and 69.64% were more than 13 years (Table-2).

**Table 3:** Distribution of bacterial pathogen in blood culture (n = 221)

Organism	Number	Percentage
<i>Salmonella typhi</i>	160	72.3
<i>Salmonella paratyphi</i>	39	17.6
<i>Eschericia coli</i>	11	5.0
<i>Staphylococcus aureus</i>	4	1.8
<i>Acinetobacter spp</i>	3	1.4
<i>Klebsiella spp</i>	2	0.9
<i>Enterobacter spp</i>	1	0.5
<i>Pseudomonus spp</i>	1	0.5
<b>Total</b>	<b>221</b>	<b>100</b>

Among the Gram-negative bacilli, Enterobacteriaceae families were predominant. The *Salmonella typhi* were isolated in 72.3% cases of BSIs followed by *Salmonella paratyphi* 17.6%, *Eschericia coli* 4.9%, *Staphylococcus aureus* 1.8% and others shown in Table-3.

**Table 4:** Antibiotic susceptibility patterns (%) of the isolates

Antibiotics	<i>S.typhi</i> (160)	<i>S.paratyphi</i> (39)	<i>E.coli</i> (11)	<i>Klebsiella</i> (2)	<i>Enterobacter</i> (1)	<i>Staphylococcus</i> (4)	<i>Acinetobacter</i> (3)	<i>Pseudomonas</i> (1)
Amoxicillin	73%	87%	-	-	-	0%	-	-
Amoxyclave	98%	-	91%	50%	0%	-	-	-
Ceftriaxone	97%	95%	36%	50%	100%	0%	100%	100%
Cefradine	97%	59%	27%	0%	0%	100%	-	-
Ciprofloxacin	95%	100%	45%	50%	100%	100%	100%	100%
Cotrimoxazole	75%	74%	36%	100%	100%	100%	-	-
Ceftazidim	-	-	73%	0%	100%	-	100%	100%
Cefuroxime	97%	51%	18%	-	0%	-	33%	0%
Cefixime	89%	85%	-	-	-	-	-	-
Cefipime	96%	97%	-	50%	-	-	-	-
Micelinum	-	-	0	-	0%	-	100%	100%
Azythromycin	42%	23%	-	0%	-	50%	-	-
Nalidixic acid	56%	5%	0%	0%	100%	-	-	-
Chloramphenicol	100%	100%	-	-	-	-	-	-
Cloxacillin	-	-	-	-	-	25%	-	-
Methycillin	-	-	-	-	-	0%	-	-
Erythromycin	-	-	-	-	-	100%	-	-
Vancomycin	-	-	-	-	-	100%	-	-
Lincolid	-	-	-	-	-	100%	-	-
Imipenem	-	-	0%	100%	100%	100%	100%	100%
Meropenem	-	-	0%	100%	100%	75%	-	-
Gentamicin	-	-	0%	50%	100%	100%	100%	0%
Amikacin	-	-	0%	50%	100%	100%	100%	100%
Netilmycin	-	-	0%	50%	100%	100%	100%	0%
Carbepenem	-	-	-	-	-	-	100%	0%
Aztreonam	-	-	0%	100%	100%	100%	100%	100%
Pipercillin	-	-	-	-	-	-	100%	100%
Colistin	-	-	-	-	-	-	0%	0%

Antibiotic sensitivity pattern of isolated organism showed in Table-4. *Salmonella typhi* and *Salmonella paratyphi* showed higher susceptibility to Ceftriaxone (97%), Amoxiclavate (98%) and Ciprofloxacin (95%). *Escherichia coli* showed higher susceptibility to amoxicillin (91%) and Ceftazidime (73%) but Ciprofloxacin and Ceftriaxone showed low sensitivity to *Escherichia coli* which were 45% and 36% respectively. *Staphylococcus aureus* were sensitive to most of the drugs. *Klebsiella spp* 100% sensitive to Ceftazidim. *Acinetobacter spp* were hundred percent sensitive to Ceftriaxone, Ciprofloxacin, Ceftazidime. Sensitivity pattern of *Salmonella typhi* and *Salmonella paratyphi* to Azithromycin were 42% and 23% respectively.

## Discussion:

Though blood culture is the gold standard for blood stream infection but its isolation rate is low and variable from place to place. This study was conducted to see the isolation rate and pattern of organism and their sensitivity in BMCH which is a tertiary care hospital. In this study isolation rate of bloodstream infection organism was 8.2%. A study from a tertiary care hospital in Kathmandu, Nepal reported 12.6% of blood culture positivity rate.<sup>4</sup> Other studies from Nepal and Ethiopia showed isolation rate of 6.9% and 8.8% respectively.<sup>5,6</sup> A very recent study done in South India also showed 8.93% culture positive samples.<sup>7</sup> A large proportion of patient presenting at tertiary care hospital are already treated with antibiotic elsewhere previously. This may be the cause of low positive yield in blood culture.

In this study most of the isolates were Gm negative organism (98%) in contrast to Gm positive organism (2%). Similar picture was found in other studies done in Nepal, India, Dhaka.<sup>4,8,9</sup> But this is different from the study results done in Ethiopia, Addis Ababa where they have found 60.9% and 62.66 of Gm positive organism as compared to 39.1% and 37.4% of Gm negative.<sup>6,10</sup> The possible explanation of this difference could be the difference in geographical location, nature of the patient population, epidemiological difference of the etiological agents, and seasonal variation.

Present study found *Salmonella typhi* (72%) as most common organism followed by *S.paratyphi* (17.6%). Study from a renowned lab at the center of Dhaka city showed 67% of *Salmonella species* among all isolates followed by *S. paratyphi* 22.2%.<sup>11</sup> Study from Nepal, found *S. typhi* 41% followed by *S. paratyphi* 11%.<sup>5</sup> In our hospital detection rate of *Staphylococcus aureus* was only 2% and study from Ethiopia was found 21.7%.<sup>6</sup> There are variation of isolation rate of *Staphylococcus aureus* from country to country and even in same country region to region like it was high in one region of Nepal (16%).<sup>4</sup> But low isolation rate (4%) were reported from another region of Nepal and of (0.28%) from one large lab of Dhaka city.<sup>5,11</sup>

There is no much divergent in sensitivity pattern of pathogen in respect to place to place in this region. *S. typhi* and *S.paratyphi* were noted to be susceptible to the most of the antibiotic like Amoxiclav (98%), Ceftriaxone (97%), Ciprofloxacin (95%), Cefixime (89%). Hundred percent of *S.typhi* were sensitive to Chloramphenicol. Reports from Nepal, and Dhaka showed more or similar sensitivity pattern.<sup>4,11,12</sup> Cotrimoxazole was sensitive to 75% of both *S.typhi* and *S.paratyphi* in our finding but study from BSMMU showed Cotrimoxazole was sensitive to 50% of *S.typhi* and 90% *S.paratyphi*.<sup>9</sup> Sensitivity pattern of *S.typhi* and *S.paratyphi* towards Azithromycin was high 82% in 2007 reported from BSMMU<sup>9</sup> but now we have found its low sensitivity pattern to *S.typhi* and *S.paratyphi* which was 42.5% and 23% respectively. Now a day's prescription of cotrimoxazole by our physician almost nil in our community which may increase its sensitivity pattern in contrast over use and misuse of Azithromycin decrease its sensitivity to *S.typhi* and *S.paratyphi*.

## Conclusion:

Low isolation rate (8.2%) of Blood stream organisms even in a high quality Microbiology laboratory indicates importance of timely investigation for bacterial flora of the blood before using antibiotic. Among the isolated organism *S.typhi* (72%) and *S.paratyphi* (17.6%) were predominant. It is also important to see the sensitivity pattern of organism as it is changing like *Salmonella* is most resistant to Azithromycin as found in this study.

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# Effect of Ramadan Fasting on Some Selected Metabolic Hormone Status in Healthy Adult Male

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## Abstract

**Background:** During Ramadan fasting Muslims abstain from food, drink, smoking each day from dawn to sunset. Frequency and quantity of having food and daily physical activities are changed during Ramadan fasting. Therefore, it has some anthropometric, metabolic and physiological effects on the healthy adult male subjects.

**Objective:** To observe the effects of Ramadan fasting on some selected metabolic hormone status in healthy adult male.

**Methods:** This longitudinal type of descriptive study was carried out in the Department of Physiology, Sir Salimullah Medical College (SSMC), Dhaka between January to December 2013. A total number of 60 healthy adult male subjects age ranged 24 to 28 years were selected in this study. They were selected on the basis of inclusion and exclusion criteria. All the subjects were the intern doctors of Sir Salimullah Medical College and Mitford Hospital, Dhaka. They were studied for two times i.e. 1-3 days before Ramadan fasting (BRF) and 25<sup>th</sup>-27<sup>th</sup> days of Ramadan fasting (ARF) accordingly. For assessing metabolic hormone levels serum cortisol and FT<sub>4</sub> levels were estimated by enzyme linked immunosorbent assay (ELISA) method. The statistical analysis was done by using paired sample 't' test as applicable.

**Results:** In this study, the mean body weight (BW), BMI, serum cortisol and serum FT<sub>4</sub> levels were significantly ( $p < 0.001$ ) decreased after 25<sup>th</sup>-27<sup>th</sup> days of Ramadan fasting than those of 1-3 days before Ramadan fasting.

**Conclusion:** The results of the present study revealed that Ramadan fasting has got some beneficial effects on metabolic hormone levels in healthy adult male.

**Keywords:** Ramadan fasting, Metabolic hormone, Serum cortisol, Serum FT<sub>4</sub>, Healthy adult male

## Introduction:

The word Ramadan comes from the Arabic root ramida or ar-ramad, which means scorching heat or dryness.<sup>1</sup> Holy Ramadan is the ninth month in the lunar calendar.<sup>2</sup> It lasts 29-30 days based on visual sightings of the crescent moon.<sup>1</sup> Ramadan is observed by over 400 million of Muslims throughout the world. Ramadan teach Muslims self-restraint and remind them of the feeling of the impoverished.<sup>3</sup>

During Ramadan Muslims abstain from food, drink, smoking each day from dawn to sunset.<sup>2</sup> They take two meals per day, Iftar at sunset and Sehri before dawn.<sup>4</sup> The timing of daily fasting varies due to geographic location of the country and the season when Ramadan fall as lunar calendar moves forward by about 11 days every year and it lasts about 12 to 19 hours each day.<sup>5</sup>

Our Prophet Muhammad (Sallallahu Alaihe Wasallam) has observed non-obligatory fasting on different days in a year. The non-obligatory fasting can be observed up to 15 days per month.<sup>6</sup> and almost 5 months in a year. The obligatory fasting along with the non-obligatory fasting have some beneficial effects on obesity prevention and its related problems like cardiovascular, hypertension and diabetes mellitus.<sup>7</sup>

During Ramadan, Muslims eat a greater variety of foods in their meals than in other months.<sup>5</sup> Many physiological and psychological changes of human subjects take place due to changes in eating patterns.<sup>8</sup> The individual life style may be influenced by variations in sleep pattern, activity, eating pattern and hydration status. Spiritual Ramadan fasting beneficially affects the mental and emotional health of individuals.<sup>4</sup>

Stress is the body's reaction to a change that requires a physical, mental or emotional adjustment. The hormones responsible for stressful conditions are adrenaline, noradrenaline and cortisol etc. Stress causes depression

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clumsiness, feeling of disqualified, pessimism and dissatisfying. The rhythmic or periodic secretion of cortisol is maintained by suprachiasmatic in hypothalamus and under control of hypothalamus-pituitary-adrenal glands. Normally, early in the morning, serum level of these hormones increase and then decrease from the evening at which the daily work is ending. So releasing of these hormones is ready by round the clock rhythm or circadian or setting the time of biology of body.<sup>9</sup>

Metabolic disorder related diseases increasing day by day due to modernization of the life style in our country. Hypertension, diabetes mellitus, dyslipidemia, coronary heart disease, cerebrovascular disease etc. are not uncommon in young adult. Different type of life style is observed during Ramadan fasting. Many physiological and psychological changes take place during Ramadan which may influence the metabolic reaction of the body. But little is known about this aspect in our country as well as in abroad.

## Material and Methods:

This longitudinal type of descriptive study was carried out in the Department of Physiology, Sir Salimullah Medical College (SSMC), Dhaka between January to December 2013. Subjects were selected by following simple random sampling procedure. The protocol of this study was approved by Institutional Ethics Committee (IEC) of SSMC. Sixty (60) healthy adult male subjects, aged 24-28 years were taken as study group. The subjects were the intern doctors of Sir Salimullah Medical College and Mitford Hospital, Dhaka. They were regularly fasted during Ramadan month. They were studied for two times i.e. before Ramadan fasting (1-3 days BRF) and at the end of Ramadan fasting (25<sup>th</sup>-27<sup>th</sup> days ARF). Subjects having history of hypertension, heart diseases, diabetes mellitus, renal diseases, thyroid diseases, liver diseases, mental disorders, smokers and alcohol users etc were excluded from the study. After proper counseling the aim, objectives, benefit, risk and procedure of the study were explained in details to the subjects. Informed written consents were taken from each subjects. Subsequently a detailed family, personal, medical and dietary history were taken. Dietary history was taken as 5 meals/day (breakfast, two tiffins, lunch and dinner) from 1-3 days as BRF and 3 meals/day (iftar, dinner and sehri) from 25<sup>th</sup>-27<sup>th</sup> days as ARF. All the information and data were recorded in a prefixed questionnaire.

BRF all the subjects were requested remaining overnight fasting for 8-10 hours. During Ramadan month after 8-10 hours fasting with all aseptic precautions, five (5) ml of venous blood was drawn from median cubital vein by sterile disposable syringe. Then it was kept in a clean and dry glass test tube and 30 minutes were allowed for clot formation. Then blood was centrifuged at 3000 rpm for 25 minutes. After that, supernatant serum was collected in labeled Eppendorf tubes for estimation of all the study parameters. All these tests were carried out as early as possible. Whenever there was delay, the serum samples were preserved in the refrigerator.

## Results:

**Table 1.** Serum cortisol and serum FT<sub>4</sub> levels before and at the end of Ramadan fasting (n=60)

Parameters	Before Ramadan fasting	At the end of Ramadan fasting	p value
Serum cortisol (µg/dl)	10.72±3.54	7.96±3.26	0.000***
Serum FT <sub>4</sub> (pmol/l)	17.02±2.09	12.07±1.90	0.000***

Table 1 shows that serum cortisol and serum FT<sub>4</sub> were significantly decreased at the end of Ramadan fasting than those of before Ramadan fasting.

**Table 2:** Body weight and body mass index before and at the end of Ramadan fasting (n=60)

Parameters	Before Ramadan fasting	At the end of Ramadan fasting	p value
Age (years)	25.78±1.18		
Height (cm)	169.36±4.89		
Body weight (kg)	61.51±1.91	58.97±1.93***	0.000***
BMI (kg/m <sup>2</sup> )	21.48±1.09	20.59±1.07 ***	0.000***

Table 2 shows that before and at the end of Ramadan fasting the mean age was 25.78±1.18 years and height was 169.36±4.89 cm. The body weight and BMI were significantly decreased at the end of Ramadan fasting than those of before Ramadan fasting.

**Table 3:** Total calorie intake for 3 days before and at the end of Ramadan fasting (n=60)

Time of meals	Before Ramadan fasting kcal/day	At the end of Ramadan fasting kcal/day	p value
Breakfast	403.67±28.6		
Tiffin-twice (Morning and evening)	631.23±33.86		
Lunch	631.23±33.86		
Dinner	634.03±9.28	677.87±12.82	
Iftar		501.63±24.51	
Sehri		424.67±25.38	
Total calorie intake	2163 ±51.39	1582.27±51.39	0.0001***

Table-3 shows that the calorie intake for three days significantly decreased at the end of Ramadan fasting than that of before Ramadan fasting.

## Discussion:

Ramadan is a time of spiritual reflection, improvement and increased devotion and worship. Ramadan fasting started in early year of Prophet Muhammad (Sallallahu Alaihe Wasallam) in Medina, precisely in the second year of Hijra. Prior to his flight to Medina, the Prophet (Sallallahu Alaihe Wasallam) observed fasting three times per month (this gives 36 days in a year) when he was in Mecca and also when he settled in Medina.<sup>10</sup>

Metabolism is sum of all chemical and physical changes that take place within the body and enable its continued growth and functioning. Ramadan fasting can induce different metabolic changes due to ingestion of nutrient at an unusual time and also affect on anthropometric measurements of people.<sup>11</sup> Usually Muslims eat greater varieties of foods than in other months.<sup>12</sup> Food frequency and quantity, sleep duration at night and daily physical activities are reduced during this month.<sup>13</sup> As a result, the Ramadan fasting provides an excellent opportunity to study the effects of various diets on human body and can serve as an excellent research model for metabolic and behavioral studies.<sup>14</sup>

The psychological preparation to remain fast in Ramadan month causes changes in the circadian rhythm in secretion of most of the body's hormones such as, thyroxin, cortisol and endorphin.<sup>15</sup> Muslims follows strictly some religious duties during Ramadan month including long Taraveeh prayer at night and special meal before dawn Sehri. They have to refrain from eating and drinking throughout the day till the sunset along with have a special meal Ifter. These special patterns in daily routine certainly affect the normal biological clock and circadian rhythms. Again, those who fast regularly during Ramadan month undergo disturbance of sleep which affect negatively on their performance and mood.<sup>16</sup> Disruption of feeding and sleep schedules have adverse effects on affect and metabolism.<sup>17</sup> Both conditions influence the stress system and increase the secretion of its mediators, including corticotrophin-releasing hormone.<sup>18</sup>

In this study, the serum levels of cortisol and FT<sub>4</sub> were significantly decreased in ARF than those of BRF. These findings are similar with some studies.<sup>19,20</sup> In contrast, significant increased level of serum cortisol at the end of Ramadan found by some studies. This inconsistency may be due to their more sleeping (5 to 7 hours) after Sehri as compared only 2 to 3 hours sleeping after Sehri by the subjects (intern doctors) of this study.<sup>21</sup>

During Ramadan fasting, the circadian pattern of circulating serum cortisol level was lower in the morning and higher in the evening than those of the pre-Ramadan value. Due to alteration of circadian pattern of circulating cortisol the morning serum cortisol level is reduced with elevation of the evening cortisol level by increasing glucocorticoid sensitivity of peripheral tissues.<sup>19</sup> Again, in Ramadan month alteration of sleeping habits, irregular sleep and sleep deprivation due to night shift work lower

serum cortisol level.<sup>22</sup> In addition, during Ramadan month the serum cortisol level is not usually elevated by poor quality of sleep may be due sleep centre dependent inhibition of the stress system including the hypothalamic-pituitary-adrenal axis.<sup>23</sup>

Again, BW and BMI were decreased in healthy adult male subjects after observing Ramadan fasting as proved by their measured values. Decreased serum FT<sub>4</sub> level indicates decreased BMR in the subjects of the present study. Again, the decrease in BMR (upto 40%) during Ramadan fasting related to decrease in BW.<sup>24</sup> However, decreased number of meals (two meals instead of three meals) especially loss of midday meal when the body is metabolically active and reduction of calorie intake also may be responsible for these changes. Decreased level of FT<sub>4</sub> was also observed by some other investigators.<sup>25</sup> This discrepancy may be related to alteration of food and fluid intake along with continued high training loads during Ramadan fasting in the subjects of that study. Again, Reduction of leptin level Inhibits the hypothalamic-pituitary-thyroid axis (HPT) and decreases serum TSH level and thereby reduces serum FT<sub>4</sub> level during Ramadan fasting.<sup>26</sup> Fasting for 12-24 hours slightly reduces serum T<sub>4</sub> level.<sup>25</sup> In addition, increase in the concentration of thyroxin binding globulin (TBG) decreases serum T<sub>3</sub> and T<sub>4</sub> levels.<sup>27</sup> However, in Ramadan month, the level of thyroid hormone changed due to delay and shortening sleeping time at night and changes in behavioral and social habits.<sup>28</sup>

Again, extra every night lengthy Taraveeh prayer during Ramadan month is a sufficient exertion on the fasting individuals and these religious activities can fulfill moderate exercise level.<sup>7</sup> The phycho-physiological mechanism involved in resolving the Niyath might helpful in improving the life style related disorders like obesity, hypertension, diabetes and metabolic syndrome.<sup>29</sup>

## Conclusion:

The effect of Ramadan on the round the clock rhythm of body biology during a month along with a discipline of diet, sleeping and behaving according to religious pattern can be effective to the type and time of food, period of sleeping or awaking. The most importantly its effect on the tranquility and lack of stress in fasting persons. To maintain a right life style that means filling the hours of activity and relaxing in a disciplined manner based on normal circadian leads to body and soul tranquility. This tranquility results from decrease of stress hormones. Thus one month religion-oriented fasting in Ramadan month can insure the other 11 months of year.

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# LMA- Option in General Anaesthesia for Breast Surgery

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## Abstract

**Background:** Different kinds of breast surgery are performed usually under general anaesthesia and endotracheal intubation is one of the most common approaches in this anaesthetic procedure.

**Objective:** To compare the usefulness of Laryngeal Mask Airway (LMA) and Endotracheal tube in simple mastectomy regarding difficult airway management, haemodynamic parameter, risk of aspiration and incidence of postoperative pharyngeal pain.

**Methods:** This cross sectional study was carried out in the Department of Anaesthesiology in Bangladesh Medical College Hospital from July 2012 to June 2014. Total 100 cases of simple mastectomy were included in this study. The patients were equally divided into two groups (Group A- LMA and Group B- endotracheal tube) consisting of 50 patients in each group. The choice of method was general anaesthesia balanced with halothane for both groups. Observations were made regarding cardiac parameter, time of insertion, number of insertion attempts, hemodynamic response to insertion and presence of blood on the device used. Incidences of sore throat, dysphagia, nausea and vomiting were assessed postoperatively.

**Results:** There was no remarkable difference in both group regarding time of insertion and attempt for successful insertion. However, significant alteration in haemodynamic parameter was observed in Group B. Sore throat and dysphagia were common in both groups with a higher incidence with endotracheal tube insertion.

**Conclusion:** LMA can be used as the main method of airway management in a range of surgical procedures provided that patient parameters are suitable for the safe and rational airway manipulation.

**Keywords:** LMA- laryngeal mask airway, ETT- endotracheal intubation, general anaesthesia.

## Introduction:

General anaesthesia, one of the most common modalities and widely used techniques in Anaesthesiology; endotracheal intubation is the gold standard for airway management. However, this maneuver demands expertise and clinical experience a lot. Moreover, both laryngoscopy and endotracheal intubation may trigger the sympathetic response which can be life threatening in some conditions like ischaemic heart disease and uncontrolled hypertension<sup>1</sup>.

Nowadays, Laryngeal Mask Airway (LMA) carries a great importance to anaesthesiologist for various approach at

airway management and has achieved great success. Primarily it was believed that LMA would bridge between facemask and endotracheal tube. With wide range of advantage and tolerability such as insertion without muscle relaxant and role in emergency kit in difficult airway situation, it is being used extensively in patient under going general anaesthesia. Currently and considering the vast amount of literature on subject, it is known that LMA offers enormous advantages over ETT specially in short duration procedures<sup>2</sup>.

## Materials and Methods:

A prospective cross sectional study was carried out in the Department of Anaesthesiology in Bangladesh Medical College Hospital from July 2012- June 2014. There were a total of 100 patients undergoing mastectomy who were selected by purposive sampling. They were divided into two groups; Group A(LMA) Laryngeal mask airway classic size 3, 4, 5 according to need and Group B (ETT) Endotracheal tube classic size 6.5, 7, and 7.5. Inclusion criteria were: 1) patients with ASA physical status I-II, 2) patients who have given consent for this study. The exclusion criteria were: 1) patients with facial and oral cavity deformities, 2) obese patients, 3) patients who did not provide consent for this study. All patients were monitored through ECG, pulse oxymeter and NIBP. Induction was done with 1.5 to 2 mg/kg propofol, 0.002-0.004 mg/kg fentanyl and 1.5-2 mg/kg suxamethonium<sup>3</sup>.

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Maintenance of mechanical ventilation with oxygen and halothane in volume percent according to need of each patient<sup>4</sup>. A proper record was maintained for counting the attempt were made for placement of LMA or ETT. Vital parameters such as blood pressure and heart rate were carefully monitored during induction and every 5 minutes after placement of ETT and LMA<sup>5</sup>.

**Results:**

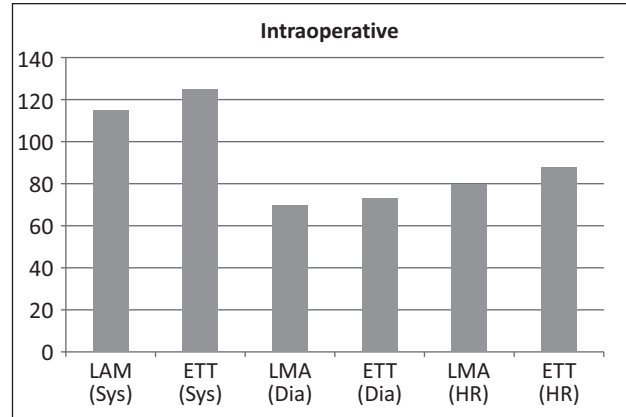
Total 100 patients were taken into this study that underwent mastectomy in the Bangladesh Medical College Hospital. Among 100 patients, 12 patients were removed from the study because of some surgical complications. There were 44 patients in group A (LMA) with average age of 51 ± 11 years and average weight of 58 ± 6.8 kg and 44 patients in group B (ETT) with average 53 ± 12 years of age and average weight of 61 ± 4.5 kg. There were no significant statistically difference in both groups (Table 1)

**Table 1:** Demographic variables in each group

Demographic variables	Group A- LMA (Mean ± SD)	Group B- ETT (Mean ± SD)	p value
Age (years)	51 ± 11	53 ± 12	0.820
Weight (kg)	58 ± 6.8	61 ± 4.5	0.730

Of the 44 patients in group (LMA), placement was easy in 38 patients and it was difficult in 5 patients and failed insertion of LMA in 1 patient and ultimately intubated. In group (ETT), intubation were easy in almost all patients with the number 7 endotracheal tube. During mechanical ventilation, pulse oximetry was above 97% in all patients.

During maintenance of anaesthesia, MAC 0.65% Halothane was administered in LMA group and MAC 0.7% in ETT group with no statistical significance. In the haemodynamic parameters during study showed the heart rate was 82 beats per minute with a base line of 74 beats per minute in LMA group and it was 95 beats per minute in ETT group with baseline of 72 beats per minute, p<0.05 statistically significant. The systolic blood pressure was 137 mmHg in LMA group with a baseline of 125 mmHg and 140 in ETT group with baseline of 130. The diastolic arterial pressure was 85 mmHg in LMA group with a baseline of 82 mmHg in LMA group and 92 mmHg in ETT group with 81 mmHg baseline (Figure 1). 11 patients of LMA group had pain in the larynx during postoperative period and 27 of ETT group had this symptom with a p<0.05 significant difference.



**Figure 1:** Comparison of Haemodynamic parameters of both groups during intra-operative period

Figure 1 showing systolic, diastolic blood pressure and heart rate during intra-operative period. LMA (Laryngeal mask airway), ETT (Endotracheal tube), sys (systolic blood pressure), dia (diastolic blood pressure), HR (Heart rate)

**Discussion:**

In our study, the observed criterion on the application form was as following: LMA with partial balloon inflation and good lubrication was placed in all patients and no difficulties were found in implementation as it has been reported<sup>6,7</sup>. It is worth mentioning that, in our protocol, the muscle relaxant was used in minimal doses, further facilitating ventilation and placement of the LMA, contrasting with the most of the publications reported<sup>8,9</sup>.

After analyzing the data, obtained from the study and proper investigation we can suggest that LMA is very useful and effective device in managing the airway and ventilation. Regarding the possibility of gastric aspiration, we always used LMA for short period and had no evidence of regurgitation in any patient. Although there have been a few reported cases of laryngospasm, but we did not experience any such case. Capnography was normal in all patients and CO<sub>2</sub> could be handled adequately at the end of expiration; the oxygen saturation in all patients remained above 98%. It is worth considering that the mask's cuff was never fully deflated, making insertion and removal without complications. The only side effects encountered and eventually reported in the literature were: mild pain of the larynx and occasionally blood streaked mask, which is unrelated to pain. The overall success rates and time required to secure the airway were similar in all treatment groups. Use of Fentanyl was also associated with a dose-related decrease in the requirement for supplemental bolus doses of propofol during intubation and removal of the LMA device. In the study positive pressure ventilation was maintained in all cases and no sign of air leakage were noted<sup>10-14</sup>.

The LMA permits single handed insertion from any operator position, without moving the head or neck from a neutral position and without placing fingers in the patient's mouth. It can be used as an airway device in its own right, permitting ventilatory control and oxygenation between intubation attempts. Indications include use during difficult airway situations, specifically including the need for manual in-line stabilisation and situations where there is restricted access to the patient or when personnel with intubation skills are not available, or where there is suspected cervical spine injury<sup>15,16</sup>.

Use of LMA has been proven successful in emergency and pre hospital settings because its efficiency over facemask in lowering the dead space and avoidance of laryngoscopy<sup>17</sup>. Moreover, it would be a better option for airway management such as traumatic cervical injury where endotracheal intubation or its maneuver might cause further damages in that region.

### Conclusion:

LMA has indeed some great advantages over ETT and from this study we suggest that LMA can be an attractive alternative to ETT because of its better managing ability in emergency situations. In addition, from the above data it has been proven that it can ensure greater comfort to patients in respect to pain, adrenergic response and haemodynamic parameters. Because of these factors we believe that better outcome can be achieved with patients of limited cardiac reserve if LMA has been used. In the patients undergoing mastectomy, LMA should be used routinely provided that there is no contraindication.

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# Role of Computed Tomography-Guided Fine Needle Aspiration Cytology of Intrathoracic Lesions

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## Abstract

**Background:** Thoracic lesions include a variety of benign and malignant lesions of lung, pleura, chest wall and mediastinum. Fine needle aspiration cytology (FNAC) is a well established technique for diagnosis of thoracic lesions. Computed tomography (CT) has extended the use of FNAC, because it is accurate for localization, needle puncture and also it permits evaluation of lesions less than one cm accurately. This diagnostic modality has a high sensitivity, specificity and is of relatively cheap.

**Objective:** To assess the role of CT-guided FNAC in the diagnosis of intrathoracic lesions. **Materials and Methods:** Seventy-seven (77) patients with various thoracic lesions were evaluated by CT guided FNAC. The cytologic findings were compared with cell blocks whenever available.

**Results:** In this study, lung lesions were the most common. Among these, neoplastic lesions accounted for 50 (65.0%) of cases. The sensitivity, specificity and accuracy of the study were 93.75%, 77.77% and 88.00% respectively.

**Conclusion:** CT-guided FNAC is a minimally invasive diagnostic procedure as well as safe, cheap and reliable also.

**Keywords:** Computed tomography guided fine needle aspiration cytology, Neoplastic lung lesions, Cell block, Thoracotomy.

## Introduction:

Thoracic lesions include variety of benign and malignant lesions of the lung, pleura, mediastinum and vertebrae also. Transthoracic fine needle aspiration cytology (TFNAC) is an established technique for work up of thoracic lesions compared to other imaging modalities available. Computed tomography (CT) is best for more accurate localization and lesions less than 1 cm can be aspirated.<sup>1,2</sup> In patients with lung cancer which is inoperable owing to local factors or the patient's general condition, FNAC confirms the diagnosis and reveals the tumor type.<sup>3</sup> Hence, TFNAC of small pulmonary lesions helps in earlier diagnosis and increased chance of effective intervention and management.<sup>4</sup> Major surgical procedures like thoracotomy can also be avoided. The aim of the present study was to assess the role of CT-guided FNAC in diagnosis of intrathoracic lesions. The high sensitivity and specificity of the widely accepted diagnostic

method and relatively low cost with minimal complications prompted us to carry out this study.

## Materials and Methods:

This study was done in a private diagnostic and consultation centre, Dhaka from June 2012 to May 2015. The study included 77 patients with various intrathoracic lesions who underwent CT guided FNAC. Among these, lung lesion 72, mediastinal 3 and 2 were pleural lesions.

## Procedure for CT guided FNAC

The clinical details of all the patients were recorded and after rule out bleeding diathesis, an informed consent was taken. A non contrast CT scan image of the lesions was obtained and the shortest distance from the lung was chosen for FNAC so that minimal amount of normal lung parenchyma was pierced.

A 23 gauge lumbar puncture needle was used for aspiration. First, we locate the lesion and then measure the density and distance from the body surface. Then the needle with the stylet was inserted into the lesion and the position of the tip of the needle within the lesion was confirmed by subsequent scan. Four to six rapid passes were made within the lesion, following which the stylet was removed and a 10 ml syringe was attached to the needle and aspirated. The aspirated material was spread on 3-5 slides and rapidly fixed in 95% ethyl alcohol. In possible cases, the material in the needle was used to prepare cell blocks and further processed as routine histopathological specimens.

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The smears were routinely stained with Hematoxylin & Eosin and Papanicolaou stains. Other stains like Ziehl-Neelsen stain and periodic acid Schiff stain are also done clinical and cytological data to reach a final diagnosis. Smears were correlated with findings of the cell block, wherever available.

## Results:

The present study comprised 77 patients who underwent CT-guided FNAC for thoracic lesions. The age of the patients in the study ranged from 30 years to 75 years. There were 60 males and 17 females with a male to female ratio of 3.5:1 (M: F=3.5:1). The most common aspirated site was lung (72 cases). The lesions were classified as neoplastic 52 (67.5%) and non neoplastic 25 (32.5%).

**Table 1:** Age distribution of the study cases (n=77)

Age group in years	Number	Percent
30-40	03	3.89
41-50	12	15.58
51-60	42	54.54
61-70	16	20.77
>70	04	5.19
Total	77	100

Table 1 showed that 54.54 % patients were within 51-60 years, 20.77 % were within 61-70 years, 15.58 % were within 41-50 years and 5.19 % were >70 years of age and rest 3.89 % patients were within 30-40 years.

**Table 2:** Types and sites of lesions.

Lesions	Site	Number	Percent
Neoplastic (total-52)	Lung	49	63.63
	Mediastinum	01	1.29
	Pleura	02	2.59
Non-neoplastic(total-25)	Lung	23	29.87
	Mediastinum	02	2.59
Total (77)		77	100

Table 2 reveals that most common aspirated site were lung (72 cases) 93.50 %, neoplastic lesions were 52 (67.50 %) and non neoplastic lesions were 25 (32.50%). In lung 63.63% were neoplastic and 29.87% were non-neoplastic lesions. Of the five cases, 01(1.29%) presented as mediastinal mass (Non Hodgkin lymphoma) and the 02 (2.59%) pleural lesions were benign solitary fibrous tumor.

**Table 3:** Pattern of lung lesions (n=72)

Lesions	Type	Number	Percent
Neoplastic (total-49)	Squamous cell carcinoma	25	34.7
	Adenocarcinoma	18	25.0
	Small cell carcinoma	05	06.9
	Large cell carcinoma	01	1.4
Non neoplastic (total-23)	Tuberculosis	10	13.9
	Acute inflammation	08	11.1
	Non-specific inflammation	04	5.6
	Pulmonary hamartoma	01	1.4
Total		72	100

Table 3 shows among the 72 lung lesions 49 (68.0%) were neoplastic and 23 (32.0%) were non neoplastic. The most common neoplastic lung lesions were Squamous cell carcinoma (25, 34.7%) case followed by 18 (25%) cases were Adenocarcinoma. Common non-neoplastic lung lesions were tuberculosis (10, 13.9%) and acute inflammation (8, 11.1%).

## Cell block study

**Table 4:** Cell block study results

FNA study lesions	Cell block study lesions		Total
	Neoplastic	Inflammatory	
Neo-plastic	15	2	17
Inflammatory	1	7	8
<b>Total</b>	<b>16</b>	<b>9</b>	<b>25</b>

Out of 77 cases, 25 cases (32.5%) were followed by cell block study. The cases included 17 neoplastic lesions and 8 non neoplastic lesions. In cell block study, among 17 neoplastic cases, 15 were neoplastic and 2 were inflammatory lesion. Among other 8 inflammatory cases, 7 were inflammatory and one was neoplastic lesion (TP-15, FP-02, TN-07, FN-01). The sensitivity, specificity and diagnostic accuracy was calculated for 25 cases followed by cell block study. Thus, the sensitivity, specificity and diagnostic accuracy of the present study were 93.75%, 77.77% and 88.00% respectively.

## Discussion:

The present study was carried out to categorize the various intrathoracic lesions by cytology. The most common site biopsied (93.5%) was the lung which is similar to study of Sonneberg et al.<sup>5</sup> The M: F ratio in the present study was 3.5:1 whereas the age range varied from 30-75 years.

### Non neoplastic lesions

Similar to the findings of Fraser et al.<sup>1</sup> cases of acute inflammatory lesions showed necrotic debris, fibrin, neutrophils and macrophages and Conces et al.<sup>6</sup> supports that TFNAC is useful in diagnosis of pulmonary infections. The specific diagnosis in inflammatory lesions can be improved by compared with other diagnostic methods such as Gram's stain, culture and other techniques such as cell block and immunocytochemistry.

### Neoplastic lesions

Among the neoplastic lesions, the malignant lesions were predominant, accounting 96.1% (50/52) which is higher to the study by Arslan et al.<sup>7</sup>(88.1%) while the benign lesions accounted for 3.9%.

Squamous cell carcinoma was the most common malignant lesion, which was followed by adenocarcinoma and small cell carcinoma.

When the differentiation in the smears of malignant lesions was not apparent, the lesions were grouped as non-small cell carcinoma (NSCC) and the smears showing large, highly pleomorphic cells with abundant cytoplasm were grouped as large cell carcinomas Koss et al.<sup>8</sup> and Brambilla C et al.<sup>9</sup>

Cell block study is instrumental which offers a conclusive opinion in cases where the cytologic findings were inconclusive. The sensitivity, specificity and diagnostic accuracy of the present study is comparable to that of Khouri et al.<sup>10</sup> and Hamper et al.<sup>11</sup>

### Conclusions:

CT guided FNAC is an easy, cheap, safe, rapid and accurate diagnostic procedure. It also helps to avoid major surgical procedures like thoracotomy. The results of cytology when interpreted in association with clinical and radiological data can prevent some of the pitfalls in diagnosis.

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# Clinical Usefulness of Serum PSA for Detection of Incidental Adenocarcinoma in Transurethral Resection Specimen of Prostate in Relation to Gland Volume

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## Abstract

**Background:** Prostate carcinoma is one of the most common tumours in middle aged and elderly men throughout the world. Serum PSA measurement is a valuable tool for the diagnosis of prostate cancer. Sampling issue of TURP (Transurethral Resection of Prostate) chips is also important and is related to detection of incidental carcinomas.

**Objectives:** The study was done to evaluate the predictive value of serum PSA levels for detection of clinically significant adenocarcinoma of prostate and to demonstrate the relationship between prostate volume and cancer detection in transurethral resection specimen.

**Methods:** The study included 65 consecutive patients who underwent transurethral resection of prostate diagnosed as benign hyperplasia of prostate (BHP) from July'2014 to June' 2015 in Dhaka Medical College Hospital, Dhaka. Preoperatively prostate volume was measured by ultrasonography, and serum PSA levels were recorded. TURP specimens were divided into two groups according to blood PSA level of the patients. One group "A" having PSA level of 0 to 4 ng/ml. and other group "B" having blood PSA level in between 4.1ng/ml and 10ng/ml. The predictive value of serum PSA level for diagnosis of adenocarcinoma and probability of cancer detection in slides were calculated and tabulated. All the tissues were submitted for histologic examination and the number of blocks prepared from the tissue for each case were recorded.

**Results:** Among 65 patients, 8 cases were diagnosed as adenocarcinoma (12.30%). Variable number of blocks showed variable probability of cancer detection. Mathematical calculation using the correlation coefficient and scatter diagram showed moderately negative correlation of prostate volume to the percentage of chips containing tumour in TURP specimen submitted totally for microscopic examination. Predictive values of serum PSA for positive result and negative result, specificity, accuracy and sensitivity were calculated.

**Conclusion:** This study suggests that more blocks should be examined in higher serum PSA levels for detection of incidental adenocarcinoma in TURP chips and minimum six blocks should be examined to obtain the probability of 0.995 where serum PSA level is more than 4ng/ml. It was also found that the percentage of TURP chips containing adenocarcinoma decreases as the volume of prostate gland increases and the probability of detecting adenocarcinoma in specific number of block decreases as the volume of prostate gland increases.

**Keywords:** Prostate, Serum PSA, Incidental adenocarcinoma, TURP chips,

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## Introduction:

Prostate carcinoma is a common tumour throughout the world.<sup>1</sup> In 1954 one autopsy study showed that approximately 30% of all men in the sixth decade of life and 67% at those between 80 and 90 years had carcinoma of the prostate.<sup>2</sup> It is much more common in developed than developing countries.<sup>3</sup> The age-adjusted incidence is on the increase in most countries of the world.<sup>4</sup> As the life expectancy is increasing in our country, the frequency of prostate cancer can be expected to reach new heights in the near future. The term prostate cancer is a combination of three entities: clinical prostate cancer, occult prostate cancer, and latent prostate cancer.<sup>5</sup>

The latent (incidental) carcinoma is unsuspected on clinical examination and found incidentally at autopsy or in prostatectomy specimens resected for nodular hyperplasia or some other conditions. There are many evidences to show that latent carcinoma occur in other organs as well.<sup>2</sup> Latent carcinoma of prostate is common, and is frequently found on microscopic examination after prostatectomy for benign disease.<sup>6</sup> Incidental carcinomas have been documented in slightly less than 10 percent of retro-pubic prostatectomy specimen and in approximately 20 percent of transurethral prostatectomy specimens (TURPs) resected for clinically benign disease.<sup>7</sup> The overall incidence of incidental carcinoma as diagnosed by TURP or enucleation is about 10 percent and varies with age and sectioning technique.<sup>8</sup>

PSA measurement is a valuable tool for the diagnosis and treatment of patient with prostate cancer. As screening for prostate cancer, serum PSA measurement has become more widespread. Lesions detected by digital rectal examination have become less common and the cancers are detected at an earlier stage by serum PSA estimation.<sup>9</sup> However, discriminating between prostate cancer and benign prostate disease is difficult where the serum PSA level is in between 4.1 and 10 ng/ml.<sup>10</sup> Moreover, prostate size is an important variable in the diagnosis of prostate cancer since it has a direct role in the relative amount of tissue in the sample. Serum PSA level may have a good predictive value for diagnosis of prostate cancer in transurethral resection of prostate. There may be a significant correlation between percentage of chips containing cancer in TURPs and the volume of prostate gland. As the serum PSA is related to the volume of prostate, it may be a determining factor for sampling of prostatic tissue.<sup>11</sup> were 93.75%, 77.77% and 88.00% respectively.

## Materials and Methods:

This cross-sectional study was carried out at the Department of Pathology, Dhaka Medical College Hospital, Dhaka, during the period from July, 2014 to June, 2015.

Specimens of TURP chips were collected from Dhaka Medical College Hospital and different clinics of the Dhaka city. In all of the cases transurethral prostatectomy was done on the basis of clinical examination and other investigations such as ultrasonography and estimation of blood PSA level and all were clinically diagnosed as benign prostatic hyperplasia.

All the clinical information including age, symptoms with durations and reports of investigations such as ESR, PSA level, serum creatinine, and ultrasonography were recorded in a prescribed proforma.

Specimens clinically diagnosed as 'Benign prostatic

hyperplasia' considering inclusion and exclusion criteria:

All the chips in TURP specimen were measured by volume and taken in cassettes for subsequent laboratory processing. Variable number of slides for each case were prepared in such a way that one slide represents one tissue block. After haematoxyline and eosin staining, the microscopic examination and diagnosis were done at a consensus among other pathologists. Calculation of probability of adenocarcinoma in specific number of blocks (slide) such as 1, 2, 4, and 6 blocks was done mathematically and was tabulated accordingly. Volume of the prostate measured by abdominal or transrectal ultrasonography and was calculated using a computer generated elliptical estimation of  $0.52 \times \text{length} \times \text{width} \times \text{height}$ .<sup>12</sup>

Percentage of chips containing tumour identified by microscopy of sampled and processed prostatic chips in H&E stained slides were calculated. Percentage or ratio of chips containing tumour to the amount of sampled tissue is related to the presence of cancer in the histologic slide prepared from randomly selected well-mixed prostatic chips.

All transurethral resection specimens of prostate for relief of lower urinary tract symptoms diagnosed clinically as BPH having serum PSA up to 10ng/ml according to inclusion and exclusion criteria were included in the study. H & E stained slides prepared from totally sampled tissue were examined and diagnosed. Other clinical informations were collected from the patients and recorded in a prescribed form. During histopathological examination, number of slide containing cancer was noted for each case. Total number of chips as well as the number of chips containing cancer were also noted.

TURP specimens were divided into two groups according to blood PSA level of the patients. One group "A" having PSA level of 0 to 4 ng/ml. and other group "B" having blood PSA level in between 4.1ng/ml and 10ng/ml. The predictive value of serum PSA level for diagnosis of adenocarcinoma was calculated and tabulated.

After calculation of probability of cancer in each case, the result was tabulated along with Blood PSA level to make inference. Other relevant data were analyzed by standard statistical methods and expressed in frequency, percentage & mean  $\pm$  SD.

## Results:

For this study TURP specimens from 65 patients diagnosed as benign prostatic hyperplasia were collected and examined. Prostatic carcinoma was detected in 8 (12.30%) transurethral resection specimens This study principally aimed to calculate the predictive value of serum PSA level and probability of cancer detection.



**Table 1:** Showing distribution of patients according to PSA level (n=65).

Group	PSA level	No. of cases	Percentage
Group A	0-4ng/ml	45	69.2
Group B	4.1-10ng/ml	20	30.8
Total	0-10ng/ml	65	100

Group "A" contains 45 cases (69.2%) having PSA level of 0 to 4 ng/ml. and other group "B" containing 20 cases (30.8%) having blood PSA level in between 4.1ng/ml and 10ng/ml (Table-1). All the carcinoma cases are in the group "B".

**Table 2:** Showing predictive value, sensitivity, specificity and accuracy of cancer detection of serum PSA level (n=65).

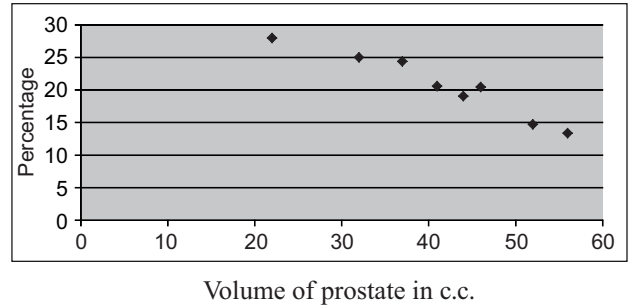
True +ve	True -ve	False +ve	False -ve	Total	Prediction for +ve result	Accuracy	Specificity	Sensitivity
8	45	12	0	65	38%	80%	77%	100%

Serum PSA level has Positive predictive value- 38%, Negative predictive value- 100%, specificity- 77%, sensitivity-100%, and accuracy- 80% for detection of prostate cancer (Table-2).

**Table 3:** Showing calculated probabilities of adenocarcinoma in 2 slides with corresponding PSA levels, prostate volume and percentage of chips containing tumour(n=8).

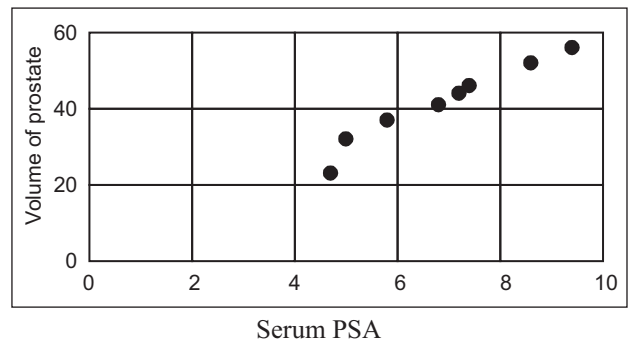
Volume of the prostat	Percentage of chips with tumour	Total no. of block	Blocks positive for cancer	PSA Level	Probability of cancer detection
25 C.C	28.00%	6	3	4.7	0.995
32 C.C	25.00%	3	2	5.00	0.946
37 C.C	24.39%	3	2	5.80	0.916
41 C.C	20.58%	3	2	6.8	0.911
44 C.C	19.04%	4	2	7.2	0.874
46 C.C	18.75%	7	3	7.4	0.857
52 C.C	14.70%	5	2	8.6	0.850
56 C.C	13.33%	7	2	9.4	0.682

Probability of detection of incidental adenocarcinoma of the prostate according to the number of blocks positive for cancer and total number of blocks for each case in 1, 2, 4, and 6 blocks (slide) was calculated and shown (Table-3). It shows that percentage of chips containing cancer vary with the volume of prostate gland and all the adenocarcinoma cases have blood PSA level more than 4 ng/ml.



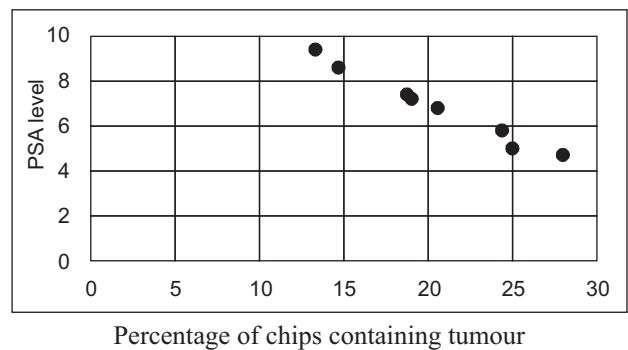
**Fig 1:** Scatter diagram showing partial negative correlation between volume of prostate gland and percentage of chips containing tumour.

Moderately negative correlation between volume of the prostate gland and percentages of chips containing tumour was observed (fig:1). So the percentage of chips containing tumour and detection rate increases as volume of prostate gland decreases.



**Fig 2:** Scatter diagram showing partial positive correlation between serum PSA levels and volume of prostate.

There is partial positive correlation between serum PSA and volume of prostate (Fig:2). Detection rate decreases as volume and PSA level increases.

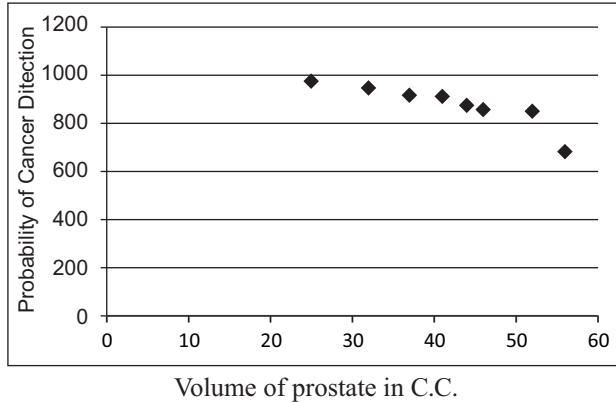


**Fig.3.** Scatter diagram showing partial negative correlation between serum PSA levels and percentage of chips containing tumour.

There is a moderately negative correlation between percentage of chips containing tumour and serum PSA.

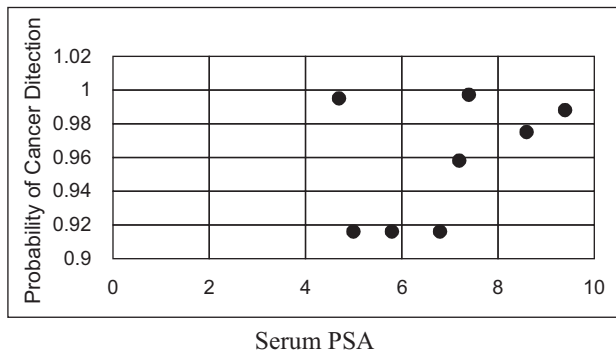
level (Fig:3), so more PSA level indicates less percentage of tumour containing chips.

Presence of more proportion of chips containing tumour indicate more detection rate of tumour in the specimen under microscope



**Fig:4.** Scatter diagram showing partial negative correlation between prostate volume and probability.

There is partial negative correlation between prostate volume and probability (Fig:4), it indicates the probability of detecting adenocarcinoma in TURP chips in specific number of block decreases as the volume of prostate gland increases.



**Fig:5.** Scatter diagram showing no correlation between serum PSA and probability of cancer detection.

No correlation was observed between serum PSA and probability of cancer detection (Fig:5) As probability is related to number of blocks prepared and amount of tissue during TURP procedure.

**Discussion:**

The measurement of PSA has an important role in diagnosis of Carcinoma of prostate.<sup>3</sup> Independently serum PSA level is a better predictor of cancer than suspicious findings on DRE or TRUS.<sup>7</sup> Other tumour markers, such as prostatic acid phosphatase (PAP) do not yield additional information where it is measured in addition to PSA.<sup>8</sup> Some investigators suggest that margin of PSA that indicates the

highest risk of CaP should be identified.<sup>11</sup>

All the carcinoma cases of present series have PSA levels in between 4 ng and 10 ng/ml and serum PSA level has a good predictive value for detection of prostatic adenocarcinoma in transurethral resection specimen of prostate(Table-2).

The positive predictive value of various combinations of diagnostic procedures used in a screening population ranges from 20% to 80%.<sup>13</sup> Investigators have suggested some modifications to distinguish between carcinoma and benign disorders of the prostate, particularly in the intermediate PSA range (4 -10 ng/ml).<sup>14</sup> If a result using any one of the three modalities is abnormal, the positive biopsy rate is 6-25%; with two abnormalities it is 18-60%; if all three modalities are positive, it is 56-72%.<sup>15</sup> Consensus has not been achieved on the application of those modifications in routine practice.<sup>16</sup> In this study, 8 (12.30%) out of 65 patients were diagnosed as adenocarcinoma. The comparative study of histopathological diagnosis of previous four studies on incidental carcinoma of prostate in Bangladesh with the present study shows that there is an increase in percentage of incidental carcinoma in the present series.

The incidence of carcinoma found in this series is comparable to those reported by the other investigators of western countries. The comparative study on incidental carcinoma of present series with other studies of western countries shows that the incidence varies from 13.04% to 21% in different series. Although the number of cases in this study is small, it appears that the incidence of incidental carcinoma in our country is almost similar to that of western countries. It has been claimed that the incidence of incidental carcinoma in eastern and western zone is almost similar.<sup>17</sup> This is in concordance with the present study. The age specific incidence of incidental carcinoma of the present series shows the highest incidence is in 70-79 years, which is comparable with other studies. Present study shows that minimum number of patients are in age group of 80-89 years in comparison with other studies, this may be due to life expectancy of Bangladeshi people is comparatively lower than other countries. Another cause is that other investigators included autopsies and prostatectomies. The present study is also aimed to estimate the probability of cancer in specific number of blocks such as 1, 2, 4, and 6. The finding in the study of Rohr (1987) was that eight blocks (12.8g) will detect all carcinomas and it is in basic agreement with the recommendation of Murphy et al (1986) that 12g (eight blocks) be submitted randomly in each case.<sup>18</sup> Further, five blocks (8 g) will detect all but a negligible number of cases of A2 carcinomas (P=99.9%).<sup>19</sup>

Present study shows that some of the block from randomly selected prostatic chips contain tumour. There is a possibility of missing of tumour in specific number of block. The probability of detecting cancer varies with the number of blocks to be submitted.<sup>20</sup> Highest number of blocks in cancer cases in this study is 7.

The highest probability has been achieved by examining 6 blocks. The table shows that probability reached 0.995 in examining 6 blocks. Specimens were classified according to serum PSA level, one group consists of TURP specimens having PSA level less than 4 ng/ml and other group contains TURP specimens having PSA level between 4.1 ng/ml and 10 ng/ml. All the carcinoma cases were found in the later group (Table-1). Calculated predictive value of serum PSA level is higher than that of the earlier. Therefore, minimum six blocks should be submitted to obtain the probability 0.995 of detecting incidental carcinoma where serum PSA level is more than 4ng/ml (Table-3). No carcinoma was detected in the group of specimens having serum PSA level less than 4ng/ml (Table-1). Although one study showed that the risk of carcinoma prostate where serum PSA less than 4ng/ml. is 6.6% to 26.9%.<sup>21</sup>

Prostate size is an important variable in the diagnosis of prostate cancer since it is a factor regulating the relative amount of tissue that is sampled for biopsy.<sup>22</sup> In fact there is no direct correlation between the amount of prostatic chips and the volume of prostate gland but presence of tumour in sampled TURP chips is related to the volume of prostate gland due to sampling error. Observation of present study shows that proportion of tumour containing chips to the sampled TURP chips is related to the volume of prostate (Fig:1).

It was also stated that decreasing prostate cancer detection rate were noted with increasing volume as detection rates decreased from 40% to 24%, in some studies, with needle biopsy, it was determined that the number of cores did not significantly influence prostate cancer detection rate and also suggesting that increasing the number of cores taken at the time of needle biopsy did not increase the prostate cancer detection rate.<sup>23</sup> Other investigations previously suggested that cancer detection rate increased with increasing number of biopsy cores.<sup>24</sup> The present study shows the variation of percentage of chips containing tumour with the volume of prostate gland. Percentage of tumour containing chips increases as the volume of prostate decreases (Fig:1). Serum PSA level varies with the volume of prostate, higher PSA levels were seen in the patients having higher prostatic volume. Also the percentage of chips containing tumour decreases as the serum PSA level increases (Fig:3). So cancer detection rate decreases in the patients having higher PSA levels. Unfortunately, no correlation was seen between serum PSA levels and probability of cancer detection (Fig-5), because probability is related to number of blocks and amount of tissue resected by the surgeon and also for the reason of tissue processing procedure in the histopathological laboratory. So detection rate decreases in higher prostatic volume. To achieve higher probability of detection rate, more tissue should be submitted in higher serum PSA levels. Further study is recommended for exploration of relationship between serum PSA level and probability of cancer detection as it was expected.

The present study shows that probability 0.995 was reached at submission of 6 blocks in the specimen of the patient with the lowest volume of prostate gland. The inference of present study is that the probability of detecting adenocarcinoma in specific number of blocks decreases as the volume of prostate gland increases and the negative predictive value of serum PSA level for detection of adenocarcinoma is significant and the serum PSA is a determining factor which influences on amount of tissue during resection by surgeon. The present study also suggests that to avoid missing of prostate cancer in TURP chips in cases having serum PSA level more than 4 ng/ml. with larger prostate, the amount of prostatic chips sampled for biopsy should be adequate.

### Conclusion:

Serum PSA level has a good predictive value for detection of incidental carcinoma of prostate in transurethral resection specimen of prostate. The probability of detecting adenocarcinoma in specific number of blocks decreases as the volume of prostate gland increases. Serum PSA is a determining factor for sampling prostatic tissue for biopsy. More amount of tissue is needed in cases having serum PSA levels more than 4 ng/ml. for cancer detection to obtain the probability of 0.995.

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# Concept about a very Rare Blood Group: Bombay Phenotype

Rahman M

### Abstract

Bombay phenotype is one of the rarest ABO blood groups. Due to lack of correct blood grouping practices, the rare Bombay Oh phenotype may be missed, subjecting patients to the risk of severe hemolytic transfusion reaction. This blood doesn't contain one antigen, the H antigen, which is found on virtually all RBCs and is the building block for the production of the antigens within the ABO blood group.

**Keywords:** ABO blood-group system, blood group incompatibility, blood transfusion, Bombay phenotype, transfusion reaction

### Introduction:

Bombay phenotype was first reported by Bhende in 1952 in Bombay, India.<sup>1,2</sup> More than 130 Bombay phenotypes have been reported in various parts of the world.<sup>3</sup> It is rare in Caucasian with incidence of 1 in 250,000.<sup>4,5,6</sup>

In 1952, a paper about the "new blood group character related to the ABO blood group" was published. This new blood group does not produce the L-fucose transferase which is necessary for formation of H antigen and it is the building block for the antigens of the ABO blood group. Named for the city in which it was first discovered, the "Bombay phenotype" describes individuals whose RBCs lack the H antigen.

This H antigen deficiency is known as the "Bombay phenotype" (h/h, also known as Oh). There is no ill effect with being H deficient, but if a blood transfusion is ever needed, people with this blood type can receive blood only from other donors who are also H deficient. (A transfusion of "normal" group O blood can trigger a severe transfusion reaction.) Because the H antigen is the precursor of the ABO blood group antigens, if it is not produced, the ABO blood group antigens are also not produced.<sup>7,2</sup> As a result, these individuals produce anti-H, anti-A, and anti-B and can therefore be transfused only with RBCs that also lacks the H, A, and B antigens i.e., they can only receive blood from another person with the Bombay phenotype and they are at risk of suffering an acute hemolytic transfusion reaction if they grouped as 'O' blood grouped and receive blood rather than Bombay grouped blood. Because of the rarity of this blood type, this normally means using blood donations from a suitable relative.<sup>1,8</sup>

The last two decades have seen blood transfusion services in developed nations trying desperately to minimize the risks of blood transfusion through transfusion transmitted infections. The need to improve transfusion safety in the

developing world has been understood and is evident through the introduction of a National Hemosurveillance Program. The role of blood group serology (BGS) laboratory is equally vital in the provision of safe and compatible blood to patients. However, it is also evident from reports that the laboratory errors continue to be one of the main causes of incompatible or inappropriate blood transfusion, compromising patient safety and resulting in mortality or severe morbidity. Rare blood group patients need to be identified and their transfusion requirements managed by the blood centers in life saving situations.<sup>3</sup>

As Bombay individual does not pose A,B antigen, their red cells do not react with anti-A, anti-B and anti-AB antisera, they can be recognized as the O blood group in cell typing. So serum typing is also necessary to identify this type of rare blood group. In a recent case report from Iran, transfusion reaction in a case of Bombay blood group patient has been described and the reason for missing out on Bombay group has been stated as, only forward grouping being performed in routine with crude slide method and inappropriate documentation of cross matching.<sup>9</sup> Three Bombay Oh phenotype patients of a center of central India and their successful management, save life with peri-operative acute normovolemic hemodilution (ANH) as per the British Committee for Standards in hematology (BCSH) guidelines.<sup>8</sup>

A field-based random population study was conducted in Bhuyan tribe of Northwestern Orissa, India for identification of a rare blood group, "Bombay (Oh) phenotype. Among 836 Bhuyan, three cases of a rare blood group, Bombay (Oh) phenotype, (2 out of 244 Khandayat Bhuyan and 1 out of 379 Paudi Bhuyan from Hemgiri and Lahunipara blocks, respectively) were found in Sundargarh district of North-Western Orissa, giving an incidence of 1 in 122 in Khandayat Bhuyan and 1 in 379 in Paudi Bhuyan, with an average of 1 in 278 among the Bhuyan tribal population. This incidence is high in comparison to earlier studies reported from India.<sup>9</sup> In a study from Bangladesh, it has been suggested to incorporate "routine serum typing or reverse grouping confirmation" along with "O" cell control in the reverse grouping procedure in every

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transfusion medicine department or blood bank or blood donor centers and this practice should be mandatory to reduce the risk of fatal hemolytic transfusion reaction.<sup>6</sup>

### Frequency of Bombay phenotype:

The Bombay phenotype and para-Bombay (present small amount of H antigen) phenotype are relatively rare. In India, where H deficiency was first discovered, the frequency of both phenotypes combined is 1 in 10,000 (10,11) and 1 in a million people in Europe and is found in 1 of 10,000 individuals in India and 1 in a million people in Europe.<sup>2,7</sup> H deficiency is slightly more common in Taiwan, affecting 1 of 8,000 people.<sup>10</sup> A relatively large number of H-deficient individuals were found on Reunion Island, which is a small French Island 800 km east of Madagascar in the Indian Ocean.<sup>12</sup> Both the classical Bombay phenotype and a new variant type of partial H deficiency was seen in the islanders.<sup>13</sup> In Europe, 1 per million people are H deficient.<sup>10</sup>

Balgir<sup>14</sup> has reported an incidence of 1 in 33 among the Kutia Kondh primitive tribe from Kandhamal district of Orissa. Bhatia and Sanghvi<sup>15</sup> calculated the incidence of this phenotype as 1 in 13,000 individuals in Mumbai. Later on, Bhatia and Sathe<sup>16</sup> found an incidence of 1 in 7600 after screening a large number of samples in Mumbai. Gorakshakar et al.,<sup>17</sup> after systematic screening of the rural population from Ratnagiri and Sindhudurg districts of Maharashtra, reported the incidence of the Bombay phenotype as 1 in 4500 in that region, while Moores<sup>18</sup> reported its incidence as 1 in 18,404 amongst Indians settled in South Africa.

Regarding the distribution and spread of the Bombay phenotype in different states of India, it is apparent that the phenotype is more common in the states of Western and Southern parts (0.004-0.005%) of India as compared to

other states.<sup>18,19</sup> Of the 179 cases recorded by Sathe et al., 112 (62.6%) cases belonged to the state of Maharashtra. A slightly higher frequency of the Bombay phenotype was also found in the neighboring state of Karnataka (14 cases), Andhra Pradesh (8 cases), Goa (6 cases), Gujarat (5 cases), Uttar Pradesh (5 cases), and so on in the decreasing order. There is no published data available in literature on the caste/tribe-wise distribution of the Bombay phenotype in India. Moreover, most of the reported cases were either referred cases or were hospital cases seeking blood transfusions. Hence, the exact prevalence of the Bombay phenotype, which is based on random population screening (not based on hospital data), is not yet precisely known in India. Further, based on the available information in India, it is interesting to note that the incidence of the Bombay phenotype is high in those states of India where consanguineous marriages are more prevalent, i.e., Andhra Pradesh, Tamil Nadu, Karnataka, Maharashtra, Gujarat, etc. than in the other states.<sup>18</sup>

The Bombay phenotypes were also detected in Japan,<sup>20,21</sup> Malayasia,<sup>18</sup> Thailand<sup>22</sup> and Sri Lanka.<sup>23</sup> Yunis et al.<sup>24</sup> found seven individuals of Oh phenotype in two generations of an Indian family settled in the USA. They were natives of Orissa state. Similarly, Moores<sup>25</sup> found 24 cases of Oh phenotypes in 11 unrelated Indian families settled in Natal, South Africa. Most of these families were either Tamil or Telugu speaking. Therefore, their origin is presumed to be Andhra Pradesh or Tamil Nadu. More recently, a large series of H-deficient individuals (~1:1000) were found in Reunion Island in the Indian.

Geneticists believe that the high number of Bombay blood group people in India is the result of consanguineous marriage among members of a caste class. Higher caste class allows consanguineous marriage to maintain their position in the society and to protect their wealth.<sup>9,26,5</sup>

### Characteristics of general ABO grouped and Bombay phenotype<sup>[27]</sup>

Phenotype	H antigen on RBCs	H antigen in saliva	Anti-H in serum	Genotype
H phenotype Secretor (ABO)	Present	Present	Absent	H/H or H/h; Se/Se or Se/se
H phenotype Non Secretor (ABO)	Present	Absent	Absent	H/H or H/h; se/se
Bombay phenotype	Absent	Absent	Present	h/h se/se
Para-Bombay phenotype	weakly expressed	Present or absent	Present	(H), Se/Se or Se/se or se/se

### Antibody Production & Clinical Significance of H antibodies

If patients with anti-H in their circulation (as in Bombay blood group) receive transfusions of blood that contains the H antigen (e.g., blood group O), they are at risk of suffering an acute haemolytic transfusion reaction. The maternal production of anti-H during pregnancy could cause haemolytic disease in a foetus who did not inherit the mother's Bombay phenotype. However, cases of Haemolytic disease of the new-born caused in this way have not been reported, possibly because of the rarity of the Bombay phenotype. Theoretically HDN is possible in babies with Bombay phenotype but practically there are no reports in literature. Bhattacharya *et al.* described a case of young lady with Bombay phenotype who had two successive uneventful pregnancies. Despite the high titer of IgG anti H antibodies (640) babies had escaped HDN<sup>28</sup> The relative mildness of the disease could be due to the weak expression of these carbohydrate antigens on RBCs in utero and in neonates or due to the predominant immunoglobulin class which is IgM which does not cross the placenta.<sup>29</sup>

### Importance of identification of bombay phenotype:

The Bombay Oh phenotype patients can have severe or fatal hemolytic transfusion reactions if the blood group is missed.<sup>30,31,32,4,5,6</sup> Since individuals with the Bombay phenotype are easily misdiagnosed as the O blood group in cell typing and because of the presence of strong anti-H in their plasma, if they receive blood group O red cells or any other blood group red cells except the Bombay group, they may develop an acute hemolytic transfusion reaction. This reaction can cause acute renal failure or disseminated intravascular coagulation (DIC) which is associated with high morbidity and mortality rates especially in unconscious patients who may receive large volumes of incompatible blood before signs of hemolytic reaction appears.<sup>30,31,32</sup>

Receiving blood which contains an antigen which has never been in the patient's own blood causes an immune reaction due to the immune system of a hypothetical receiver producing immunoglobulins not only against antigen A and B, but also against H antigen<sup>31</sup> The maternal production of anti-H during pregnancy could cause haemolytic disease in a foetus who did not inherit the mother's Bombay phenotype. However, cases of Haemolytic disease of the new-born caused in this way have not been reported, possibly because of the rarity of the Bombay phenotype<sup>33,34</sup>

The most common immunoglobulins synthesized are IgM and IgG (and this seems to have a very important role in the low frequency of hemolytic disease of the newborn among non-Bombay offspring of Bombay mothers).<sup>30,35</sup> It is very important, in order to avoid any complications during a blood transfusion, to detect Bombay phenotype individuals, because the usual tests for ABO blood group system would show them as group O. Since Anti-H

immunoglobulins can activate the complement cascade, it will lead to the lysis of red blood cells while they are still in the circulation, provoking an acute hemolytic transfusion reaction. This, of course, cannot be prevented unless the lab technologist that is involved has the means and the thought to test for Bombay group.<sup>9</sup>

The ABH phenotyping was carried out by applying the standard forward and reverse grouping tube techniques. The Bombay phenotype detected was further confirmed by certain specialized tests like absorption-elution studies, titration of naturally occurring antibodies at different temperatures, hemagglutination-inhibition study on anti-H by O Saliva secretor, and secretor-status of the person as described by Flynn<sup>36</sup> and Boorman and coworkers.<sup>37</sup>

### Conclusion:

Awareness amongst treating doctors is a very important issue in managing such patients. It is very important that a simple test like blood grouping should be done with serious intention and correct method of including both forward and reverse grouping (a practice still needs full implementation) so that no patient is missed out or receives wrong blood, which could lead to serious hemolysis due to transfusion. The Bombay Oh phenotype can be missed if O cells are not used in reverse blood grouping and moreover routine anti-H lectin not being used in forward grouping increases the possibility further. Implementing a quality system in the laboratory minimizes errors and ensures that the right test is performed on the right sample, the right results obtained and the right blood product provided to the right patient at the right time.

### Recommendation:

Although molecular research and advanced modern technology is playing a very important part in blood banks in developing countries also, however, the matter of concern is that the patients of rare blood groups like Bombay phenotype are still missed and are at risk of being transfused wrong blood group causing hemolytic transfusion reactions leading to even death. All blood banks should strictly adhere to adopting quality standards in performing basic blood grouping tests, giving away the obsolete methods and should realize the responsibility and role in avoiding life-threatening situations for the patients. Programs for implementation of the standard methods in blood banking have been started through training on a national level but it seems that they still need the due attention.

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## Psychosis- A Rare Presentation of Thyrotoxicosis

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### Abstract

Psychosis, as a presentation of thyrotoxicosis, is very rare. Consequently, thyrotoxic psychosis is often misdiagnosed as primary psychiatric disorder leading to treatment failure and long term morbidity. This is an unusual case of a 31 years old man who was admitted to hospital with complaints of loose motion, history of weight loss and a variable range of neuropsychiatric symptoms that initiated with insomnia, anxiety and irritability but later on progressed to frank psychotic features such as delusion, episodes of depression and mania, irrelevant talks and suicidal ideations. Patient was previously treated at a psychiatric ward but his condition did not improve. An absence of family history of psychiatric illness added to his other manifestations and certain clinical findings such as persistent tachycardia with high volume bounding pulse, moist palm etc. made thyrotoxicosis an important differential. Later on thyroid hormone levels were investigated that gave a picture of primary thyrotoxicosis and the aetiology was confirmed as Grave's disease by thyroid scan that showed high uptake of tracer. Patient's overall condition rapidly improved upon commencing antithyroid medication and no further recurrence has been reported in the last 5 months.

**Keywords:** Thyrotoxicosis, Grave's disease, Psychosis

### Introduction:

Thyrotoxicosis is often associated with neuropsychiatric symptoms- anxiety, irritability, restlessness, impairment in memory and concentration etc. and less commonly such patients develops seizure, movement disorder or catatonia. However, very rarely, certain psychotic symptoms can be found as a complication in patients with thyrotoxicosis.<sup>1</sup> Hyperthyroid patient with secondary psychosis are often misdiagnosed as primary psychosis and mistreated with only antipsychotics, both before and after the diagnosis of thyrotoxicosis.<sup>2</sup> This fact, if avoided, may lead to diagnostic uncertainty and thus inappropriate management. The disease thyrotoxicosis itself is often initially ruled out in men due to its higher statistical prevalence in women. Here we report an unusual case of a middle aged man diagnosed with thyrotoxicosis with features of psychosis.

### Case Presentation:

A 31 years old male was admitted to hospital with a 3 years' history of loose motion and insomnia and a 3 months' history of abnormal behavior. During inpatient evaluation, patient's family described new onset and rapidly deteriorating paranoid delusion that was demonstrated by

episodes of aggressive behavior followed by episodes of isolation. He was also reported to become verbally abusive and often muttering irrelevant speeches. For instance, he was once heard saying- "I won't be elected as the chairperson in the election if my dresses are not clean." although he was only a college teacher by profession with no connection to the election. Patient complained of increasing anxiety that led him to undergo some unnecessary operations of asymptomatic DNS and first degree haemorrhoid. A history of weight loss of around 10-12 kg over the last 3 years was reported. Patient denied any co-morbid condition and no family history of psychiatric illness is present. Few days before his admission to this hospital, he was treated in another hospital by antipsychotic drugs, due to his odd behavior.

After admission his physical examination revealed warm moist palm, tachycardia with high volume bounding pulse and a normal blood pressure. Systolic flow murmur was audible in precordial auscultation. There was no eye abnormality and no visible enlargement of thyroid gland. Mental examination showed anxiety and restlessness while perception examination revealed delusion of reference and persecutory delusion. Nervous system examination showed features of extrapyramidal signs that resolved when treated with anti-parkinson's drugs. Other assessments were unremarkable.

Looking into patient's previous medical records, it was found that he underwent various tests for his complaint of loose motion but nothing significant was found that could be linked to his symptoms.

On this admission, persistent tachycardia and other presenting features raised suspicion of thyrotoxicosis as an important differential. Thyroid function tests were advised and the results were consistent with that of thyrotoxicosis- TSH: <0.004 uIU/ml (Reference range: 0.40-4.0)

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Free T3: 7.58 pg/ml (Reference range: 2.77-5.27)

Free T4: 2.71 ng/ml (Reference range: 0.71-1.85)

USG of thyroid gland: Bilaterally enlarged heterogenous thyroid gland.

Thyroid Scan: Enlarged thyroid gland with elevated uniform tracer concentration.

Thyroid autoantibody assay could not be performed due to patient's financial constraints.

With these reports a diagnosis of Grave's disease was made. Patient showed marked improvement in his overall symptoms on starting antipsychotic medications and beta blocker and later on carbimazole was prescribed. He was discharged with recommendations for follow up visits to outpatient psychiatry and endocrine clinics. After almost a month it was reported that patient was in a stable condition after resolution of his major symptoms and no re-emergence of psychotic features was reported in the last 5 months.

## Discussion:

Thyrotoxicosis is a state of thyroid hormone excess and is often interchangeably used with an overlapping but not synonymous term 'hyperthyroidism' that refers to excessive thyroid function. The most common aetiology of thyrotoxicosis is Grave's disease (as seen in this patient), which is felt to be an HLA-related organ specific defect in suppressor T cell function.<sup>3,4</sup> It commonly occurs in the age group 30-50 years and like almost every other autoimmune diseases, Grave's disease also has a female predominance with a male to female ratio of 1.5: 10. The presentation of thyrotoxicosis may be variable and at a time might affect one or many systems. A younger patient tends to exhibit symptoms of sympathetic activation, as seen in our 31 years old patient, while cardiovascular symptoms are more prominent among the elderly.<sup>5</sup> In the elderly features of thyrotoxicosis may even be subtle or masked and patient may present with only fatigue or weight loss, a condition known as apathetic thyrotoxicosis. It is also noteworthy that features of thyrotoxicosis are often more marked in patients with Grave's disease than any other aetiologies and it is fair to say that our patient who has been diagnosed with Grave's disease has also shown strong forms of his thyrotoxic features.

Thyrotoxicosis along with its physical manifestations can be associated with a wide range of neuropsychiatric sequelae.<sup>6,7</sup> Although psychosis as one of the manifestations of thyrotoxicosis is rare, it is in fact a recognized complication and unlike our patient who showed multiple manifestations of thyrotoxicosis, psychosis may even be the only presenting symptom.<sup>1,8</sup> In fact, statistical analysis with thyrotoxic patient with concurrent psychosis showed an incidence well above chance occurrence.<sup>9</sup> Psychosis generally occurs in around 1% of patients with thyrotoxicosis.<sup>1,3,10</sup> Thyrotoxicosis due to various causes such as Grave's disease, toxic adenoma,

subacute thyroiditis have been held responsible in various other reports. Even thyrotoxicosis associated with transient thyroiditis or factitious thyroiditis can also result in severe behavioral disturbances including frank psychosis.<sup>11</sup> Duration and severity of thyrotoxicosis as well as patient's susceptibility to psychiatric instability are main determinants of development of psychosis.<sup>3</sup>

The exact link between psychosis and thyrotoxicosis is poorly understood. However, a number of theories attempt to explain the pathogenesis. A large number of thyroid hormone receptors are localized in limbic system (hippocampus and amygdala) and cortex. Augmentation of these receptors and modulation of beta-2 receptor sensitivity to catecholamines is thought to be responsible for these clinical features.<sup>3,11,12</sup> Interaction between catecholamines and thyroid hormones in CNS is strengthened by their common origin from the amino acid tyrosine and their metabolic process.<sup>11</sup> Another possible mechanism includes thyroid hormones affecting serotonin, dopamine or secondary messengers.<sup>3</sup> It has been experimentally demonstrated using PET scan that there is alteration of glucose metabolism in brains of patient with Grave's disease and its reversal upon treatment. Also thyroid hormones are shown to increase sodium current density in the hippocampal region of the rat model, causing neuronal excitability.<sup>12</sup> All these causes may be held responsible for psychosis in thyrotoxic patients. 3 months, he can utter words and stands with support.

It is also important that we distinguish it from hyperthyroxinaemia that may occur secondary to other psychiatric disorders. Such thyroid abnormalities are characterized by transient rise in thyroid hormones and TSH in upper part of the normal reference range. However, our patient had developed other thyrotoxic features well before developing psychosis. This entity has not been established but may be considered a form of non-thyroidal illness or sick euthyroid syndrome. In addition, several case reports have noted the development of a thyroid condition in bipolar patients either on lithium maintenance therapy or recently on lithium treatment.<sup>13</sup>

While dealing with such case it is important to make a precise diagnosis and exclude other possibilities. Several other medical conditions can cause mood disorders-cushing's syndrome, addison's disease, electrolyte imbalance, rheumatoid arthritis, infectious disease (such as infectious mononucleosis) etc.<sup>11</sup> All such possibilities had been excluded in our case.

In thyrotoxic psychosis, standard antithyroid therapy along with beta blockade remains 1<sup>st</sup> line of treatment. However, for abrupt resolution of symptoms dopamine receptor blockers or phenothiazines may be given for a short time and later discontinued.<sup>3,12,14</sup> We followed this approach for our patient and satisfactory result was achieved. More radical approach such as radiofrequency ablation or surgery may be necessary if medical management fails to achieve thyroid control.

## Conclusion:

We presented a rare case of secondary psychosis due to thyrotoxicosis. To the best of our knowledge this is the first reported case of thyrotoxic psychosis in a Bangladeshi male. Although medical attention was sought considering psychotic manifestations, presence of some clinical features of thyrotoxicosis raised a high index of suspicion in favor of thyrotoxic psychosis. Absence of any prior psychiatric disorders and resolution of psychotic features upon treatment of thyrotoxicosis supported this rare diagnosis.

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# Maffucci Syndrome: A Rare Case Report

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## Abstract

Maffucci syndrome is a rare developmental disorder, which starts out as simple benign tumours of the bones (enchondromas) and vessels (haemangiomas) and rapidly deteriorates into deformities, fractures and malignancies. We herein report such a presentation of this disease in a 19-year-old female suffering from diffuse swellings of her left hand, bone distortions and protuberances, giving rise to the clinical diagnosis of Maffucci syndrome, which was supported by radiographical features of early osteolytic changes, phleboliths and venous malformations. Her condition was further complicated by severe anaemia and bleeding from intestinal arterio-venous malformations. The objective of this article is to highlight this unusual disease, its diagnostic criteria and its inevitable regression to mesenchymal as well as non- mesenchymal malignancies so as to avoid a missed diagnosis, as well as improving clinician and patient awareness.

**Keywords:** Enchondromatosis, Haemangiomatosis osteolytica, Kast syndrome, Ollier disease, Enchondromas with multiple cavernous haemangiomas

## Introduction:

Maffucci syndrome is a congenital nonfamilial disorder characterized by the presence of multiple enchondromas along with cutaneous, soft tissue or visceral haemangiomas and less commonly lymphangiomas.<sup>1</sup> Enchondromas are defined as benign overgrowth of the cartilage affecting mainly the tubular bones and the flat bones. Chuveilheir in 1835 and Hanssen in 1863 described similar cases but the syndrome acquired its name after Angelo Maffucci, professor of pathological anatomy at the University of Pisa, Italy.<sup>2</sup> In 1881 Maffucci reported the case of a 40-year-old woman with frequent and severe bleeding from a vascular tumour. Amputation of the distal extremity was performed to control the bleeding and the patient later died of complications secondary to infection. Maffucci carried out a thorough autopsy and detailed all the main points of the syndrome that was to be named after him. Carleton et al<sup>2</sup> proposed the eponym Maffucci syndrome in 1942.



**Figure 1:** Photograph of the left hand showing large haemangiomas

## Case Presentation:

A 19-year-old girl was admitted with multiple swellings along with pain and heaviness affecting her left upper extremity. The girl's mother noticed these nodules on her left hand soon after birth and gradually it spread upto the lateral chest wall and back. Over time, the lesions had grown considerably; from small unremarkable bumps to gross malformations of the hand. The child also suffered from per rectal bleeding, fatigue and dizziness since the age of 5. The mother had an uncomplicated normal vaginal delivery and there was no family history of genetic diseases. On examination, the girl was severely anaemic; soft non tender nodular masses affected the digits of the left hand, the skin over it had bluish discoloration which blanched on pressure; consistency was spongy and compressible; similar nodules with a grittier feel was found near her elbow; Limb length discrepancy measured: *left* shoulder to finger ratio 57cm & *right* 64cm; DRE and proctoscopy revealed per rectal bleeding from 3<sup>rd</sup> Degree Haemorrhoids.

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## Investigations findings:

- *Hb* 3.6g/dl; *Reticulocytes* 1.91%; *PBF* microcytic hypochromic anemia, pencil cells, target cells; *Iron profile* - total iron 28 µg/dl, TIBC 469 µg/dl, Ferritin 10.40 µg/dl
- *X-Ray of the Left hand*: Multiple radiolucent areas with thinning of the cortex, suggestive of enchondromas
- *X-Ray of the Left Forearm*: Ulna- Shortened in length, lower end is thinner, Radius- Bowing observed, Visualized Metacarpals - thinning, Soft tissue swelling with flakes of calcification is noted in the dorsal aspect of lower forearm and wrist, suggestive of phleboliths within haemangioma
- *USG of Abdomen*: Small Splenic Cyst 25mm at lower pole
- *MRI of the left chest wall with contrast*: Lt Subclavian Vein Stenosis associated with low flow vascular malformation (Capillary-Venous Type) along the Lt Posterolateral Chest Wall and over the shoulder. Telangiectatic Capillary Channels are extending into the skin in these regions
- *Duplex study of the left upper limb*: Multiple Hypoechoic Areas within the swelling containing both arterial and venous type of blood flow with fistulous connection, suggestive of AV Malformation (AVM)
- *Colonoscopy*: Mucosa-grossly erythematous, dilated vessels and AVM noted in rectum, 3<sup>rd</sup> degree prolapsed haemorrhoids

Her anaemic status was corrected and stapled haemorrhoidopexy (Longo) was performed. The patient and her family were informed about her condition and its high possibility for developing cancer. She was advised to have regular follow ups and for further repair of the AV malformations, sclerotherapy was recommended.

## Discussion:

Maffucci syndrome is an exceedingly rare disease and it was classified as a subclass of Enchondromatosis by the World Health Organization in 2002. Its incidence is not known, but since its first description in 1881, fewer than 200 cases have been reported worldwide.<sup>3</sup> The disease manifests typically within 4-5 years of age. In 25% of cases, the clinical symptoms are present at birth or manifest in the 1st year of life; in 45% cases, it develops before the age of 6 years, and in 78% cases, before puberty.<sup>4</sup> While literature regarding its genetic analysis is sparse, no familial pattern of inheritance has been demonstrated and it is considered as a somatic mutation (mutation that occurs after fertilization) causing dysplasia in mesenchymal

tissues. Due to its asymmetrical distribution in presentation, seen in most patients, it is suggestive of mosaicism.<sup>1</sup> In 1986, an inversion of chromosome bands p11 and q21 of chromosome 1 was reported in one patient with Maffucci syndrome.<sup>5</sup> In 2004 & 2008, subsequent studies conducted by Rozeman and Couvineau, 26 patients with Maffucci syndrome were screened for mutations in the parathyroid hormone receptor PTH1R but revealed absence of mutation.<sup>6,7</sup> However, 10% of patients with Enchondromatosis (multiple enchondromas) harbor a mutation in the PTH1R receptor; these mutations were shown to decrease the function of the receptor by 30%. In 2012, Pansuriya and his research team discovered mutations in the gene encoding isocitrate dehydrogenase 1 and 2 in enchondromas and spindle cell haemangiomas. 81% of patients with Ollier disease and 77% of patients with Maffucci syndrome carried IDH1 (98%) and IDH2 (2%) mutations. Despite these developments a causative gene is yet to be identified.<sup>8</sup> It affects both male and female equally and there is no ethnical predilection. Patients are of average intelligence without any associated mental or psychiatric abnormalities.<sup>9</sup>

Maffucci Syndrome (MS) initially presents with benign overgrowths in the skeletal systems and vascular malformations in the skin. Lesions in both systems tend to have a unilateral predominance.<sup>10</sup> Skeletal lesions appear in the metaphyseal regions of tubular bone such as the phalanges and metacarpals of the hand, less commonly the feet, long bones of the legs and arms. Often, they can be more extensive involving the ribs, vertebrae and the skull.<sup>11</sup> Lewis et al<sup>4</sup> reviewed ninety-eight cases where fibula was most frequently affected. As the bone grows, cartilage material, from the epiphyseal plate, migrates into the metaphyseal regions and grows irregularly, developing into masses known as enchondromas.<sup>10,12</sup> These enchondromas can result in painless swellings of the digits, deformities, bulging and bowing of the arms and legs, limb-length discrepancies (as seen in our patient) or pathological fractures, malunion of fractures and short stature. Radiological findings of the affected bones are pathognomic- enchondromas appear as multicentric radiolucent areas with predominant thinning of the cortex and endosteal scalloping. Matrix mineralization in the osseous lesions is frequent and shows the typical arc-and-ring appearance of chondroid lesions.<sup>13,14</sup>

Presence of vascular tumours in MS sets it apart from other subtypes of Endochromatosis, such as Ollier disease. These vascular tumours or haemangiomas occur commonly as superficial skin lesions but can involve mucous membranes in the respiratory tract and gastrointestinal tract. The patient can suffer from severe

intraabdominal haemorrhages from such visceral haemangiomas. Clinically they appear as bluish soft subcutaneous nodules which can be emptied by manual compression. Histologically they are mostly of cavernous types- dilated venous lakes, highly prone to thrombosis and dystrophic calcifications. Radiologically, these calcifications appear as phleboliths, a diagnostic criterion of MS.<sup>15</sup> One of the major concerns in MS is malignant transformations of enchondromas and haemangiomas to chondrosarcomas and vascular malignancies respectively. Others malignancies can occur including haemangiosarcomas, lymphangiosarcomas, fibrosarcomas, gliomas, ovarian tumors, and carcinoma of the pancreas. It has been suggested patients with Maffucci syndrome will develop a malignancy with certainty.<sup>16</sup>

**Table 1:** Classification of Multiple Enchondromatosis<sup>17</sup>

Condition	Clinical Features
Ollier disease (Spranger type I)	Multiple enchondromas of tubular and flat bones, predominantly unilateral
Maffucci syndrome (Spranger type II)	Same as Ollier disease, with hemangiomas
Metachondromatosis (Spranger type III)	Multiple enchondromas and exostoses
Spondyloenchondrodysplasia (Spranger type IV)	Multiple enchondromas with severe platyspondyly
Enchondromatosis with irregular spinal lesions (Spranger type V)	Multiple enchondromas with dysplasia of vertebral bodies
Cheirospdyloenchondromatosis (formerly generalized enchondromatosis) (Spranger type VI)	Multiple enchondromas, severe hand and foot involvement, mild platyspondyly, erosion of iliac crests
Dysspondyloenchondromatosis	Multiple appendicular enchondromas with hemivertebrae, dwarfism, limb-length discrepancy
Genochondromatosis	Medial clavicular enlargement, lucent lesions of long bones
<i>Spranger type IV and genochondromatosis do not involve the hands, whereas other types, especially types I, II, III, and VI, do involve the hands.</i>	

The diagnosis of MS is made based upon clinical, radiological and pathological evidence of hemangioma and enchondroma. Management is aimed at providing symptomatic relief and regular follow up. Vascular lesions can be treated with anticoagulant therapy, compression dressing, laser treatment and sclerotherapy and use of antiangiogenic drugs, like rapamycin, injected into the sites of lesions. Surgical interventions are needed to correct skeletal deformities and improve limb ambulation and for

excision of chondrosarcomas, as these are resistant to chemotherapy and radiotherapy.

## Conclusion:

Although MS is extremely rare, it must be kept as a differential while evaluating patients with congenital hemangiomas. Due to its high malignant potentials, patient must be kept under surveillance and advised for regular follow-up and to contact if they experience sudden growth or pain in the affected regions. Our patient was last heard to be in good health and now 24 yrs of age. She, however, has not continued with her follow up programs.

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## Transfusion in Blood Group A<sub>2</sub> with Anti A<sub>1</sub> Recipient

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### Abstract

Blood group A<sub>2</sub> and A<sub>2</sub>B are extremely rare blood groups. Usually A<sub>2</sub> and A<sub>2</sub>B individuals have anti-A<sub>1</sub> antibody which reacts at a temperature below 25°C and do not pose problem in transfusion. Reactivity of anti-A<sub>1</sub> at 37°C can lead to haemolytic transfusion reaction if a compatible unit is not found and a least incompatible unit is transfused therefore an anti-A<sub>1</sub> antibody having a thermal range up to 37°C is called as clinically significant. We report a case of A<sub>2</sub> with anti-A<sub>1</sub> antibody reacting at 37°C.

### Introduction:

The ABO blood group system was the first red cell blood group system to be identified by Landsteiner in 1901 marked the beginning of safe transfusion<sup>1,2,3,4,5</sup>. There are four main blood groups enlisted in this system namely A, B, AB and O.<sup>1,6</sup> Landsteiner ABO blood group system is the most important for transfusion medicine and has subtypes of A Antigen, A<sub>1</sub> and A<sub>2</sub>, upon which further groups of A and AB have been classified. Individuals with A antigen, approximately 20% belong to A<sub>2</sub> while rest 80% belong to A<sub>1</sub>. Anti-A<sub>1</sub> Lectin, a cold agglutinin which destroys A<sub>1</sub> cells is clinically significant when they react at 37°C, causing transfusion reactions.<sup>7</sup>

Subgroups of A antigen weaker than A<sub>2</sub> are not frequent. A<sub>1</sub> and A<sub>2</sub> are distinguished by the reactivity of lectin i.e., anti-A<sub>1</sub> which act as a cold agglutinin and exclusively agglutinates A<sub>1</sub> cells. About 0.4% A<sub>2</sub> and 25% of A<sub>2</sub>B subgroups possess anti-A<sub>1</sub>. These antibodies become clinically significant if they react at 37°C destroying A<sub>1</sub> cells.<sup>2</sup>

### Case Presentation:

A 65-year-old male, known case of DM (Diabetes Mellitus) with HTN (Hypertension) with CKD (Chronic Kidney Disease) with NSTEMI (Non ST Elevated Myocardial Infarction) was admitted with generalized weakness and respiratory distress. Investigations revealed features of cardiogenic shock with UTI and septicemia. During course of hospitalization, his haemoglobin dropped to 6.5 gm/dl, haematocrit value was 18.7% with electrolyte imbalance. Urgent blood demand was placed and blood specimen for cross-match was collected. His specimen was processed as per laid down protocol for 'urgent blood demand'.

As a part of cross matching, blood grouping was done for both patient and donor first. Initial rapid cell and serum grouping result of patient revealed cell group- A and serum group- O with Rh-D positive. Then blood group of the patient was repeated with 'washed RBC' by tube method and serum grouping also repeated which revealed the same result as before (Table 1).

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Simultaneously compatibility with A<sub>1</sub>B Rh positive unit was undertaken and an abbreviated cross-match at room temperature (RT), major was compatible but minor was incompatible. Further compatibility test with another two available A<sub>1</sub> Rh positive units had same results. Again both forward and reverse blood grouping was repeated with Anti A<sub>1</sub> lectin. Blood group reaction was confirmed macro and microscopically (Table 2) and indirect Coombs test at 37°C revealed 2+ agglutination due to patient's anti A<sub>1</sub>.

The blood group of patient was confirmed as 'A<sub>2</sub> with anti A<sub>1</sub> antibodies-Rh-D positive'. Due to non-availability of A<sub>2</sub> group blood unit, compatibility test with two units each of O Rh positive and A<sub>1</sub> Rh positive was undertaken. Blood group O units had minor match problems in minor slide with compatible major slide as expected due to donor anti B; however, both A group blood units were found incompatible. A decision to transfuse with washed "O" positive concentrated red cell units was taken. (Table 3). Patient was transfused with one unit of washed "O" positive concentrated red cell. His haemoglobin rise to 10.30 gm/dl.

**Table 1:** Blood group of the patient

Grouping	Cell group			Rhesus group	Serum group		
	Anti A	Anti B	Anti AB	Anti D	A1 cell	B cells	O cells
Test Substance							
Test Result	2+	N	2+	3+	1+	2+	N

**Table 2:** Blood group of the patient

Grouping	Cell group				Rhesus group	Serum group		
	Anti A	Anti A <sub>1</sub>	Anti B	Anti AB	Anti D	A1 cell	B cells	O cells
Test Substance								
Test Result	2+	N	N	2+	3+	3+	2+	N

**Table 3:** Cross Matching of A<sub>2</sub> recipient

Donor	1	2	3	4
	A1 group Donor1	A1 group Donor 2	O group Donor 3	O group Donor 4
Major part	Incompatible	Incompatible	Compatible	Compatible
Minor part	Compatible	Compatible	Incompatible	Incompatible

## Discussion:

In 1911 Von Dungern described two different A antigen based on reactions with Anti A and Anti A1 antisera. Group A red cell that react with Anti A only and not with Anti A1 are classified as A<sub>2</sub> subgroup and Group A red cell that react with both Anti A and Anti A1 are classified as A<sub>1</sub> subgroup. Blood group AB also sub grouped into A1B and A2B depends on reactions with same antibody<sup>8</sup> (Table 4).

**Table 4:** A1 versus A2 phenotype

Reactions of patients red cell with		
Blood Group	Anti A	Anti A1 Lectin
A1, A1B	Positive	Positive
A2, A2B	Positive	Negative

The blood group A<sub>2</sub> and A<sub>2</sub>B are extremely rare blood groups which can cause discrepancy in ABO blood grouping.<sup>9</sup> At times ABO discrepancy leads to haemolytic transfusion reaction, hence it is necessary to include anti A<sub>1</sub> lectin in blood group test protocol. About 1-8% of A<sub>2</sub> individuals and 22-26% of A<sub>2</sub>B individuals have anti A<sub>1</sub>.<sup>9</sup> It was noted that A<sub>2</sub> in AB blood-group, as A<sub>2</sub>B, was more frequent than presence of A<sub>2</sub> as an A blood group.<sup>10</sup> Anti-A<sub>1</sub> has thermal range of up to 25°C because of which it is clinically not significant. In fact, published cases that have reported clinically significant anti-A<sub>1</sub> antibody are in patients who had undergone cardiac surgery using cold cardioplegia.<sup>11,12</sup> Cases of anti A<sub>1</sub> reactive at 37°C leading to transfusion reactions are rare.<sup>13,1</sup>

In our case anti A<sub>1</sub> was reactive at 37°C and transfusion with A<sub>2</sub> group units would have been ideal but it was not available and transfusion of O group red cell is also recommended in these recipients.<sup>9</sup> But we did not transfuse O group whole blood units as anti B present in plasma of O whole blood units leading to haemolytic transfusion reactions.<sup>9</sup> So we decided to transfuse O grouped Red blood cell only after cell wash with normal saline.

Total four cross matching was performed with this recipient's sample where two were with A1 grouped donor and two were with O grouped donor and only major part of cross matching of O grouped donor and minor part cross matching of A1 grouped donor was compatible.

So for safety and urgency of the patient we decided to transfuse washed O grouped Rhesus positive concentrated red cells. In management of this case, the importance of blood grouping and AHG phase in compatibility test has been highlighted.<sup>1</sup> The successful transfusion of "O grouped Rhesus positive concentrated red cells" units to the recipient of blood group A<sub>2</sub> with anti A<sub>1</sub> antibody in management of life threatening condition makes this case rare.

## References:

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## College News

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### College Events:

- International Mother Language Day was observed in Bangladesh Medical College and Hospital on 21<sup>st</sup> February 2019 at the local premises.
- National Independence day was observed in Bangladesh Medical College and Hospital on 26<sup>th</sup> March 2019 at the local premises.
- National nutrition week was observed in Bangladesh Medical College Hospital from 23-29 April, 2019.
- National health service week was observed in Bangladesh Medical College Hospital from 16-22 April 2019.
- Celebration of the “World Cancer Day” was held on 4<sup>th</sup> February 2019 in the Bangladesh Medical College and Hospital premises.

### Participation in the International Conferences/Seminars/Workshop/Congress/ Meetings:

- Dr. Farha Rahman, Lecturer, Dept. of Microbiology, BMC attended the 8th Annual Conference of the Clinical Infectious Diseases Society held on 16-18 August, 2018 in Vellore, India.
- Prof. Dr. Md. Zahid Hasan Bhuiyan, Professor, Dept. of Urology, BMC attended the 52<sup>nd</sup> Annual Conference of Urological Society of India held from 23 - 26 January, 2019 at Bhubaneswar, Odisha, India.
- Dr. Kamrun Nahar, Associate Professor of Radiology and Imaging attended the 18th MRI Teaching Course organized by Nanavati Super Specialty Hospital in Mumbai, India on March 2019.