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Karalus NC, Cursons RT, Leng RA, et al. Community acquired pneumonia: aetiology and prognostic Index evaluation. Thorax 1991; 46 : 413-12.

c) No author given;
Cancer in South Africa (editorial). S Afr Med J 1994; 84-15.

d) Organization as author
The Cardiac Society of Australia and New Zealand. Clinical exercise stress training. Safety and performance guideline. Med J Aust 1996; 164 : 282-4.

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ORIGINAL ARTICLE

Comparison of FEV_1/FEV_6 and FEV_6 with FEV_1/FVC and FVC for Spirometric Detection of Airway Obstruction and Restriction In Bangladeshi Adults

Nirmal Kanti Sarkar,[1] AKM Mustafa Hassan,[2] Khairul Hasan Jessy,[3] Syed Rezaul Huq,[3] Md. Khairul Anam,[4] Nihar Ranjan Saha,[4] Jibesh Kumar Pramanik,[4] Habib Uddin Ahmad,[1] Abdullah Al Mujahid,[4] Bipul Kumar Biswas[5]

Abstract

Introduction: *Spirometry is gold standard for accurate and repeatable measurement of lung function. It is an essential tool in the diagnosis of both airway obstruction and restrictive lung disease. The standard FVC has the problem of being dependent on expiratory time. Six-second FVC maneuver (FEV_6) makes spirometry more easier, less exhausting and enhances the reproducibility of the test.*

Methods: *This cross-sectional study was carried out in NIDCH from January 2010 to December 2010. Total 1153 subjects were enrolled in the study. Two hundred and eighty subjects were discarded as they could not complete the maneuver. Each subject was categorized as having "airway obstruction" and "no airway obstruction" by comparing both FEV_1/FVC and FEV_1/FEV_6. FEV_1/FVC was used as gold standard for diagnosing airway obstruction. Similarly, each subject was categorized as having spirometrically diagnosed restriction defined as a reduced FVC in the presence of normal FEV_1/FVC and by a reduced FEV_6 in the presence of a normal FEV_1/FEV_6. Two by two tables were used to calculate sensitivity and specificity for FEV_1/FEV_6 as a predictor of obstruction. Similarly sensitivity and specificity were determined for FEV_6 as a predictor for a restrictive spirometric pattern. For indices, positive predictive value and negative predictive value were calculated.*

Result: *The mean age was 39.2±12.1 years with range from 20 to 60 years and male female ratio was 2.8:1. The prevalence of obstruction was 56.9% in the whole study patients. The FEV_1/FEV_6 sensitivity was 92.5% and specificity 98.0%. Positive predictive value (PPV) was 98.6% and negative predictive value (NPV) 89.4%. The FEV_6 sensitivity was 92.8% and specificity 96.5%. Positive predictive value (PPV) was 89.5% and negative predictive value (NPV) 97.7%.*

Conclusion: *It can be concluded that the FEV_1/FEV_6 is equivalent to FEV_1/FVC as sensitive and specific in diagnosing airway obstruction and can be used as a valid alternative. FEV_6 is equivalent to FVC as sensitive and specific in spirometric diagnosis of restrictive lung disease. FEV_6 has additional advantage of simplifying the test, reducing test variability and improving accuracy in diagnosis of airway obstruction and restriction.*

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Introduction:

Assessment of airway obstruction plays a key role in the diagnosis and management of chronic obstructive pulmonary disease. The GOLD and other national guidelines advised spirometry as the gold standard for accurate and repeatable measurement of lung function.[1] Spirometry is a method of assessing lung function by measuring the volume of air that a person can expel from the lungs after a maximal inspiration.[2, 3] Several spirometric indices are currently using in clinical practice. These are - FEV_1, FVC and FEV_1/FVC. FEV_1 (forced expiratory volume in one second) - the volume of air that a person is able to exhale in the first second of forced expiration. FVC (forced vital capacity) - the total volume of air that a person can exhale in one breath. FEV_1/FVC - the ratio of FEV_1 to FVC expressed as a fraction. Recently, increased attention has been given to the use of the forced expiratory volume at 6 second of exhalation (FEV_6) as an alternative to FVC.[2]

Spirometric examination is an essential tool in the diagnosis of not only airway obstruction, but to some extent in the detection of restriction. However, variability of spirometric measurement is greater than in most other clinical laboratory tests, because the result is highly dependent on the consistency of the efforts made by patients and technicians.[2] The effort to empty lung completely, in order to reach FVC, can be particularly difficult for some patients. The measurement of FVC requires the patient to empty his or her lungs completely, a process that may take up to 20 second and that can be physically exhausting for older or impaired individuals or those with severe respiratory diseases. The standard FVC also has the problem of being dependent on expiratory time.These problems have sparked an interest in identifying a surrogate for FVC, preferably one that requires a shorter exhalation and that offers an explicitly mentioned end of test criterion. Six-second FVC maneuvre minimize the possible risk of syncope due to prolonged expiratory effect, makes the test less exhausting and enhance the reproducibility of the test.[4]

Materials and methods:

Study design, place and duration

This cross-sectional study was conducted at National Asthma Center of National Institute of Diseases of the Chest and Hospital (NIDCH), Mohakhali, Dhaka, during the period from January 2010 to December 2010. Total 1153 subjects between 20-60 years of age, both male and female and those who were able to exhale at least six seconds, were primarily included in the study. Prior to the commencement of study, the research protocol was approved by the ethical committee of NIDCH.

Instruments

- Prescribed questionnaire.
- Spirometer used for the study was Spirobank G (MIR, Italy; version winspiroPRO 3.6) and Jaeger (VIASYS Healthcare Gmbh, Hoechberg, Germany; version 4.6). The device, the program algorithms and the presentation of measured data have been developed according to specification of American Thoracic Society (ATS). [5]
- Stadiometer was made with wood and measuring tape for measurement of height.
- Standard weight machine (Bath room scale) for measurement of weight.

Study procedure

After taking informed consent, prescribed questionnaire was given to all participants. Person who fulfilled the inclusion criteria, were requested to fill the questionnaire's Bengali written portion. Height was measured to the nearest centimeter without shoes, and weight was recorded to nearest kilogram.

Spirometry was performed by the mentioned spirometers. Each spirometer was calibrated daily with a 3 liter syringe. Subjects were demonstrated thoroughly before doing the test by themselves. Subjects were tested while seated and procedures as per ATS guidelines were followed. Three readings were taken and the best was recorded. Separate disposable plastic mouthpiece was used for each subject. Particular attention was made to ensure at least 6 second exhalation. After completion of spirometric procedure it was observed that 280 participants could not perform the test according to ATS-ERS criteria. So, at last 873 subjects were included in the study.

Statistical analysis

Each subject was categorized as having "airway obstruction" and "no airway obstruction" by

comparing both FEV_1/FVC and FEV_1/FEV_6. FEV_1/FVC was used as gold standard for diagnosing airway obstruction. Similarly, each subject was categorized as having spirometrically diagnosed restriction defined as a reduced FVC in the presence of normal FEV_1/FVC and by a reduced FEV_6 in the presence of a normal FEV_1/FEV_6.

Two by two tables were used to calculate sensitivity and specificity for FEV_1/FEV_6 as a predictor of obstruction. Similarly sensitivity and specificity was determined for FEV_6 as a predictor for a restrictive spirometric pattern. For indices, positive predictive value and negative predictive value was calculated. Results were presented for male, female and total population. For statistical analysis, statistical software (SPSS 16.0) was used.

Result:

A total number of 873 subjects (644 male, 229 female) in an age group of 20-60 years (mean age 39.2±12.1 years) were finally enrolled in this study. Maximum number of subjects was found within age group of 41-50 years. The mean height was 160.5±7.9 cm which ranged from 135 to 185 cm. Maximum number (41.5%) of subjects was found within the height group of 161-170 cm. Mean weight was 54.2±12.5 kg. The BMI of the study subjects varied from 12.02 to 32.5 kg/m^2 and the mean BMI was 20.9±4.2 kg/m^2. Nearly half (48.7%) of the study subjects had normal weight and 30.4% of the subjects were under weight (Table I, II, III).

Table-I

Distribution of the study population according to age and sex (n=873)

Age (years)	Number of population (n=873)	Percentage
20 - 30	225	25.8
31 - 40	173	19.8
41 - 50	246	28.2
51 - 60	229	26.2
Mean±SD	39.2±12.1	
Range (Min -Max)	(20 - 60)	
Sex		
Male	644	73.7
Female	229	26.3

Table-II

Distribution of the study population according to height and weight (n=873)

Height (cm)	Number of population (n=873)	Percentage
<150	115	13.2
151 - 160	330	37.8
161 - 170	362	41.5
171 - 180	62	7.1
181 - 190	4	0.5
Mean±SD	160.5	±7.9
Range (Min -Max)	(135	- 185)
	Weight (Kg)	
£40	150	17.2
41 - 50	243	27.8
51 - 60	227	26.0
61 - 70	167	19.1
71 - 80	70	8.0
81-90	16	1.8
Mean±SD	54.2	±12.5
Range (Min -Max)	(23	- 90)

Table-III

Distribution of the study population according to BMI (kg/m^2) (n=873)

BMI (kg/m^2)	Number of population (n=873)	Percentage
Under weight (<18.5)	265	30.3
Normal (18.5 - 24.9)	425	48.7
Over weight (25.0 - 29.9)	157	18.0
Obese (³30.0)	26	3.0
Mean ±SD	20.9	±4.2
Range	(12.02	- 32.5)

Airway obstruction (FEV_1/FVC <70% predicted) was detected among 530 subjects and rest (343) had no airway obstruction. Among the subjects with obstructive airway disease, most (56.5%) had severe obstruction (FEV_1 d"50% predicted) and 39.4% had moderate obstruction (FEV_1 e"50 - 70%) of airway (Table IV).

Table-IV

Airway obstruction (i.e. FEV_1/FVC <70% predicted) and it's severity among study population

Grading (FEV_1% predicted)	Number of population (n=530)	Percentage
Mild (e"70 - 100%)	22	4.1
Moderate (e"50 - 70%)	209	39.4
Severe (d"50%)	299	56.5

A large portion of population under study was either current smoker or had previous history of smoking 482 (54.0%). Though many patients presented with respiratory symptoms like wheeze (39.3%), cough (39.1%) and chest tightness/breathlessness (34.5%), there was relatively small number of patients with physician diagnosed asthma 112 (12.8%) & COPD 88 (10.1%). One hundred & eighty four subjects (21.1%) had family history of asthma. Though patient with current tuberculosis was low (2.2%), 34.2% had previous history of T.B. Thirty two subjects (3.7%) had history of cardiothoracic surgery & 124 subjects (14.2%) had been suffering from cardiovascular disease. Sixty eight subjects (7.8%) had been suffering from other pulmonary disease (bronchiectasis and DPLD).

FEV_1/FEV_6 was compared with FEV_1/FVC for diagnosis of airway obstruction. In FEV_1/FEV_6 for evaluation of obstruction out of the 873 cases, true positive 490 and false positive 7, false negative 40 and true negative 336 cases. In FEV_1/FEV_6 for evaluation of obstruction in male cases out of the 644 cases, true positive 392 and false positive 4, false negative 33 and true negative 215 cases. In FEV_1/FEV_6 for evaluation of obstruction in female cases out of the 229 cases, true positive 98 and false positive 3, false negative 7 and true negative 121 cases (Table V). For the total population, the FEV_1/FEV_6 sensitivity was 92.5% and specificity was 98.0%. The PPV of FEV_1/FEV_6 was 98.6% and the NPV was 89.4%. In male subjects, the FEV_1/FEV_6 sensitivity was 92.2%, specificity was 98.2%, positive predictive value (PPV) 99.0% and negative predictive value (NPV) 86.7%. Similarly in female subjects, the FEV_1/FEV_6 sensitivity was 93.3%, specificity was 97.6%, positive predictive value (PPV) 97.0% and negative predictive value (NPV) 94.5% (Table VI). The prevalence of obstruction was 530 of 873 subjects (56.9%).

Table-V

Spirometric diagnosis of airway obstruction (n=873)

Variables	FEV_1/FVC				Total	Percentage
	Obstruction		No Obstruction			
	n	%	n	%		
FEV_1/FEV_6 , obstruction	490	92.5	7	2.0	497	56.9
FEV_1/FEV_6 , no Obstruction	40	7.5	336	98.0	376	43.1
Total	530	100.0	343	100.0	873	100.0
Male						
FEV_1/FEV_6 , obstruction	392	92.2	4	1.8	396	61.5
FEV_1/FEV_6 , no obstruction	33	7.8	215	98.2	248	38.5
Total	425	100.0	219	100.0	644	100.0
Female						
FEV_1/FEV_6 , obstruction	98	93.3	3	2.4	101	44.1
FEV_1/FEV_6 , no obstruction	7	6.7	121	97.6	128	55.9
Total	105	100.0	124	100.0	229	100.0

Table-VI

Test of validity of FEV_1/FEV_6 for diagnosis of obstruction

Test of validity	Total	Male	Female
Sensitivity	92.5	92.2	93.3
Specificity	98.0	98.2	97.6
Positive predictive value	98.6	99.0	97.0
Negative predictive value	89.4	86.7	94.5

Among 343 subjects who didn't have spirometrically detected airway obstruction, diagnostic validity of FEV_6 was evaluated for detection of restrictive abnormality keeping FVC as gold standard. In FEV_6 for evaluation of restriction out of the 343 cases, true positive 77 and false positive 9, false negative 6 and true negative 251 cases. In FEV_6 for evaluation of restriction in male cases, out of the 219 cases, true positive 62 and false positive 6, false negative 5 and true negative 146 cases. In FEV_6 for evaluation of restriction in female cases, out of the 124 cases, true positive 15 and false positive 3, false negative 1 and true negative 105 cases (Table VII). In all subjects with normal FEV_1/FVC, the usefulness of FEV_6 as an alternative of FVC in detection of restrictive spirometric pattern was assessed. For the total population, FEV_6 sensitivity was 92.8% and specificity was 96.5%. The PPV was 89.5% and the NPV was 97.7%. In male subjects, the FEV_6 sensitivity was 92.5%, specificity was 96.1%, positive predictive value (PPV) 91.2% and negative predictive value (NPV) 96.7%. Similarly in female subjects, the FEV_6 sensitivity was 93.8%, specificity was 97.2%, positive predictive value (PPV) 83.3% and negative predictive value (NPV) 99.1%. In this subgroup the prevalence of a restrictive pattern was 83 of 343 subjects (25.1%) (Table VIII).

Table-VII

Diagnosis of spirometric restrictive pattern in patients with normal FEV_1/FVC (n=343)

Variables	FVC					
	Restriction (<80.0%)		Normal (>80.0%)		Total	Percentage
	n	%	n	%		
FEV_6 restriction (<80.0%)	77	92.8	9	3.5	86	25.1
FEV_6 normal (³80.0%)	6	7.2	251	96.5	257	74.9
Total	83	100.0	260	100.0	343	100.0
Male						
FEV_6 restriction (<80.0%)	62	92.5	6	3.9	68	31.1
FEV_6 normal (³80.0%)	5	7.5	146	96.1	151	68.9
Total	67	100.0	152	100.0	219	100.0
Female						
FEV_6 restriction (<80.0%)	15	93.8	3	2.8	18	14.5
FEV_6 normal (³80.0%)	1	6.2	105	97.2	106	85.5
Total	16	100.0	108	100.0	124	100.0

Table-VIII
Test of validity of FEV_6 for diagnosis of restrictive pattern

Test of validity	Total	Male	Female
Sensitivity	92.8	92.5	93.8
Specificity	96.5	96.1	97.2
Positive predictive value	89.5	91.2	83.3
Negative predictive value	97.7	96.7	99.1

Discussion:

This cross sectional study was carried out with an aim to determine whether FEV_6 is comparable to FVC and also to see whether FEV_1/FEV_6 is equivalent to FEV_1/FVC in diagnosing airway obstruction and to determine whether FEV_6 is equivalent to FVC in spirometric detection of restrictive lung disease.

In this study it was observed that the mean age was 39.2±12.1 years with range from 20 to 60 years. Akpinar-Elci et al.[6] showed median age was 37 years with ranged from 18 to 71 years, which is comparable with the present study. On the other hand, Vandevoorde[7] and Lamprecht[4] observed higher median age in their study. Similar higher median age was also observed by other workers.[8-12] Nearly two-third (73.7%) of subjects was male and 26.3% were female and male female ratio was almost 2.8:1 in this study. Similar observations were found in different studies.[4, 6-11] Mean height of the study population was 160.5±7.9 cm which ranged from 135 to 185 cm and most (41.5%) of patients were found within the height group of 161-170 cm. On the other hand it was observed that the mean weight was 54.2±12.5 kg ranging from 23 to 90 kg. Vandevoorde[7], Swanney[8] and Gleeson[9] observed median height 170 cm, 171 cm and 175 cm respectively in their studies. Nearly a half (48.7%) of the study subjects had normal weight (BMI 18.5-24.9) and 30.4% were under weight (BMI<18.5). The findings of the other studies showed higher BMI.[10-12] Demographic variability between current and other studies may be due to racial, geographical and nutritional difference between the study populations.

In this present study, among the subjects with obstructive airway disease, most (56.5%) had severe obstruction. More than thirty nine percent (39.4%) had moderate and 4.1% had mild obstruction, which is comparable with observations by Swanney and colleagues where the author found 31.3% subjects had sever obstruction, 16.7% had moderate obstruction and 10.9% had mild obstruction.[8]

More than a half (54.0%) of the study population were either current smoker or had previous history of smoking. Respiratory symptoms like wheeze, cough and chest tightness/ breathlessness was present in 39.3%, 39.1% and 34.5% subjects respectively. Regarding the smoking status Lamprecht showed 23.5% were current smoker, 44.2% were former smoker and 32.4% were non smoker.[4] Similar observations were made by Akpinar-Elci[6] and Melbye.[13]

The prevalence of obstruction was 56.9% in the whole study population. Bellia and colleagues showed 25.3% had obstruction in their study population.[12] Obstructive airway disease (COPD and asthma) is emerging in our country. The BOLD-BD study (2007)[14] estimated prevalence of COPD 4.3% and NAPS study[15] estimated prevalence of asthma 5.2% in general population. So it was not surprising to get high prevalence of obstructive airway disease among the current study population.

In this study, it was observed that for spirometric diagnosis of airway obstruction, the FEV_1/FEV_6 sensitivity 92.5%, specificity 98.0%, positive predictive value (PPV) 98.6% and negative predictive value (NPV) 89.4%. Vandevoorde and co-workers observed the sensitivity was 94.0%, specificity 93.1%. PPV 89.8% and NPV were 96.0% in their study. Similar result was obtained when considering male & female subjects separately.[7] Swanney showed the FEV_1/FEV_6 sensitivity was 95.0% and specificity was 97.4%. The PPV of FEV_1/FEV_6 was 98.6% and the NPV was 97.4%. The prevalence of obstruction was 63.2% of the study population.[8] Demir et al.[11] found that the FEV_1/FEV_6 sensitivity was 86.09% and specificity was 100% and Akpinar-Elci and colleagues[6] identified for obstruction, the FEV_1/FEV_6 sensitivity was 92% and specificity was 98%. All these results closely resembled with the present study.

In all subjects with normal FEV_1/FVC, the usefulness of FEV_6 as equivalent to FVC in detection of restrictive spirometric pattern was

assessed. It was observed that the FEV_6 sensitivity 92.8%, specificity 96.5%, positive predictive value (PPV) 89.5% and negative predictive value (NPV) 97.7%. Vandevoorde and colleagues[7] showed the usefulness of FEV_6 as a surrogate of FVC in detection of restrictive spirometric pattern. They found FEV_6 sensitivity was 83.2% and specificity was 99.6%. The PPV was 97.4% and the NPV was 96.9%. In this subgroup the prevalence of a restrictive pattern was 15.7%. Similar result was obtained for male & female subject separately. Swanney[8] and Akpinar-Elci[6] also observed FEV_6 is highly sensitive and specific in their study, which well corresponds with the present study. Moreover high NPV in current study when comparing FEV_6 and FVC as a predictor of restrictive pattern makes the use of FEV_6 suitable for exclusion of restriction.

Conclusion:

It can be concluded that the FEV_1/FEV_6 is equivalent to FEV_1/FVC as sensitive and specific in diagnosing airway obstruction and can be used as a valid alternative. FEV_6 is equivalent to FVC as sensitive and specific and can be used as an acceptable surrogate in spirometric diagnosis of restrictive lung disease. FEV_6 has additional advantage of simplifying the test, reducing test variability and improving accuracy in diagnosis of airway obstruction and restriction. Since FEV6 seems to have a greater reproducibility than FVC and the end-of-test criteria are more easily met, it is possible that FEV_1/FEV_6 is not only as good, but could even be more accurate than FEV_1/FVC in the detection of airway obstruction, especially when screening high-risk populations for COPD in primary care.

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ORIGINAL ARTICLE

Study of Clinical Presentation of Abdominal Tuberculosis Patients in Medicine Units of Sir Salimullah Medical College and Mitford Hospital, Dhaka, Bangladesh

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Abstract:

Abdominal tuberculosis is common in Bangladesh and its presentation can be vague, no-specific and can masquerade as other conditions. Symptoms and signs of tuberculosis are no-specific and protean. The diagnosis of abdominal tuberculosis is often delayed, increasing morbidity associated with this treatable condition. So this study was done to evaluate the clinical presentation of abdominal tuberculosis.

This prospective study of descriptive nature was done between November 2009 to October 2010 at the department of Medicine, Sir Salimullah Medical College, Mitford hospital, Dhaka, Bangladesh. Total 50 patients were diagnosed as abdominal tuberculosis as per symptoms, signs and investigations and treatment was given.

Total number of patient was 50. The range of age was 13-70 years and mean ± SD = 33.2 ± 14.77 and male female ratio was o.72:l. 22(44%) patients were house wife, 6(12%) student, 7(14%) service holder, 8 (16%) business man and 7(14%) farmer. Total 38(76%) patients were married and 12(24%) unmarried. 2(4%) patients had past history of TB infection, 7(14%) history of TB contact, 8(16%) history of smoking, 6(12%) history of tobacco chewing and 1(2%) history of alcohol intake. Total 47(94%) patients presented with abdominal pain, 48(96%) fever, 47 (94%) anorexia, 7(14%) diarrhoea, 4(8%) constipation, 41(82%) vomiting, 41(82%) night sweating and 1(2%) haematochezia. But no one presented with melaena. On clinical examination, abdominal tenderness was recorded on 45(90%), ascites 29(58%), hepatomegaly 4(8%), abdominal

mass 20(40%), intestinal obstruction 6(12%), intestinal perforation 1(2%) and abdominal lymphadenopathy 1(2%). But splenomegaly was not found. The mean value of body weight before treatment was 39.1 ± 10.6.

With these clinical presentation and result of investigations the patients were diagnosed and treatment was given according to national guideline of tuberculosis of Bangladesh.

Key words: Abdominal tuberculosis, Clinical presentation.

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Introduction:

The problem of tuberculosis is worldwide and is a major health problem in developing countries.[1,2] Tuberculosis can involve any organ system in the body. While pulmonary tuberculosis is the most common presentation,

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extra-pulmonary tuberculosis (EPTB) is also an important clinical problem.[3,4,5] Abdominal TB has a good prognosis if promptly diagnosed and treated[6]. Abdominal TB is common in Bangladesh and other tropical countries and poses a significant health hazards.[7] The diagnosis of gastrointestinal tuberculosis is often delayed, increasing the morbidity associated with this treatable condition.[8] A high clinical index of suspicion and judicious use of diagnostic procedure can certainly help in timely diagnosis and treatment and thus reduce the mortality of this curable but potentially lethal disease.[9] There is no extensive study done in our country regarding abdominal tuberculosis. One retrospective study, done by Rouf HMA in general Hospital. Sirajgonj.[10] He showed that 16 cases presented with acute surgical emergencies out of 43 cases, 12 of them presented with intestinal obstruction (25%), and rest 27%had chronic symptoms. Faiz MA did another retrospective study in 1989 in IPGM&R on extra- pulmonary tuberculosis.[11] He found intestinal tuberculosis in 5 cases out of 47 patients having extra-pulmonary tuberculosis.[11] Abdominal TB has a good prognosis if promptly diagnosed and treated.[12] A high clinical index of suspicion and judicious use of diagnostic procedure can certainly help in timely diagnosis and treatment and thus reduce the mortality of this curable but potentially lethal disease[13]. Marshal et al and Anond et al also recommend clinical trial in endemic countries.[13,14]

There is still contradiction in the treatment of abdominal tuberculosis about its duration of treatment. Most of the clinician and specialist are still continuing the previous duration of treatment. There has been no attempt before to see the outcome of national guideline based treatment before.

So, this study was done in the department of Medicine, SSMC & Mitford Hospital to evaluate the clinical presentation of abdominal tuberculosis.

Materials and Methods:

This prospective study of descriptive nature was done between November 2009 to October 2010 at the department of Medicine, Sir Salimullah Medical College, Mitford hospital, Dhaka, Bangladesh. Total 50 patients were purposively selected, after screening and considering inclusion and exclusion criteria. All adult patients aged 13 to 70 years, both male and female, and Diagnosed as abdominal tuberculosis and getting anti-TB drugs following National guide line. The patients, getting anti-TB-drugs on the basis of clinical suspicion (Not confirmed cases).

The Detailed clinical history was obtained from patient admitted with suspected abdominal tuberculosis attending in the department of medicine, gastroenterology and surgery of SSMC & Mitford Hospital or other teaching hospitals in Dhaka city. The suspected case was sought and screened from focused history and examination. In taking history certain points were undertaken as screening part. These are: l)History of contact with TB. Patient, 2)History of smoking or non smoking tobacco,3)History of alcohol intake4)History of hypertension 5) History of diabetes mellitus 6)Past history of tubercular infection and 7) History of relevant symptoms-Abdominal pain, Fever, Weight loss, Anorexia, Diarrhoea, Constipation, Nausea/ vomiting, Night sweating, Melaena, Haematochezia. Thorough physical examination was done in all cases, which includes especially for abdominal examination -Abdominal tenderness, Ascites, Hepatomegaly, Splenomegaly, Abdominal mass, intestinal Obstruction, Intestinal perforation, Abdominal lymph-adenopathy. After screening procedure, 5ml blood was taken from every patients and sent to SSMC pathological laboratory for TC, DC, ESR, Hb & PBF (ESR > 50 mmHg was considered as high ESR), Urine-routine microscopic examination, Fasting Blood sugar, CXR PA view (Evidence of active PT was observed). Hundred and fifty ml (At least) Ascitic fluid was drawn whenever patient presented with this sign and sent for cytology (Lymphocyte predominance in a total cell count excessive of 150 was searched), biochemistry(protein raised was searched) and bacteriology for AFB was searched in every case. The standard laboratory procedure for ascetic fluid study was performed. An USG of whole abdomen by an expert single handed radiologist was done in every case. Those fulfilling criteria for other diagnosis from USG were excluded from the study.

Mantoux test (> 10 mm indurations was considered as positive) was done in every case. In selected cases few invasive Investigation was done like Peritoneal fluid analysis, ADA for ascitic fluid (> 37 IU/L is diagnostic of abdominal TB), Colonoscopy and biopsy (Presence of granulation tissue with caseation necrosis), CT-scan (if needed, Laparoscopic biopsy (Presence of granulation tissue with caseation necrosis).

The diagnosis of tuberculosis was confirmed by fulfilling One or more of the following four criteria along with high clinical index of suspicion —

- Histological evidence of tubercle with caseation necrosis.
- Histological demonstration of acid fast bacilli in a lesion.
- Culture of suspected tissue resulting in growth of M. tuberculosis.
- Increased ADA (Adenosine deaminase) in ascitic fluid (> 37IU/L)

All patients of diagnosed abdominal TB were under treatment of ATT cat-1 for six months as per national guide line in which Rifampicin, INH, Ethambutol and Pyrazinamide were given in first two months and after that Rifampicin and INH for next four months according to index dose. But no one was under treatment by ATT cat-2.

Data collection and statistical analysis: Statistical analysis related with this study was performed by use of SPSS 16.0 package program (SPSS -16 package Chicago lllionois).The data gathered was expressed by descriptive statistical methods (frequency distribution, percentage, mean & standard deviation) as applicable. Result of this study was shown by different tables.

Ethical issue: The study protocol was approved by the Institutional review board of SSMC, Dhaka. Informed consent was obtained from each subject. In every steps of methodology ethical consideration were followed strictly (e.g-blood collection, biopsy, peritoneal fluids aspiration, consent proceedings etc). Data was collected in an approved data collection form.

Results:

During the period of November 2009 to October 2010 total 50 patients were selected as per inclusion and exclusion criteria for evaluation of clinical presentation of abdominal tuberculosis. All patients were treated with 6 months regiment of ATT.

Table-I

Socio demographic status (n=50)

Parameters		Patient number	Percentange
Age (years)	MeanlSD	33.2 ± 14.77	
	Range	13-70	
Sex	Male	21	42
	Female	29	58
	M:F(Ratio)		0.72:1
Occupation	House wife	22	44
	Student	6	12
	Service holder	7	14
	Business man	8	16
	Farmer	7	14
	Married	38	76
	Unmarried	12	24

Table-I shows- Total number of patient is 50. Of which range of age is 13-70 years and mean ± SD =33.2 ± 14.77. 21(42%) patients were male, 29(58%)patients were female and male & female ratio is o.72 : 1. 22(44%) patients were house wife, 6(12%) were student, 7(14%) were service holder, 8 (16%) were business man and 7(14%) were farmer. Among the total patients 38(76%) patients were married and 12(24%) were unmarried.

Table-II

clinical profile of patients during presentation (n=50)

Characteristic	Patient number	Percentage
Past history of TB infection	2	4
History of TB contact	7	14
History of smoking	8	16
History of tobacco chewing	6	12
History of alcohol intake	1	2

Table-II shows-Out of total 50 patients 2(4%) patients had past history of TB infection, 7(14%) had history of TB contact, 8(16%) had history of smoking, 6(12%) had history of tobacco chewing and 1(2%) had history of alcohol intake.

Table-III

Distribution of patient according to age group (n=50)

Age interval (In years)	Patient number	Percentage
11-20	10	20
21-30	20	40
31-40	7	14
41-50	7	14
51-60	3	6
61-70	3	6

Table-III shows out of total 50 patients, 10(20%) patients were in 11-20 yrs.of age group, 20(40%) in 21-30 yrs. of age group, 7(14%) in 31-40 yrs. of age group, 7(14%) in 41-50 yrs. of age group, 3(6%) in 51-60 yrs. of age group and 3(6%) in 61-70 yrs. of age group .

Table-IV

Distribution of symptoms of patients at presentation (n=50)

Symtoms	Patient number	Percentage
Abdominal pain	47	94
Fever	48	96
Anorexia	47	94
Diarrhoea	7	14
Constipation	4	8
Vomiting	41	82
Night sweating	41	82
Melaena	0	0
Haematochezia	1	2

Table-IV shows among the total 50 patients 47(94%) patients presented with abdominal pain, 48(96%) with fever, 47 (94%) with anorexia, 7(14%) with diarrhoea, 4(8%) with constipation, 41(82%) with vomiting, 41(82%) with night sweating and 1(2%) with haematochezia. But no one presented with melaena.

Table-V

Distribution of signs of patients at presentation (n=50)

Signs	Patient number	Percentage
Abdominal tenderness	45	90
Ascites	29	58
Hepatomegaly	4	8
Splenomegaly	0	0
Abdominal mass	20	40
Intestinal obstruction	6	12
Intestinal perforation	1	2
Abdominal lymphadenopathy	1	2

Table-V shows among the total 50 patients, abdominal tenderness was recorded on 45(90%), ascites on 29(58%), hepatomegaly on 4(8%), abdominal mass on 20(40%), intestinal obstruction on 6(12%), intestinal perforation on 1(2%) and abdominal lymphadenopathy on 1(2%). But splenomegaly was not found.

Table-VI

Body weight before and after treatment (N=45)

Parameter	Before treatment	After treatment	t-value	p-value
Body weight	39.1 ±10.6	47.5 ± 10.6	-13.67	0.001

Results are expressed as Mean ± SD, Geometric mean ± *SD,* t/p value was calculated using Student's paired 't' test.

Table-VI shows the mean value of body weight before treatment was 39.1 ± 10.6. And after treatment was 47.5 ± 10.6 . Pair t-test was done and recorded value was -13.67. Here P-value was recorded 0.001

Table-VII

Investigation profile of patients (n=45)

Parameters	Before treatment	After treatment	t-value	P-value
Hb% (gm/dl)	9.711.6	11.711.5	-10.94	<0.001
ESR {In mm/lst hour)	56127	28115	8.09	<0.001
Absolute lymphocyte count (per cu mm of blood)	2425+926	17091260	4.74	<0.001

Results are expressed as Mean ± SD, Geometric mean 1 SD, t/p value was calculated using Students paired 't' test.

Table-VII showing mean value of haemoglobin of total 45 patients which were under treatment out come measurement was 9.711.6 before treatment and 11.711.5 after treatment. Student pair t-test was done with recorded t-value was -10.94. P-value was <0.001. Mean value of ESR (In mm/l^{st} hour)$_7$ before treatment was 56127 and after treatment was 28+15. Student pair t-test was done with recorded t-value was 8.09. . P-value was <0.001. Mean value of absolute lymphocyte count (per cu mm. of blood) before treatment was 24251926 and after treatment was 17091260. Student pair t-test was done with recorded t-value was 4.74. . P-value was <0.001.

Table-VIII

Result of Mantoux test (n=42)

Mantoux test	Patient number	Percentage
MT- Positive	37	88.1
MT-Negative	5	11.9

Table-VIII shows mantoux test was done over total 42 patients out of 50 patients. MT-Positive 37(88%) and MT-Negative 5(11.9%).

Table-IX

Mode of diagnosis (n=50)

Tools	Patient number	Percentage
Increased ADA level (In ascitic fluid)	24	48
Tissue biopsy (Histopathology)	26	52

Table-IX shows out of 50 patients 24(48%) were diagnosed on the basis of increased ADA level (In ascitic fluid) and 26(52%) on the basis of Tissue biopsy (Histopathology) along with high index of clinical suspicion.

Discussion:

This study was under taken to evaluate the clinical presentation of abdominal tuberculosis. It is a prospective study, done by purposive sampling, conducted between November 2009 to October 2010 for one year at the department of Medicine, Sir Salimullah Medical College, Mitford hospital, Dhaka, Bangladesh.

There are few studies in Bangladesh on clinical aspects of abdominal tuberculosis.

In this study total 85 patients were assessed for eligibility. 30 patients of them did not fulfill the diagnostic criteria and 5 patients were excluded by exclusion criteria. Finally 50 patients were selected by meeting inclusion and exclusion criteria.

In this study, out of total 50 patients, 10(20%) patients were in 11-20 yrs. of age group, 20(40%) in 21-30 yrs. of age group, 7(14%) in 31-40 yrs. of age group, 7(14%) in 41-50 yrs. of age group, 3(6%) in 51-60 yrs. of age group and 3(6%) in 61-70 yrs. of age group. It was seen that highest number of cases were recorded in 21-30 yrs. of age group. Abdominal tuberculosis can occur at any age, but most commonly in young age. The mean age of 33.2 years in the present study reflects the observations of various studies.[15] Age distribution of this study does not coincide with another studies.[16] Mean age of presentation in their study was 6-11 years, because, their study was among the children.

The number of total female patient was 29 (58%) and total male was 21(42%) and male-female ratio was 72:1. In another studies the disease was observed with female predominance, which coincides with this study.[17] More-over, in this study, age of the patients was not in the same age group but it was also observed in the later part of second decade with a female preponderance and the numbers of female patients were more than other series. Sheldon et al also observed similar age distribution in Bangladeshi migrants in East London.[18]

In this study, among the total 50 patients, abdominal pain was 47(94%), fever 48(96%), anorexia 47 (94%), diarrhoea 7(14%), constipation 4(8%), vomiting 41(82%) night sweating 41(82%) and haematochezia 1(2%) . But no one presented with melaena. Non-specific abdominal pain, low grade fever, anorexia and night sweating are common symptom in this study which coincides with the studies of Tanrikulu AC et al.,[19] Demir k et al,[20] Talwar BS et al[21], though abdominal distension, ascites and anorexia have also been reported as the common presenting symptoms in some studies.[22]

Present study revealed abdominal tenderness was 45(90%), ascites 29(58%), hepatomegaly 4(8%), abdominal mass 20(40%), intestinal

obstruction 6(12%), intestinal perforation 1(2%) and abdominal lymphadenopathy 1(2%) cases. But splenomegaly was not recorded. This data is consistent with other studies[23]. These signs were not coincided with the findings of Bernhard JS et al.[24]

Peripheral lymphadenopathy was uncommon findings in patients with intestinal or peritoneal tuberculosis. It was not reported in the earlier studies.[25]

Routine laboratory investigations though non-specific but those were helpful in our study to suspect the possibilities of abdominal tuberculosis.

ESR was raised in all cases but mean value of ESR (In mm/lst hour) was 56. Raised ESR has been reported in 50-100% of patients in earlier studies.[26]

Total and differential count of WBC were non-specific in our series, other studies had similar findings. But mean value of absolute lymphocyte count (per cu mm. of blood) was 2425, which is consistent with earlier studies.[26]

In this study Mantoux test was done over total 42 patients out of 50 patients. MT-Positive was 37(88%) and MT-Negative was 5(11.9%) .These findings are similar with the report of a 10-year review by Gilinsky NH et al.[26] In other studies, tuberculin test was positive in 70-80% patients.[27] Patients with abdominal tuberculosis may have a negative tuberculin test and a normal ESR[27]. One study has reported high ESR in 60% and positive Mantoux test in 24% of cases.[28] In areas where TB is highly endemic, positive Mantoux test neither confirms nor excludes the diagnosis.[29]

In this study, 24(48%) were diagnosed on the basis of increased ADA level (In ascitic fluid) and 26(52%) were on the basis of Tissue biopsy (Histopathology) along with high index of clinical suspicion. In other studies ascitic fluid ADA hasbeen considered to be a useful screening test with ATB, which are consistent with this study.[30]

Bacteriological diagnosis by culture of AFB was not possible due to lack of

facilities. Other studies have also faced similar difficulties in the microbiological confirmation of the disease; most of them relied on histopathological diagnosis.[31]

The strengths of this study are that abdominal TB diagnosis was confirmed histologically 26 (52%) and by increased level of ADA in ascitic fluid 24(48%) among total 50 patients. Diagnostic accuracy was thus high. Which are consistent with another study.[32] The study must however be interpreted against the background of potential limitations.

Conclusion:

Though diagnosis of abdominal tuberculosis is very complicated, but there are some definite signs and symptoms and reliable investigations which may help to diagnose the disease and save the life of many patients after giving accurate treatment.

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Conflict of interest: There is no conflict of interest in the design, conduction and publication of the study.

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ORIGINAL ARTICLE

Isolation,Identification and Drug Susceptibility Pattern of Mycobacteria from Extra-pulmonary Specimen at NTRL,NIDCH,Bangladesh

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Abstract:

This retrospective study was attempted to see the frequency of isolation of Mycobacterium among different extra Pulmonary specimens at NTRL, NIDCH, Bangladesh. Mycobacteria infect almost all tissue and organ of the body. In this regard, detection of Mycobacterium Tuberculosis from 514 different extra pulmonary specimens was performed by Lowenstein-Jensen culture and DST methods. Out of 514 patients 299(58.2%) were male, 188(36.6%) were female and 27(5.3%) had no data. M. tuberculosis *was detected in 113 cases through the conventional Lowenstein-Jensen culture method. The total positivity rate was 22.0% among all cases. Out of positive cases 53.1% (60) were male and 46.9%(53) were female. Standard Biochemical tests were performed for identification.Out of 113 positive isolates 02 cases were atypical mycobacterium. Drug susceptibility tests were performed by proportion method. All isolates were sensitive against 4 first line(Rifampicin, Isoniazid,Ethambutol,Streptomycin) anti-TB drugs. For extrapulmonary specimen, liquid culture or molecular tests will be more appropriate.*

[Chest & Heart Journal 2012; 36(2) : 111-115]

Introduction:

Tuberculosis (TB) affects not only lungs but also the other parts of the body system which is generally termed as extra-pulmonary tuberculosis.[1,2] The majority of TB manifestations are pulmonary, with extra-pulmonary TB comprising around 15% of the reported cases, especially among the immunocompromised patients[3]. As a whole TB is one of the fatal health problems in Bangladesh with 353,103 new cases every year and 70000 deaths annually.[4] However, the incidence of the extra-pulmonary TB still remains obscure in our country due to the lack of proper diagnosis.

Currently, several diagnostic methods of TB detection are in practice in Bangladesh, among which the Lowenstein-Jensen (L-J) culture and Bright Field (BF) microscopy are being exercised more frequently.[4] Use of light emitting diode (LED) fluorescence microscope has also been introduced recently in National Tuberculosis Reference Laboratory (NTRL) in Bangladesh.

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Objectives:

Therefore the objective of this retrospective study was to see the frequency of isolation of mycobacteria and then identification and sensitivity pattern.

Experimental

Materials and Methods

Settings

The study was carried out at National Tuberculosis Reference Laboratory (NTRL), National Institute of Diseases of Chest and Hospital (NIDCH), Bangladesh from January 2008- June 2009.Samples were reffered from different treatment centre of Dhaka city. NTRL has been certified by Supranational Reference Laboratory (SRL), Antwerp, Belgium, and is under their regular supervision.

Sample Collection

A total of 514 extra-pulmonary specimens including pus (75),Lymphnode(62), FNA Lymphnode(57), Tissue(24),Gastric larvae(6), Ascitic fluid(3),P.Fluid(132), CSF(3), Synoviel fluid(4), Urine(34), BAL(112) were tested. Samples were collected by applying techniques based on the type of sample. Liquid specimens were aseptically collected in a sterile plastic container. Early morning midstream urine was collected in a sterile falcon tube. Gastric larvae were collected from empty stomach. Transbronchial and other biopsies were taken aseptically and were kept wet during transportation by adding few drops of sterile 0.9% saline to the tissue.

Sample Processing

All tissue were homogenized by tissue homoginator before decontamination.[5] 2-5 ml of all samples except urine was decontaminated by mixing properly with an equal volume of 4% NaOH. After 15 minutes, 7 mM phosphate buffer saline (PBS) solution (pH 6.8) was added making the final volume 45 ml. The sample was centrifuged at 3000g for 15 minutes, and the pellet was subjected to further analysis.[5] Urine samples were centrifuged at 3000g for 15 minutes before decontamination. The pellet was then decontaminated using 0.4% sulfuric acid, neutralized by adding sterile distilled water, and was centrifuged at 3000g for 15 minutes (5).About 5gm stool specimen was taken in a sterile 50ml Falcon tube and dissolved with sterile distilled water and kept for 15 minutes to settle undissolved particle and supernatant was to another sterile 50 ml Falcon tube.The remaining deposits were processed by modified Petroff's Method.

Detection of *M. tuberculosis* through L-J culture

3 to 4 drops of the processed sample were introduced on to the slopes of L-J media, incubated at 37°C and were examined within 3 days for the early recognition of rapidly growing mycobacteria (if present) and of the contaminated cultures (if any), followed by the subsequent observation once a week up to 48 days[6]. The final species identification of *M. tuberculosis* was based on their relatively slow growth rate, appearance of buff colonies, and the characteristic biochemical traits including nitrate reductase and catalase activities. *P*-nitrobenzoic acid (PNB) sensitivity test was done since PNB is known to be a selective inhibitor of *M. tuberculosis*.[7]

Drug Susceptibility Test (DST)

Culture positive isolates were tested for drug susceptibility patterns by the proportion method[8] against the four commonly used first line anti-tubercular drugs: streptomycin (SM), isoniazid (INH), rifampicin (RIF) and ethambutol (EMB) at a concentration of 4 μg/ml, 0.2 μg/ml, 40 μg/ml and 2 μg/ml, consecutively. A sterile platinum loop was scraped across the growth along the L-J culture media slope, and was gently shaken over 5-7 sterile glass beads in a tube. After 30 minutes, aggregates settled at the bottom of the tube, and 2 ml of tween 80 was added to the homogenous upper part of the supernatant with the similar dimension of the 0.5% MacFarland standard. Then, serial dilutions of the bacterial suspension were prepared with normal saline up to 10^{-5}. L-J media containing the above-mentioned drugs as well as the drug free media (i. e., control) were inoculated with the inoculums from the dilutions 10^{-3} and 10^{-5}. The relative resistance was estimated using the following formula:

$$\frac{\text{No. of colonies on the drug media}}{\text{No. of colonies on the control media}} \times 100 = \% \text{ proportion resistant}$$

A result of >1 was considered as resistant, while a result giving <1 was interpreted as sensitive.

Results:

Frequency of detection of *M. tuberculosis* by conventional culture method.

Out of 514 samples, 111 were found to harbor *M. tuberculosis* and 2 were atypical mycobacterium detected through the culture method (Table-4). The positivity was determined by the appearance of relatively small and buff colored growth on L-J culture media during 4 - 5 weeks of incubation. Positive reactions in nitrate reduction and catalase tests, absence of growth on L-J media containing PNB (500 µg/ml) confirmed the culture positive isolates as the typical *M. tuberculosis*. The total positivity rate was 22.0%.

Positivity according to specimen types and method of detection

Among the extra-pulmonary specimens, the lymph node aspirate samples were found to pose 38(61.29%) positivity in culture. The overall numbers of positive cases were found relatively higher in FNA Lymphnode(68.42%) than other samples.Positive cases were also found from tissues, gastric lavage,pleural fliuid,BAL and urine samples.Laryngeal swabs and fluid samples such as ascitic fluid, synoviel fluid and stool had no positive cases (Table I).

Positivity based on Gender analysis

Out of 514 cases 299(58.2%) were male, 188(36.6%) were female and 27(5.3%) cases had no data. The positivity rate among male was 60(53.1%) and in female was 53(46.9%).(Table-2).

Table-I

Sample type

Sample Type	No. of sample	Positive	Negative
Lymph node	62	38	24
FNA Lymph node	57	39	18
PUS	75	4	71
Other Tissue	24	1	23
GL	6	2	4
Ascitic fluid	3	0	3
P. Fluid	132	14	118
CSF	3	0	3
Synoniel fluid	4	0	4
Urine	34	3	31
Stool	2	0	2
*BAL	112	12	100
Total	514	113 (22.0%)	401 (78.0%)

Table-II

Positive analysis based on Gender

Type	Number	Percentage
Male	60	53.1
Female	53	46.9
Total	113	

Table-III

Drug Susceptibility pattern

Drugs	No. of susceptible	Percentage
Streptomycin	111	100
Isoniazid	111	100
Rifampicin	111	100
Ethambutol	111	100

Table-IV

Identity of the isolates

Type	No
Mycobacterium tuberculosis	111
Atypical Mycobacterium	02

Discussion:

The diagnosis of extra pulmonary tuberculosis is challenging for a number of reasons: the lack of adequate sample amounts or volumes; the apportioning of the sample for various diagnostic tests (histology/cytology, biochemical analysis, microbiology, and PCR), resulting in nonuniform distribution of microorganisms; the pauci-bacillary nature of the specimens; the presence of inhibitors that undermine the performance of nucleic acid amplification-based techniques; and the lack of an efficient sample processing technique universally applicable on all types of extrapulmonary samples.

Among communicable diseases, tuberculosis (TB) is the second leading cause of death worldwide, killing nearly 2 million people each year. It is estimated that about one-third of the world population are infected with TB (2 billion people) and about 10% of this figure will progress to disease state. Most cases are in the under developed countries of the world.[9] Bangladesh is the most densely populated country in the

world; extreme poverty, malnutrition, and overcrowding create a substantial risk for infection with *M. tuberculosis* among its population.

Tuberculosis (TB) is an ancient infectious disease that has appeared once again as a serious worldwide health problem and now comprises the second leading cause of death resulting from a single infection.[10]

In, Bangladesh, Dhaka is a chrammed full and grimy area in supplementary precarious to propagate the disease which influenced this study to make the sampling from NIDCH, Mohakhali, Dhaka. The suspected untreated new (primary) and previously treated TB patients were used in this study. Random sampling was made from daily incoming suspected patients and TB patients for diagnosis in NIDCH, Mohakhali, Dhaka. According to the clinical demography of the studied patients, this experiment found that the males (71%) were susceptible than female (29%). One the other hand, this study also showed that the incidence among male and female peaks at 21-30 years of age. In this age group, rates among male are usually higher than those among female. The reason of higher male tuberculosis cases than female cases might be explained by the fact that males are active population in the community and may come in contact with TB infected persons. Whereas female members in Bangladesh still reside at home and do not attend at TB clinic for treatment, so chance of exposure is much less.

In the present study ,out of 514 different extra pulmonary samples analyzed for detection of mycobacterium tuberculosis 113 cases (22%) were positve in culture on Lowenstein Jensen media. Small and buff colored colonies on L-J media were selected as presumptive *M.tuberculosis.* The isolates were then identified biochemically by nitrate reduction and catalase tests.Out of 113 positive isolates 111 isolates gave positive reactions (pink to red color)in nitrate reduction test which is the typical characteristics of M.tuberculosis and 2 isolates gave negative reactions that is atypical mycobacteria..In catalase test .oxygen bubbles were observed only in unheated tubes which means they possessed heat labile catalase as they showed no catalase activity at 68C identified as M.tuberculosis.In case of drug susceptibility testing 111 isolates were sensitive against to PNB as no growth was observed on any of L-J media containing PNB.Only two isolates showed resistance against PNB.The isolates were proved to be typical *M.tuberculosis*..Lowenstein -Jensen (L-J) medium ,which is specific for *M.tuberculosis* gave 84(84%)AFB positive results. This result also indicates that culture is a gold standard for diagnosis of TB.L-J media contain malachite green that inhibits the growth of others. Culture results were used as the gold standard for assessment.

In this study DST had been performed for INH,RIF,EMB, and SM four first line anti TB drugs..According to DST results all four first line drugs were susceptible to all positiuve isolates.(Table-3)

The majority of the isolates were from Lymphnode and lymphnode aspirate.So therefore, culture appeared as a substantial tool for bacterial evidence of tuberculos lymphadenitis but still treatment history required to declared negative TB cases.Liquid culture and molecular tests like GeneXpert MTB/RIF will more appropriate for this type of study.

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ORIGINAL ARTICLE

Airway Stenting : A New Step in Bangladesh

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Abstract:

Background: *Self-expanding metal stents have been used successfully to overcome large airway obstruction due to malignant pulmonary disease. The technique has been modified to place stents under direct vision using the fibreoptic bronchoscope. The effect of this procedure on lung function and patient well being was investigated in three patients in NIDCH, Dhaka, Bangladesh. Stent insertion was uncomplicated.*

Methods: *Three patients with malignant tracheobronchial tumours were treated for symptoms of life threatening airways obstruction or collapse of a lung by the insertion of an expandable metal stent(s) under local anaesthetic using a fibreoptic bronchoscope. All had inoperable cancer and histopathological diagnosis was conclusive. All patients had the stents inserted at one sitting and one patient needed the debulking of the tumour. Measurements were performed in all the patients before and after stenting and included objective measures (pulmonary function tests, arterial blood gas tensions) and non-objective measures (patient well being, performance status).*

Results: *Overall, 100% of patients showed symptomatic improvement. Patients in whom measurements were performed all the patients showed improvement in forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), peak expiratory flow rate (PEFR) and arterial oxygen tension (PaO_2). There were no perioperative complications.*

Conclusions: *In suitable patients with either extraluminal or intraluminal tumour, or both, the insertion of expandable metal stents using a fibreoptic bronchoscope and local anaesthetic is a valuable addition to other palliative therapies in the treatment of lung cancer.*

[Chest & Heart Journal 2012; 36(2) : 116-119]

Introduction:

Large airway obstruction due to primary lung cancer or spread from non-bronchial malignancies can produce life threatening and distressing breathlessness, either as an acute presenting symptom of the underlying disease or when recurrence occurs after other treatment. Expandable metal stents have been used successfully to relieve airway obstruction in such patients.[1,2] In different centre, the procedure was carried out under general anaesthesia using a rigid bronchoscope and fluoroscopic imaging. This approach limits its use to centres where rigid bronchoscopy is available, and to those patients who are well enough to withstand general anaesthesia.

To overcome these difficulties we have modified the procedure by inserting these expandable stents under direct vision using a fibreoptic bronchoscope and local anaesthesia only. We

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report here our experience of this novel approach in 3 patients, and our assessment of the effectiveness of this therapy in the palliation of inoperable lung cancer.

Methods:

A total no. of 3 patients with respiratory distress due to malignant obstruction of the trachea and/ or a main bronchus have now undergone this procedure (all patients) of mean age of 55 years (range, 45-60). All had primary bronchial carcinoma. All the patients received conventional treatment with radiotherapy and chemotherapy in addition to stent insertion as a primary procedure. The sites of obstructions within the tracheobronchial tree are shown in Table 1. The stents used (see below) are available in a range of widths and lengths. In this procedure, we used the following sizes: two cases - 40mm (length) x 16mm (width), one case – 60mm (length) x 16mm (width). In general the 20mm width stents are used for obstruction in the main bronchi and 30mm stents for obstruction in the trachea. But it varies according to race as diameter of trachea is not equal in all races.

Table-I

Site of malignant obstruction in 3 patients

Site of obstruction	No. of patients
Trachea	1
Right principal bronchus	2

Response to treatment was firstly assessed by the patient's account of their symptoms (using a visual analogue score for breathing and another for well being).[3,4] The results of lung function studies before and after stenting were recorded including forced expiratory volume in one second (FEV_1), forced vital capacity (FVC) and peak expiratory flow rate (PEFR).[5] Arterial blood gas tensions were also measured before and after stenting.

All patients received supplementary oxygen via nasal canuale (6l/min), and oxygen saturation was monitored using an oxymeter attached via a finger probe.

Technique

The fibreoptic bronchoscope was passed through the mouth via a mouth gag and positioned above the obstructing lesion in the trachea or main bronchus. A flexible guide wire was then inserted through the biopsy channel of the bronchoscope and pushed beyond the malignant narrowing. The bronchoscope was then removed whilst threading the wire through the suction channel to ensure the wire was left in position in the tracheobronchial tree. The bronchoscope was then reinserted through the mouth and positioned just above the vocal cords. The stents with applicator was threaded over the wire and placed beyond the narrowing under the direct vision of the bronchoscopist. The wire was then removed, taking care not to displace the stent with applicator.

Under direct vision through the fibreoptic bronchoscope the stent was pushed out of the applicator and expanded as it was released. Initial immediate dilatation is followed by a further gradual increase in diameter of the narrowed airway over the next 24 hours. The position and opening of the stent was checked by a chest radiograph immediately and 24 hours following the procedure.

Results:

In all the patients, the stenting was carried out at one session. Histological types of primary and tracheal bronchial malignancy are shown in Table 2.

Table-II

Histological types of primary tracheobronchal carcinomas (n=3)

	No. of patients
Tumour type (n=3)	
Squamous cell	1
Adenocarcinoma	2

Lung Function Studies

Patients who underwent stenting complete physiological data are available for all. Irrespective of the site of the obstruction the results are shown in Table 3. There were significant improvements in the FEV_1 ($p=0.001$), FVC ($p<0.05$), PEFR ($p=0.05$), and PaO_2 ($p<0.05$).

Table-III

Comparison of mean (SD) values for spirometric parameters, PEFR, and arterial blood gases before and after stenting

	Before stenting	After stenting	P value	Increase
All patients (n=3)				
FEV_1 (1)	1.13 (0.41)	1.38 (0.57)	0.001	0.25 (0.4)
FVC (1)	1.96 (0.7)	2.15 (0.76)	<0.05	0.19 (0.48)
PEFR (1/min)	134 (12)	158 (14)	0.05	24 (65)
PaO_2 (kPa)	8.81 (2.7)	10.24 (3.14)	<0.05	1.43 (3.2)

Patient Orientated Measure

Scores for walking (as revealed by 6 minutes walk test and breathing as revealed by respiratory rate) all changed significantly after stenting.

Chest Radiographs & Bronchoscopy

All the patients showed in radiological and bronchospic improvement as evidence by patency of airway after stenting as shown in Fig. 1(a), 1(b), 2(a), 2(b) and Fig. 3.

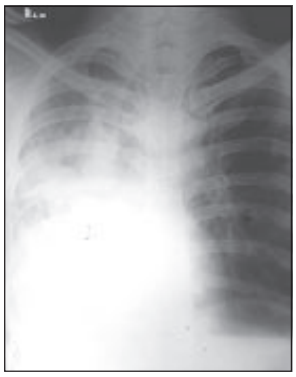

Fig.-1(a): *Radiological evidence of growth before Stenting*

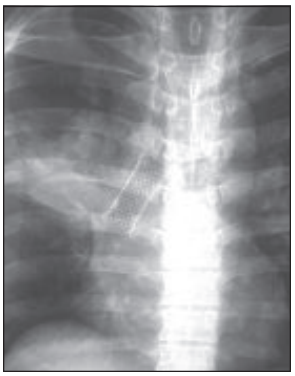

Fig.-1 (b): *Significant radiological improvement after Stenting*

Discussion:

There are now a number of treatment options available for the relief of distressing breathlessness due to major airway compression from inoperable carcinomas. These include endoscopic surgery,[6] cryotherapy,[7] laser photoresection,[8] and the insertion of silastic[9] or self-expanding metal stents.[10] All are usually under taken via a rigid broncoscope using general anaesthesia, thereby limiting their application to centres where these facilities are available.

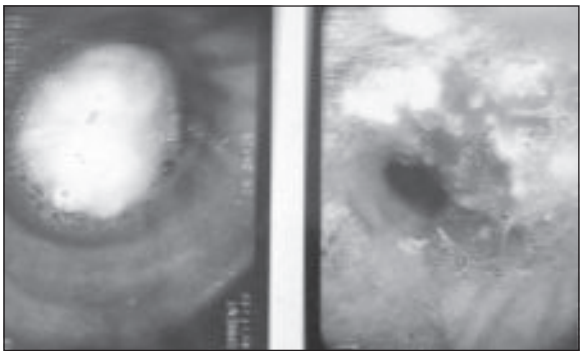

Fig.-2(a): *Bronchoscopic evidence of growth and debulking done before stenting*

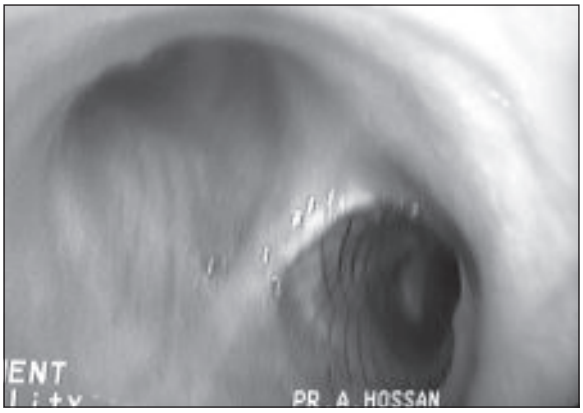

Fig.-2(b): *Bronchoscopic evidence after stenting*

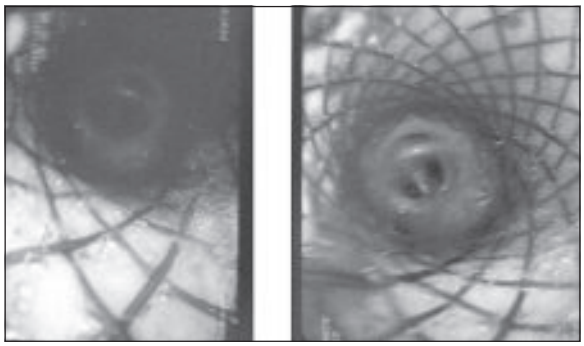

Fig.-3: *Luminal patency restored after stenting*

The results presented here demonstrate that self-expanding metal stents can be inserted under local anaesthesia using the direct vision afforded by a fibreoptic bronchoscope. In our view this could be carried out in any centre where firbreoptic bronchoscopy is available. However, facilities to transfer a patient to a centre offering rigid bronchoscopy should be available in case patients cannot tolerate a fibreoptic bronchoscopy. Rigid bronchoscopy is also indicated for the removal of stents that have been positioned incorrectly.[10]

In our patients, stenting was carried out as a primary palliative procedure with other therapies (Chemotherapy ±radiotherapy). For patients treated before external or endobronchial radiotherapy, stenting provides protection of the airway and thereby may reduce the risk of sudden death due to complete airway obstruction as a result of post irradiation oedema.[11] This technique has two other potential advantages when compared with other palliative endoscopic procedures for inoperable tracheobronchial cancer. The first is that the insertion of the stent often results in an immediate improvement in the patient's breathlessness and/or stridor. This improvement occurs in cases with either intraluminal or extraluminal compression, or both, in contrast to laser photoresection or cryotherapy which is only of value with intraluminal tumours. Secondly, the radio-opaque metal stents can act as markers for planning of such radiotherapy.

Conclusions:

Endobronchial interventions are important adjuncts in the multimodality management of lung cancer and should become standard considerations in the management of patients with advanced lung cancer. For patients with respiratory symptoms associated with their disease, these interventions provide symptom palliation and improved quality of life.

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ORIGINAL ARTICLE

Pulmonary Function Following Lobectomy Depends Upon Lobe Excised

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Abstract:

Introduation: *Lobectomy for a variety of pulmonary diseases is a common procedure in thoracic surgery. It is a surgical procedure where a lobe of the lung is removed. Lung function tests measure the severity of lung problems and asses operative risk. There are several pulmonary function tests , but there is no single measure that is a "gold standard" in accurately predicting postoperative complications. Estimation of pre-operative FVC, FEV1,%FVC,%FEV1 measured in spirometry are frequently used criterion for assessment of postoperative pulmonary function after lobectomy.This study presents a new approach to compare spirometric data between pre-operative and different visits after lobectomy and evaluate the relationship of ventilatory function with the anatomical side of lung's lobe (before and after operation).*

Aims & objectives: *The purpose of this study was to find out the changes of pulmonary function (spirometric variables) after lobectomy, to determine the relationship of ventilatory function with the anatomical side of lobe excised and also to verify the improvement of pulmonary function after lobectomy.*

Materials & Methods: *This prospective observational study was conducted in the Department of Thoracic Surgery, NIDCH, Mohakhali, Dhaka during the period of January 2008 to December 2009. Total 50 patients under gone lobectomy were included in the study.Patients were selected consecutively. All the patients were undergone pre-operative lung function test by Spirometry (spirometric variables). Pre-operative spirometric variables were considered as baseline values in this study. All Patients with satisfectory outcome was discharged and patients were followed up for three times at 1^{st} , 3^{rd} & 5^{th} month after discharge. Each follow up Patients were evaluated clinically, radiologically and spirometrically. All relvent datas were analyzed using standard statistical method.*

Results: *On the basis of lung's lobe, the distributions of four different spirometric outcomes (FVC (L), FEV_1 (L), % FVC and % FEV_1) at baseline and at different visits were studied. Despite variability, there was no*

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significant and independent effect on the functional capacity of lung after lobectomy and pulmonary function remain unchanged or even increased after lobectomy. Patient's follow-up after surgery revealed a significant decrease in FVC and FEV_1,but function had improved again at 3 months after surgery and remained stable at 5 months after lobectomy. Regarding lung's lobe no significant differences among the lobes related to changes in the lung function after lobectomy were observed and there was no significant relationships between right side & left side. They highlight the fact that the changes of spirometric values are not dependent on the anatomical side of the lobe excised.

Conclusion: *The current study demonstrated that changes in pulmonary function after lobectomy does not co-relate with the anatomical side of the lobe excised & ventilatory function recovers to the preoperative level from 3 to 5 months after lobe resection.*

[Chest & Heart Journal 2012; 36(2) : 120-127]

Introduction:

Lobectomy is a surgical procedure where a lobe of the lung is removed. The operation is performed when an abnormality has beeen detected in a specific part of the lung. The affected lobe is removed and the healthy tissue remains. Common indications for lobectomy include both neoplastic and non-neoplastic lung diseases. For malignant conditions, non small cell carcinomas are the most frequent indications followed by small cell carcinomas and metastatic tumours. Among the patients with non-neoplastic diseases, the main indications for lobectomy are bronchiectasis with unremitting symptoms & complications, lung abscess, infected pulmonary cyst, pulmonary tuberculosis with complications, fungal infections (aspergilloma), trauma with hemorrhage, hemoptysis (massive, severe & recurrent). Other indications for lobectomy include chronic obstructive pulmonary disease (emphysematous bulla, bronchitis which cause airway obstruction), congenital anomalies, large benign tumor and other more rare conditions, such as pulmonary infarction, arterio-venous malformations.

Although lobectomy is a therapeutic procedure, it is not free from its own complications. Complications vary from infection and hemorrhage to pneumothorax. Fractured ribs are one of the potential complications along with pulmonary embolism, atelectasis, pneumonia, persistent space, prolonged air leak from the remaining lung tissue with developing empyema and an irregular heart rhythm.[1] Minor complications include abnormal or painful scar formation, skin numbness, nerve injury, minor infections, nausea and vomiting. Operative risk with increased possibilities of developing postoperative complications are heavily dependent on the surgical site and patient-related factors: include pre-existing pulmonary disease, cardiovascular disease, pulmonary hypertension, dyspnea upon exertion, respiratory infection,cough (particularly productive cough), advanced age (>70 years), malnutrition, general debilitation, obesity, and prolonged surgery.[2]

Lung function test evaluate dyspnea and respiratory impairment, detect pulmonary disease, monitor effects of therapies used to treat respiratory disease, perform surveillance for occupation related lung disease and asses operative risk. Pulmonary function tests include: spirometry, diffusion capacity, arterial blood gas analysis, radionuclear lung scanning, cardiopulmonary exercise testing ; but no single pulmonary function test can effectively predict intraoperative and postoperative morbidity and mortality from pulmonary complications. Predicted values of pulmonary function depend on age, height, gender and race. Spirometry (meaning the measuring of breath) is the most common of the pulmonary function tests (PFT), measuring lung function, specifically the measurement of the amount (volume) and speed (flow) of air that can be inhaled and exhaled.

Spirometry is simple, inexpensive, standardized & readily available test that can provide cut-off values of acceptable risk in patients for thoracic surgery. It assesses the integrated mechanical function of the lung, chest wall and respiratory muscles by measuring the volume and capacity of lung. The FVC (reflect lung volume) and FEV_1 (reflect airflow) obtained by spirometry are the most commonly used parameters to assess suitability of patients for surgery. The FVC and FEV_1can be expressed in either absolute values or as a percentage of predicted values. The interpretation of the results can vary depending on the physician and the source of the predicted values. Generally speaking, results nearest to 100% predicted are the most normal, and results over 80% are often considered normal.

The FVC and FEV_1 obtained from good quality spirometry are useful tool that can be used to estimate postoperative function to compare the actual postoperative pulmonary function with the predicted function.[2] We can calculate the predicted postoperative pulmonary function according to the formula **:** *predicted postoperative* FEV_1 *= preoperative* FEV_1 *x [1-(No. of segments in lobe to be resected x 5.25)/ 100].* In brief, the calculation was based on the number of segments that remained after the operation. The lower lobes were considered to have 5 pulmonary segments each, the right upper lobe had 3 segments, and the left upper lobe had 4 segments and middle lobe has 2 segments. Each segment was supposed to represent 1 / 19 or 0.0526 of the preoperative function.[9] Estimation of pre & postoperative FEV_1% is a frequently used criterion to define operability in patients undergoing lobectomy. More specific tests do not seem to add predictive information. In addition, individual tests do not seem to correlate with specific complications.[3]

A close look at Korst and associates' data, reveals that of a total of 10 patients who underwent lobectomy with a preoperative FEV_1 of less than 1.7 L, 4 (40%) actually increased their FEV_1 postoperatively. A prospective study in 32 patients after lobectomy show that the patients who have pure obstructive airway disease are most likely to increase FEV_1 after lobectomy [4]. A study in 50 (36 males and 14 females; mean age 61 yrs) underwent a lobectomy, was done to determine the effect of lobectomy on pulmonary function tests (PFT).Three months after lobectomy, forced vital capacity (FVC), forced expiratory volume in one second (FEV_1) were significantly lower than Preop. values, increasing significantly from 3 to 6 months after resection.[5] Yoshinori and co-workers perform a study for longitudinal objective evaluations of recovery of exercise capacity based on expired gas analysis during exercise testing up to 1 year after pulmonary resection. The study included 18 patients who underwent lobectomy. They concluded that the extent of recovery of exercise capacity at 1 year after surgery was approximately 95%. Furthermore, the anaerobic threshold per square meter of body surface area was restored to the preoperative level by 1 year after surgery.[6]

To determine the effect of lung resection on spirometric lung function and to evaluate the accuracy of simple calculation in predicting postoperative pulmonary function, a review of preoperative and postoperative pulmonary function test results done on 60 patients who underwent lung resection between July 1991 and March 1994 .The predicted postoperative FEV_1 and FVC were calculated based on the number of segments resected and were compared with the actual postoperative FEV_1 and FVC. The actual postoperative FEV_1 and FVC correlated well with the predicted postoperative FEV_1 and FVC for patients undergoing lobectomy ; however, the predicted postoperative FEV_1 consistently underestimated the actual postoperative FEV_1 by approximately 250 ml.[7]

Good preservation of postoperative pulmonary function is a great benefit for patients undergoing lobectomy. The improved PFR and FEV_1 were reported to be correlated with the ability to expectorate retained bronchial secretions. Therefore, it seems that good pulmonary function could reduce postoperative complications and help faster recovery especially for high-risk patients.[8]

Aims and Objectives:

General objective of this study was to see the change of pulmonary function after lobectomy by measuring spirometric variables.Specific

objectives were aimed at assessing immediate and late post-operative morbidities after lobectomy ,to observe the relationship of pulmonary function after lobectomy with the anatomical side as well as the pathological condition of the lobe excised and also to evaluate indication for lobectomy. And the study was hypothesized that pulmonary function not always improves after lobectomy.

Materials And Methods :

It was an Observational prospective study conducted in the department of Thoracic Surgery, NIDCH, Mohakhali,from January, 2008 to December, 2009. Data was collected through a pre-designed data collection Sheet.Sample Size was 50 (fifty).Sampling was consecutive and purposive. Inclusion criteria was those patients who were admitted in NIDCH underwent elective lobectomy in different etiology and exclusion criteria was those patients who failed to come for three times after operation as follow up visits.

Pre-operative variables were demographic (age , sex) ; presenting complaints (cough, sputum production, hamoptysis , dyspnoea,chest pain ,wheeze,fever) ; prensence of co-morbid illness (DM,HTN,PTB , asthma,COPD); pre-operative investigation '! non-specific (complete blood count, blood sugar, renal function tests, serum billirubin were done in all cases and electrocardiogram was done to those patients who were aged over 40 years) and specific (X-ray Chest P/A and lateral view, sputum AFB & C/S, CT scan of the Chest done in almost all patient,CT-guided FNAC & broncoscopy done in selected cases, spirometry done in all patients : measured values were FVC ,% FVC ,FEV_1,% FEV_1) ; clinical diagnosis (made on history, clinical findings & investigation results).

Per-operative variables were surgical approach (elective thoracotomy); side of resection (right lung ,left lung) ; site of resection (upper lobe, middle lobe, lower lobe , bi-lobe : right upper bi-lobe , right lower bi-lobe , left lower lobe & lingual).

Post operative variables were hospital stays (total hospital stays, total post-operative period); postoperative complications (post-operative bleeding : >300ml within first 24 hours of postoperative period, atelectasis, pneumonia, wound infection , persistent air leak); histopathological report; final diagnosis (made on history, clinical findings, investigation results, Per-operative findings and histopathological reports).

Patients were followed up for three times '! 1 (one) month after discharge, 2 (two) months after first follow up , 2 (two) months after second follow up. Each follow up patients were evaluated by clinical features (cough,sputum,fever,chest pain,dyspnoea,haemoptysis,wheeze, deformity) ; radiological findings ; spirometric variables (FVC ,% FVC ,FEV_1 ,% FEV_1).

All relvent data was collected from each participants using predesigned data collection sheet . A major data sheet was compiled and prepaerd from information gathered through individual data sheet.Collected data was expressed as Mean ±SD. Age, sex, presenting complaints, co-morbid illness, underlying disease and other variables analysis were carried out using SPSS (Statistical Package for Social Science) [version 16.0].

Results:

The analysed data were presented by crossing of variables in the form of tables and line chart. A *p* value of equal to or less than 0.05 was considered significant.

Table-I

Distribution of patients by age

Age (in year)	Frequency	Percent
d"25	18	36.0
25-35	12	24.0
35-45	10	20.0
45-55	06	12.0
>55	04	08.0
Total	50	100.0

Mean ± SD (Range) = 35.50 ± 15.29 (18-80)

Table-II

Distribution of patients by sex

Sex	Frequency	Percent
Male	37	74.0
Female	13	26.0
Total	50	100.0

Male: Female = 2.85: 1

Table-III

Distribution of patients by presenting complaints

Presenting complaints	Frequency	Percent
Cough	50	100.0
Sputum	32	64.0
Chest pain	33	66.0
Dyspnoea	26	52.0
Haemoptysis	17	34.0
Fever	17	34.0
Wheeze	14	28.0

Table-IV

Distribution of post operative complications before discharge

Post operative complications	Frequency	Percent
Post-operative bleeding (>300ml within 24 hours of postoperative period)	17	34.0
Atelectasis	11	22.0
Pneumonia	10	20.0
Wound infection	04	08.0
Persistent air leak	01	02.0

Table-V

Comparison of FVC (L), FEV_1 (L), %FVC and $\%FEV_1$ between baseline and different visits

Spirometry	p value			
	FVC (L)	FEV_1 (L)	%FVC	$\%FEV_1$
Baseline vs 1st visit	0.001	0.010	0.001	0.001
Baseline vs 2nd visit	0.040	0.219	0.064	0.158
Baseline vs 3rd visit	0.531	0.829	0.618	0.301

Table-VI

Distribution of patients by post operative hospital stay

Post-operative hospital stay (day)		Frequency	Percent
Mean ± SD (Range)	13.06 ± 3.96 (10-34)		
10 days		26	52
10-15 days		15	30
>15 days		09	18

Table-VII

Distribution of patients by side of operation

Side of operation	Frequency	Percent
Left		
Upper	13	44.8
Lower	13	44.8
Lower & lingula	03	10.3
Right		
Upper	10	47.6
Middle	03	14.3
Lower	04	19.0
Upper & middle	02	09.5
Lower & middle	02	09.5

Table-VIII

Distribution of post operative complications after discharge in 1st visit, 2nd visit and 3rd visit

Complaints	1st visit	2nd visit	3rd visit
Chest pain	49 (98.0)	40 (80.0)	09 (18.0)
Cough	19 (38.0)	10 (20.0)	09 (18.0)
Fever	03 (06.0)	02 (04.0)	01 (02.0)
Dyspnoea	07 (14.0)	06 (12.0)	00
Wheeze	04 (08.0)	04 (08.0)	00
Sputum	03 (06.0)	00	00
Haemoptysis	00	00	01 (02.0)
Space infection	00	01(02.0)	00
Deformity			
!)Flattened chest wall	00	00	03(06.0)
!!)Scoliosis	00	00	02(04.0)

Figure within parentheses indicates inpercentage.

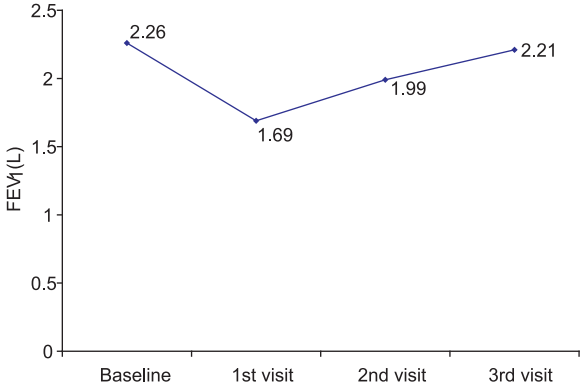

Fig.-1: *Line graph of FEV_1 (L) in baseline, 1st visit, 2nd visit and 3rd visit*

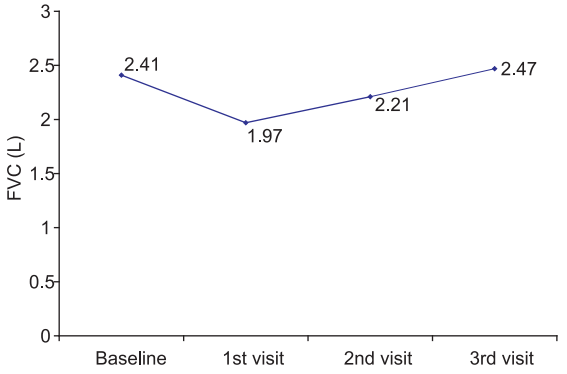

Fig.-2: *Line graph of FVC (L) in baseline, 1st visit, 2nd visit and 3rd visit*

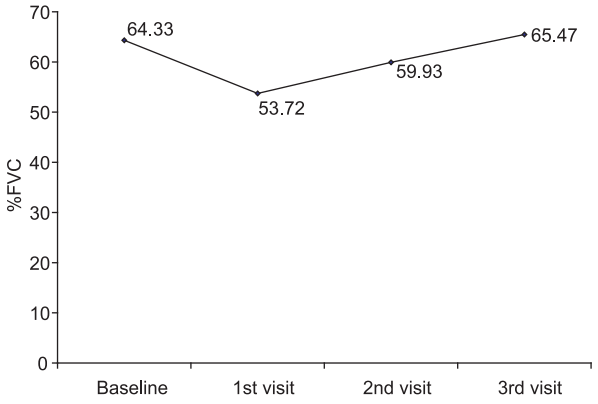

Fig.-3: *Line graph of %FVC in baseline, 1st visit, 2nd visit and 3rd visit*

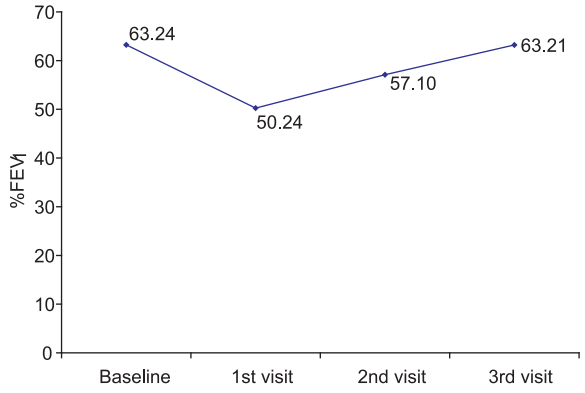

Fig.-4: *Line graph of %FEV$_1$ in baseline, 1st visit, 2nd visit and 3rd visit*

At baseline. among the patients with left sided operation the mean ± SD of FVC (L), FEV_1 (L), %FVC, $\%FEV_1$ were 2.44 ± 0.68, 2.01 ± 0.43, 66.55 ± 14.80 and 63.90 ± 13.34 respectively. Among the patients with right sided operation the mean ± SD of FVC (L), FEV_1 (L), %FVC, $\%FEV_1$ at baseline were 2.36 ± 0.78, 2.59 ± 2.19, 61.27 ± 11.86 and 62.34 ± 12.75 respectively.

At 1st visit. among the patients with left sided operation the mean ± SD of FVC (L), FEV_1 (L), %FVC, $\%FEV_1$ were 1.99 ± 0.39, 1.68 ± 0.39, 55.46 ± 11.79 and 50.93 ± 11.91 respectively. Among the patients with right sided operation the mean ± SD of FVC (L), FEV_1 (L), %FVC, $\%FEV_1$ at 1st visit were 1.95 ± 0.41, 1.72 ± 0.40, 51.31 ± 9.18 and 49.28 ± 9.05 respectively.

At 2nd visit. among the patients with left sided operation the mean ± SD of FVC (L), FEV_1 (L), %FVC, $\%FEV_1$ at 2nd were 2.23 ± 0.49, 1.98 ± 0.49, 62.09 ± 12.91 and 58.39 ± 11.41 respectively. Among the patients with right sided operation the mean ± SD of FVC (L), FEV_1 (L), %FVC, $\%FEV_1$ at 2nd visit were 2.19 ± 0.56, 2.00 ± 0.59, 56.95 ± 10.42and 55.31 ± 11.61 respectively.

At 3rd visit. among the patients with left sided operation the mean ± SD of FVC (L), FEV_1 (L), % FVC, % FEV_1 at 3rd visit were 2.43 ± 0.48, 2.15 ± 0.52, 65.50 ± 11.74 and 62.85 ± 11.40 respectively. Among the patients with right sided operation the mean ± SD of FVC (L), FEV_1 (L), % FVC, % FEV_1 at 3rd visit were 2.52 ± 0.69, 2.29 ± 0.67, 65.42 ± 12.54 and 63.70 ± 11.73 respectively.

Table-VIII

Distribution of final diagnosis

Diagnosis		Total
1.Bronchiectasis		14(28%)
2.Malignancy		8 (16%)
	!)Adeno-carcinoma	5(10%)
	!!)Sqamous cell carcinoma	3(06%)
3.Cavitary lession		7(14%)
	!)Abscess	5(10%)
	!!)Carcinoid	1(02%)
	!!!)Cystic-hydatid	1(02%)
4.Pulmonary Cyst		5(10%)
	!)Hydatid cyst	4(08%)
	!!)Infected bula	1(02%)
5.Aspergilloma		5(10%)
6.Encysted Empyema		3(06%)
7.Bullae		2(04%)
8.Post Tb Fibrosis		2(04%)
9.Carcinoid		2(04%)
10.Others		2(04%)
	!)Chronic Inflamatory	1(02%)
	!!)Trapped Lung (post traumatic)	1(02%)
a"%% Total =		50(100%)

Discussion:

It was thought that the lung resection may cause loss of pulmonary function & there are some data that indicate considerable loss of function after lobectomy especially for lung cancer patients . But several other studies were found, that revealed patients who underwent lobectomy actually increased their postoperative pulmonary function after lobectomy. The fact is that the lost ventilatory function after lobectomy is restored by allowing the more normal lung to expand and ventilate more efficiently. And also by the increasing ability to expectorate retained bronchial secretion which was markedly detoriated by the concomitant disease process prior to surgery.[9] Some study showed that the postoperative ventilatory function in patients who underwent middle or lower lobectomies had better preserved respiratory function than predicted and there were no significant relationships between right & left groups.

In the present study the mean ± SD of the age of the patients was 35.50 ± 15.29 with a range of 18-80 years. Highest number of patients (36.0%) was in the age group of d"25 years. About three fourth patients (74.0%) were male and 13 (26.0%) were female.Highest number of patients was clinico-histopathologically diagnosed as bronchiectasis (26.0%) followed by mass lesion (22.0%). All patients were presented with cough. Sputum present in 32 (64.0%) patients and chest pain present in 33 (66.0%) patients. The left lung was more frequently operated upon than the right - this may reflect anatomic peculiarities of the tracheobronchial tree or other factors not yet fully understood. Lobectomies were performed more frequently on the upper lobes (23/50,46%), followed by the lower lobes (17/50, 34%) and the middle lobe (3/50, 6%). Seventeen (34.0%) of the patients had post operative complication of bleeding within 1st 24 hours. Most common complaints in 1st visit, 2nd visit and 3rd visit were chest pain followed by cough.

Regarding lung's lobe, no significant negative relationships was observed with the functional capacity of lung after lobectomy ; and there were no significant differences among the lobes related to changes in the lung function after lobectomy.

The comparison of FVC (L), FEV_1 (L), %FVC and $\%FEV_1$ between baseline and different visits showed that there was significant difference of FVC (L), FEV_1 (L), %FVC and $\%FEV_1$ observed between baseline and 1st visit ($p<0.05$). There was significant difference of FVC (L) observed between baseline and 2nd visit ($p<0.05$). There was no significant difference of FEV_1 (L), % FVC and % FEV_1 observed between baseline and 2nd ($p>0.05$). There was no significant difference of FVC (L), FEV_1 (L), % FVC and % FEV_1 observed between baseline and 3rd visit ($p>0.05$)

What is the mechanism of the improved FEV_1 in patients after lobectomy? If FVC increased, as it does in patients who underwent lung volume reduction, one could speculate that nonventilated lung is being resected, allowing the more normal lung to expand and ventilate more efficiently. As FVC falls (1st & 2nd visit) this phenomenon is probably not the active mechanism.[10] The most likely mechanism for the improved obstruction would be the relief of hyperinflation which improves airway conductance and allows these patients to expire more volume in 1 second. Improved chest wall and respiratory muscle mechanics may also play a role.[11]

Conclusion:

Although this study was based on measurements of conventional pulmonary function tests (spirometric variables) which alone can overestimate or underestimate the functional capacity of lung after lobectomy (lung resection), it had been concluded that changes in pulmonary function after lobectomy does not co-relate with the anatomical side of the lobe excised & ventilatory function recovers to the preoperative level from 3 to 5 months after resection — that means it actually improves.

This was a single centre study. However, the nature of our institute (tertiary care centre for chest diseases) provides the specialized expertise and patient pool to conduct such a study and has the potential to be a platform from which future studies can be developed to continue to improve the accuracy and other research work on various aspect of pulmonary lobectomy and may provide an elegant solution for complex and longstanding problems.

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ORIGINAL ARTICLE

Pulmonary Hydatid Disease: Surgery is the Way to Cure It

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Abstract :

Hydatid (Latin-hydatis) means a drop of water. It implies a cyst shaped structure that contains water like fluid. Hydatid disease caused by tapeworm Echinococcus granulosus. Dogs and other canines are the definitive host, sheep & cattle are intermediate host. Humans are accidental intermediate host. Liver and lungs are the most frequently involved organs. Pulmonary hydatid disease is mostly asymptomatic. But may be symptomatic due to compression and rupture of cyst . Diagnosis can be made radiologically and immunologically.

60 patients were evaluated that treated surgically in NIDCH and some private centers of Dhaka in the period of January 2007 to December 2011. Male female ratio was 4:1, mean age was 30 ± 3, ranging from 10-50 years. 30 patients were symptomatic presented with cough, shortness of breath, haemoptysis and 20 patients were diagnosed during routine chest radiograph. 10 patients were diagnosed peroperative period. Surgical treatment offered with thoracotomy and enucleation of cyst in 20 patients, 10 patients treated with VATS & 5 patients treated with simple cystectomy with capitonnage. Post operative recovery was well in 85% of patients, 15% patients developed infection and bronchopleural fistula that they managed conservatively. Surgery remains the treatment of choice for pulmonary hydatid cyst & a parenchyma-saving operation is usually possible. So, we prefer surgical treatment of pulmonary hydatid cyst.

[Chest & Heart Journal 2012; 36(2) : 128-133]

Introduction:

Hydatid (Latin Hydatis) means a drop of water. It implies a cyst shaped structure that contain water like fluid. Hydatid disease caused by tape worn Echinococcus gronulosus. Dogs & other canies are definitive host. [1]Human are accidental intermediate host. Liver, Lungs are most frequently involved organ. There is no consensus regarding the most appropriate drug treatment regimen for Cystic Hydatid disease. Some authorities advocate one month [2]albendazole regimen without interruption, subject to tolerance, along with Praziquantel for 2 weeks, At end of 3rd months, the disease should be evaluated & a decision taken either to proceed with surgery or to continue the course for one year. But Surgery is the choice of treatment for pulmonary hydatid disease. Surgical treatment included thoracotomy with enucleation of cyst with or without closure of bronchial fistula, Enucleation of Cyst through VATS, and simple Cystectomy with Capitonnage.

Materials & Methods:

During the last 5 years (Jan, 2007 to Dec. 2011) a total number of 60 diagnosed cases of pulmonary hydatid disease has been reviewed at National Institute of Diseases of the Chest and Hospital. All the cases were underwent various surgical methods of treatment.

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6. Junior Consultant, Orthopaedic Surgery, UHC, Savar, Dhaka.

Results:

Out of 60 cases 48 were male & 12 female. M:F = 4:1, the age range was 22 - 50 years. Sex and age incidence is shown in table 1 & fig: 1. Most of the patients were villagers with low socio-economic condition.

Table-I

Distribution of patients by age (n = 60)

Age in Yrs.	No	%
< 10	5	8.3%
10 - 20	10	16.7%
20 - 30	15	25%
30 - 40	25	41.7%
40 - 50	5	8.3%

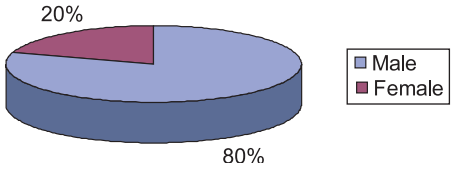


Fig-1: *Distribution of patients by sex (n = 60)*

Presentation:

30 patients were symptomatic presented with cough, shortness of breath, haemoptysis. 20 patients were diagnosed when they attended their physicians with other complains and subsequently had routine chest X-Ray examination. 10 patients were diagnosed at per operative period.

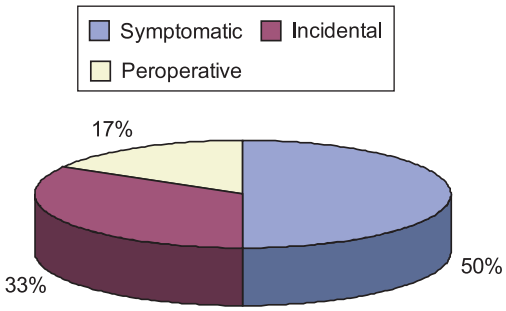


Fig.-2:

Investigations:

Radiology:

50 patients had an initial plain X-Ray of the chest depicting more or less typical of hydatid cyst of different location, 10 patients X-Ray chest had shown no typical cystic leision but consolidation.

Haematology:

Haematological findings reflected mild to moderate degree of anaemia in most of the patient. Eosinophillia was seen in 30% of cases.

Table-II

Location of Hydatid Cysts (n = 60)

Site	No. of case
Right lung	38
Left lung	15
Both lung	7

Operative details:

All 60 patients were operated, by standard posterolateral thoracotomy incision depending on the location of cyst whether right or left. Only enucleation of the cyst was done in 20 patients. Cyst of 25 patient's were communicate with bronchus. After enucleation, the bronchial communications were closed either direct stitch (15 patients) or free muscle flap (10 patients). 10 patients were treated by enucleation through VATS. Simple cystectomy with capitonnage were done in 5 patients.

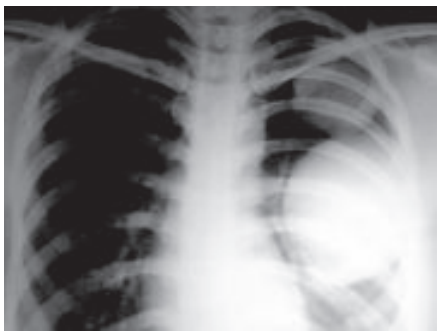
Table-III

Operative Details

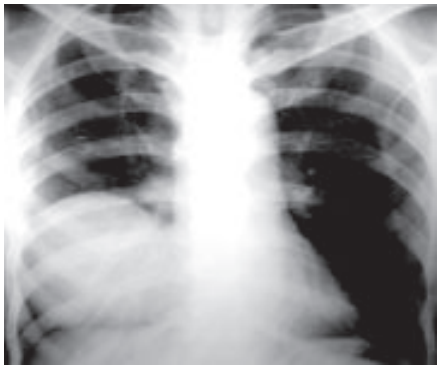
Type	No. of patients (n=60)	%
Only enucleation	20	33.33
Enucleation with closure of bronchial fistula Direct Stitch	15	25.00
Free muscle flap	10	16.67
Enucleation through VATS	10	16.67
Simple cystectony with capitonnage	5	8.33

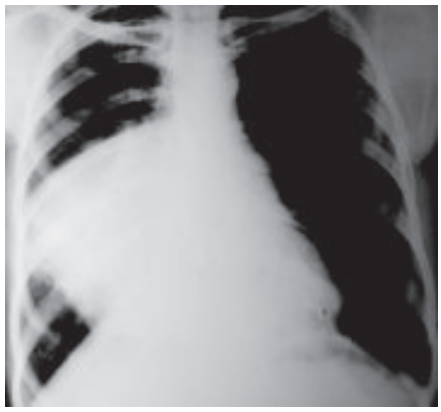
Surgical Outcome:

About 85% patients had immediate cure, 15% patients developed some complications like wound infection, bronchopleural fistula and atelectasis of the affected lobe. The bronchopleural fistula (2 patient) was treated by remaining the chest drain tube longer time & tetracycline wash. Wound infection (5 patient) was manged by sensitive antibiotics & surgical dressing, 2 patient developed atelectasis of affected lobe and recovered completely after bronchoscopic toilating & other measures.

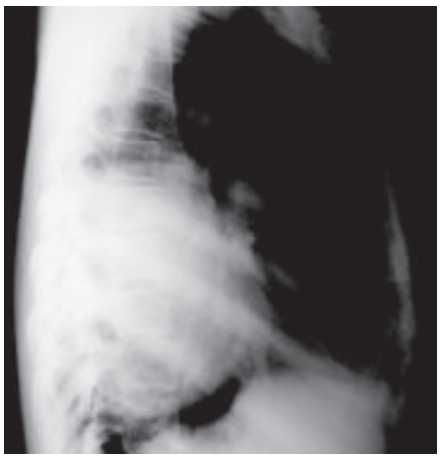


Hydatidosis left lung

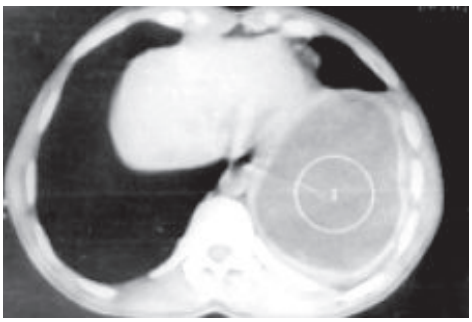




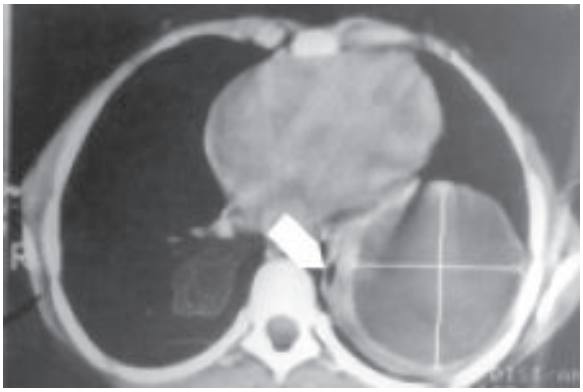
Complicated hydatid cyst after aspiration



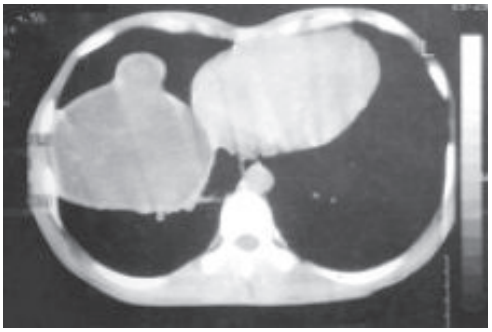
Lateral film



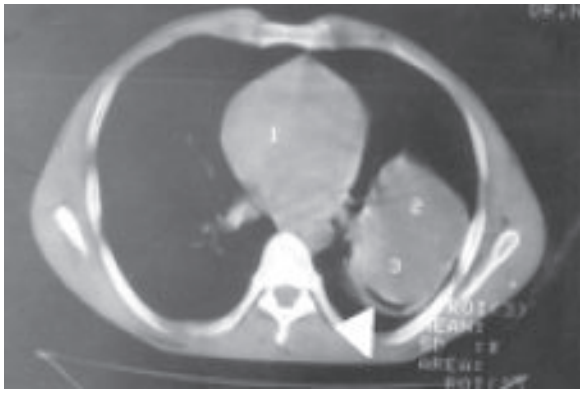
CT Scan Of Chest (Hydatid cyst)



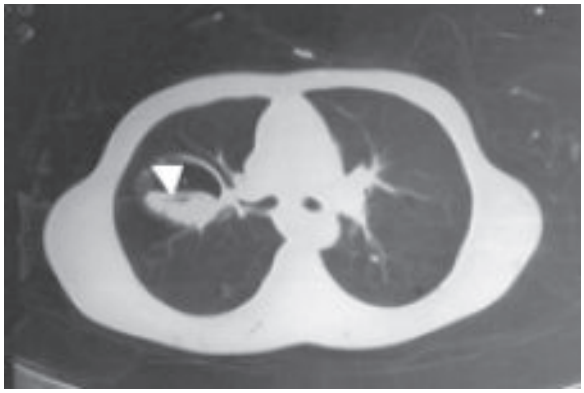
Membrane of cyst separating (Signet ring sign)



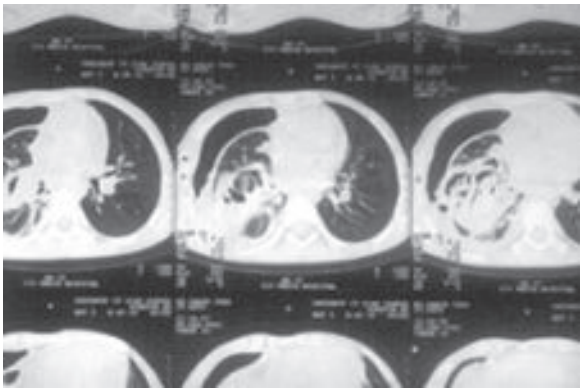
Prograntе Shaped Hydatid cyst



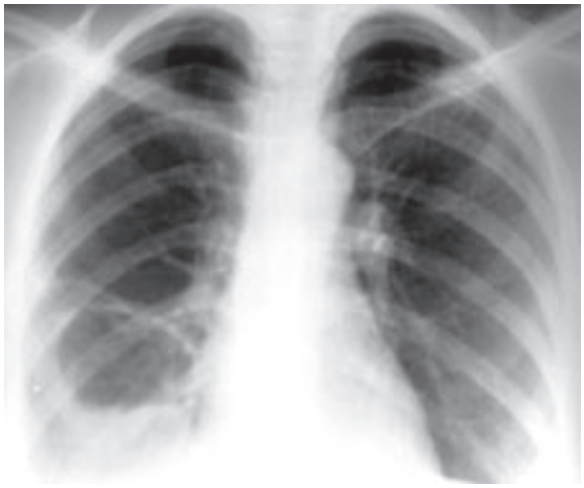
Inverse Crescent sign



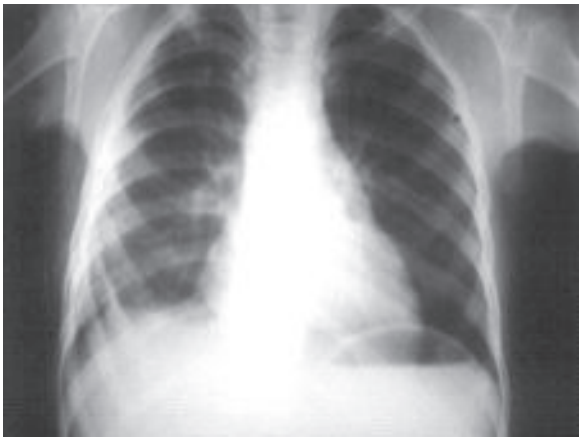
Ruptured Hydatid cyst (Water Lily Sign)



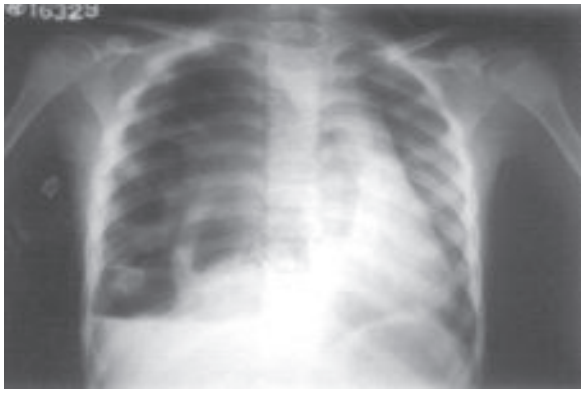
Complicated hydatid cyst



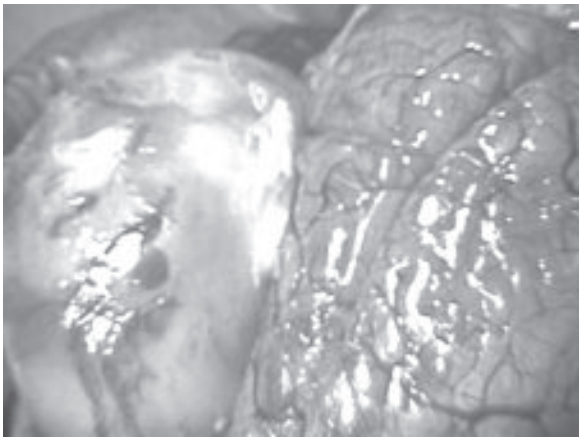
Complicated hydatid cyst (R) needed decortication



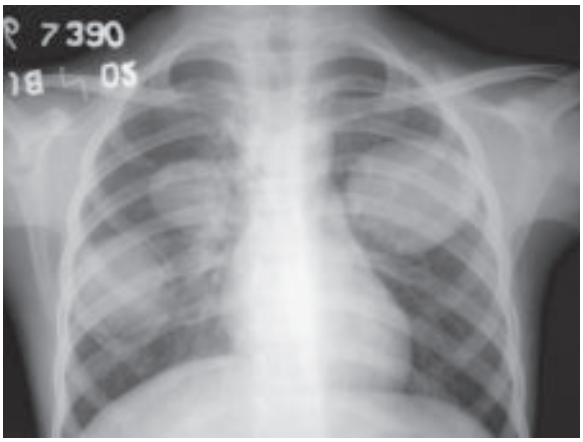
Post operative CXR



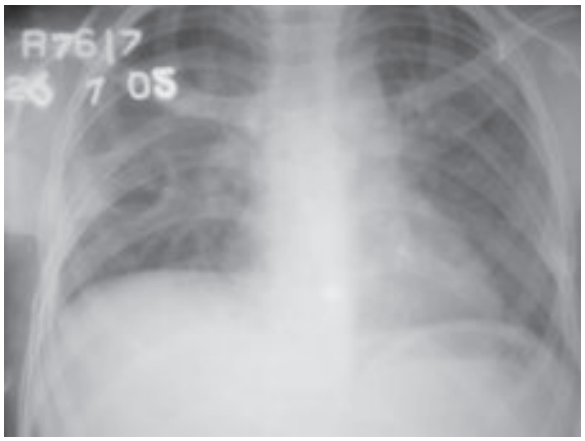
Complicated hydatid cyst



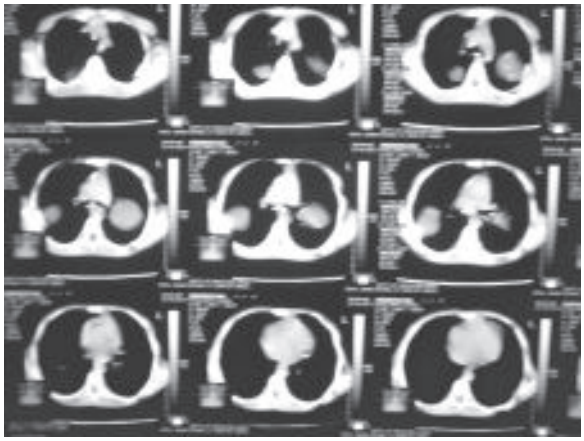
Un complicated Pulmonary Hydatid cyst



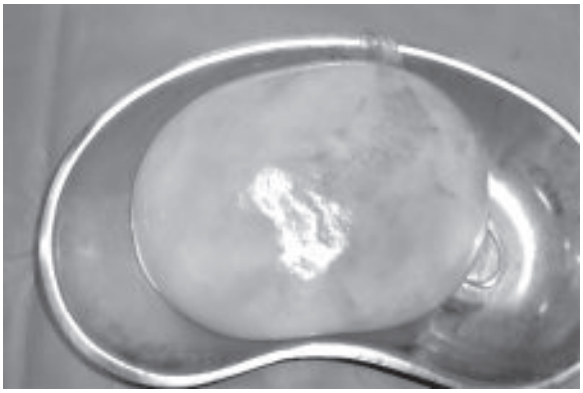
Bilateral Pulmonary Hydatidosis



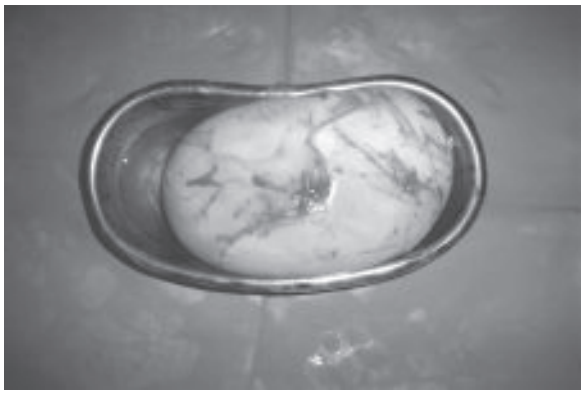
Right side also operated



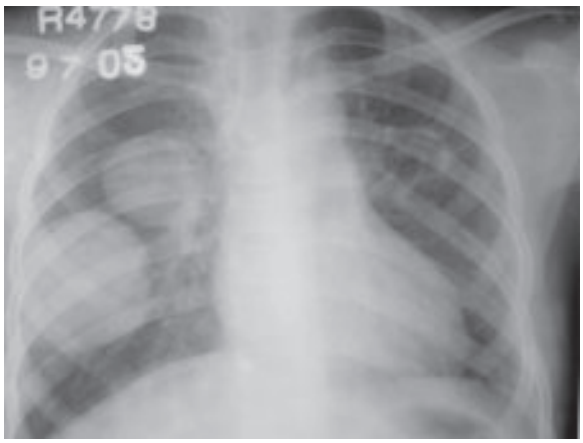
CT of Bilateral Hydatid cyst



Intact Enucleated Cyst



Intact Cyst



Left side operated

Table-IV
Surgical Outcome

Type	No. of Patients (n=60)	%
Immediate cure	51	85.00
Mortality	00	0.00
Morbidity		
Bronchopleural fistula	2	3.33
Wound infection	5	8.33
Atelectasis	2	3.3

Discussion:

60 patients of hydatid disease of the lung were studied with mean age of 35.3 ± 6.4 yrs. Turna et al (2002) reviewed 75 patients had showed average age 30.2 ± 17.4 yrs. in his observation. Age of our study group was consistent with that series. In our study among 60 cases, 80% the patients were male & 20% were female. Hacubrahimo glu et al (2003) in his series shown 93 patients, 48 was male & 43 was female. The higher percent of male patients in our series due to more conciousness of male people in our country.

About 50% of patients were symptomatic, 33.3% incidental & 16.7% per operatively diagnosed. [3]Ahsan et al (1997) reviewed 137 patients & showed symptomatic 24% & asymptomatic 76% of the patients. The difference in diagnosis of the patients is possibly due to more awareness developed in the community for illness. The location of pulmonary cyst with predominence of right lower lobe involvement have been shown in different studies.[4,5,6]

In our series we have done only enucleation 33.3% of the patients, enucleation with closure of bronchopleural fistula by direct stitch with atraumatic 2.0 proline in 25% & free muscle flap taken from chest wall in 16.67% of the patients. Rest of the 16.67% of patients were operated by enucleation through VATS 8.33% of the patient underwent simple cystectomy with capitonnage operation. Simple cystectomy without bronchial opening closure were due to non communicated pulmonary hydatid cyst with bronchus. The recovery of the patients were excellent. Ahsan et al reviewed 137 patients and showed enucleation with bronchial closure in 80% of the patients with free muscle, teflon felt & direct stitch. But in our series it was 41.67% of the patients. It was less than Ahsan's series. It may be due to earlier diagnosis and operation, needs further evaluation. [7]Unchikov PA et al showed in his series of 11 patients that all patients recovered without sequelae. Our series showed 16.67% (10) of the patients operated through VATS. The number of patients were almost same in both series. This is due to more interest in VATS. [8]Alam SM et al (2009) showed 46.6% of the patients underwent enucleation of cyst with capitonnage. We showed 8.33% of the patients underwent capitonnage, possibly due to capitonnage prolongs the operation time & increases the risk of haemorrhage. We administered albendazole post operatively for the purpose of prophylaxis.

Conclusion:

Surgery remains the treatment of choice for pulmonary hydatid cyst and a parenchyma-saving operation is usually possible. Preservation of, parenchyma is the fundamental to surgical management. However, in cysts that cause parenchymal damage by involving more than 50% of a lobe or that are associated with such sequelae of chronic abscess, bronchiectasis, or severe haemorrhage required lobectomy. There are some report that small cyst can be cured with albendozole. However, we observed that patients who do not undergo surgical treatment develop ruptures, infections, haemoptysis after albendozole treatment. That is why we prefer surgical treatment of pulmonary hydatid cyst.

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Chest & Heart Journal
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ORIGINAL ARTICLE

Serum Homocysteine Level in Myocardial Infarction

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Abstract:

Background: Myocardial infarction is one of the global fatal problems in both developed and developing countries. There is a link between myocardial infarction and serum homocysteine. Hypothesis: Total serum homocysteine level is increased in myocardial infarction. Objective: To asses the total serum homocysteine level in myocardial infarction. Methods: This cross sectional study was conducted from July 2010 to June 2011 in the Department of Physiology, Rangpur Medical College, Rangpur. For this, 35 newly diagnosed patients of myocardial infarction were included in the study group as experimental. These patients were selected from the Cardiology Department, Rangpur Medical College & Hospital, Rangpur. For comparison age matched 35 apparently healthy subjects were included as control. For statistical analysis independent sample 't' test was performed by computer based software SPSS – 15.0 version for windows. Total serum homocysteine level was measured by fluorescence polarization immunoassay (FPIA) in 'AxSYM system' (Abbott, USA) by Enzyme-Linked Immunosorbent Assay (ELISA) technique. Result: Mean total serum homocysteine level was significantly higher (P<0.001) in myocardial infarction in comparison with the healthy subjects. Conclusion: The total serum homocysteine level increased in newly diagnosed patients of myocardial infarction.

Key words: Serum Homocysteine, Myocardial Infarction.

[Chest & Heart Journal 2012; 36(2) : 134-138]

Introduction:

Cardiovascular diseases are one of the leading causes of mortality and morbidity in the developed countries. They are also emerging as prominent public health problems in the developing countries. The high burden of mortality from cardiovascular causes in the developing countries was estimated at 9 million in 1990 and is being expected to increase to 19 million by 2020.[1] Ischemic heart disease (IHD) is the syndrome resulting from myocardial infarction, angina pectoris, chronic ischemic heart disease with heart failure and sudden cardiac death. It comprises not only insufficiency of oxygen, but also reduced availability of nutrients and inadequate removal of metabolites. Myocardial infarction is common among ischemic heart disease. It is an imbalance between the supply and demand of the heart for oxygenated blood. In more than 90% of cases, the cause of myocardial ischemia is reduction in coronary blood flow due to atherosclerotic coronary arterial obstruction..[2-5]

Homocysteine is a sulfur containing amino acid. It has atherogenic effect on vascular smooth

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muscle cell migration and proliferation. It has also prethrombotic properties by inhibition of thrombomodulation activity, reduction of protein C activation. It also stimulates the platelet generation of thromboxane A_2 which is a vasoconstrictor and increases platelet aggregation.[6, 7] Auto oxidation of homocysteine generates superoxide anion radicals which cause oxidative modification of low density lipoprotein. A raised total serum homocysteine level has been found to be an independent risk factor for atherosclerotic and thromboembolic disease like myocardial infarction. [8, 9] An emerging pattern of atherosclerosis due to formation of fibrous plaques and loss of vascular elasticity associated with hyperhomocysteinemia was reported by some author.[10] The elevated total serum homocysteine level is considered cytotoxic and are found in 5 to 10 % of the general population and in upto 40% of patients with cardiovascular disease. [11]

The aim of this study is to evaluate the association between the elevated total serum homocysteine level and myocardial infarction in the population of Bangladesh. So, the practical recommendation for screening the elevated total serum homocysteine level can be justified and treatment of this modifiable risk factor should be recommended.

Methods:

This is a cross sectional analytical study conducted in the Department of Physiology, Rangpur Medical College, Rangpur during July 2010 to June 2011. The study has been designed to estimate total serum homocysteine level in myocardial infarction. The ethical committee of Rangpur Medical College, Rangpur approved the study protocol. 35-65 years old diagnosed 35 patients of both sexes of myocardial infarction who were admitted in the Cardiology Department of Rangpur Medical College & Hospital, Rangpur were included as experimental group B. Age matched apparently healthy 35 subjects of both sexes were selected form the community as control group A. Patients suffering from valvular heart disease, congenital heart disease, kidney diseases, liver diseases, diabetes mellitus, hypertension and obesity were excluded from the study. After selection of subjects, the objectives and procedures of the study were explained to them and their informed written consent was taken. A standard questionnaire was filled after taking history and thorough physical examination. The subjects were instructed to be in overnight (8-10 hours) fasting state. Then next day at 8.00AM five (5) ml of blood was collected from antecubital vein from each subject under all aseptic precautions by a disposable syringe. The needle was detached from the nozzle and then blood was immediately transferred into a dry sterilized deionized test tube with a gentle push to avoid haemolysis. The test tubes were kept in slanting position till formation of clot. As synthesis of homocysteine continues in the red blood cell after blood drawn so, serum was separated by centrifuging the blood at 3000 rmp for 5 minutes. The clear supernatant was taken and kept in ependorfs. Samples were stored at -70°c. Quantitative measurement of total serum homocysteine was estimated by fluorescence polarization immunoassay (FPIA) in 'AxSYM system'. It was done in the laboratory of the Department of Biochemistry of BSSMU. Data were expressed as mean ± SD. All the data were recorded systematically in a preformed data sheet and statistical analysis were done by computer based software SPSS 15.0 version for windows. Comparison of total serum homocysteine level of myocardial infarction with control group were done by unpaired 't' test .In the interpretation of results, <0.05 level of probability (P) was accepted as significant.

Results:

Total serum homocysteine level was significantly higher (P<0.001) in myocardial infarction (Group – B) than control subjects (Group – A).

Table-I

Mean ± SD total serum homocysteine levels-

Variable	Group A (n=35)	Group B (n=35)	P value
Total Serum Homocysteine (µmol/L)	10.8297± 1.92761	23.5886± 9.23476	0.000***

(Normal range of total serum homocysteine level is: 3.36 – 20.44 µmol/L [12])

*** Highly significant (P<0.001) with unpaired t-test.

n = Number of subjects.

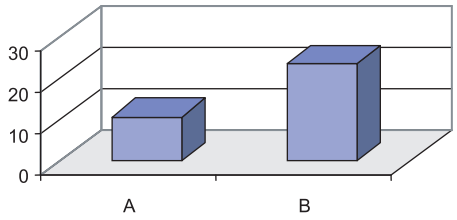

Fig I : *Mean total serum homocysteine levels (µmol/L)-*

Discussion:

Many authors of different countries reported significant raised mean total serum homocysteine level in myocardial infarction [6 -11, 13 – 28] It might be due to deficiency of vit. B_6, B_{12} and folic acid deficiency. Homocysteine is metabolized by trans-sulfuration and re-methylation pathway. In trans-sulfuration pathway, homocysteine is condensed with serine to form cystathionine. This reaction is catalyzed by vit. B_6 dependent enzyme cystathionine beta synthase. Cystathionine subsequently hydrolysed to form cysteine which is further metabolised to sulfate and excreted through urine. Due to deficiency of vit. B6, this trans-sulfuration pathway is hampered which leads to elevation of total serum homocysteine. In remethylation pathway, homocysteine is remethylated back to methionine by transfer of a methyl group from 5 - Methyltetrahydrofolate in a reaction catalysed by cobalamine (vit B12) dependent enzyme methionine synthase. Remethylation pathway also requires folic acid. In deficiency of vit B12 and folic acid the remethylation of homocysteine is impaired and causes elevation of total serum homocysteine level.

Raised serum homocysteine induces vascular dysfunction, platelet generation of thromboxane A2 and platelet aggregation through oxidative stress and also by inhibiting nitric oxide synthesis. Thromboxane A_2 released from platelet causes vasoconstriction, platelet aggregation and platelet plug formation. Reduced nitric oxide impairs endothelial nitric oxide dependent vasodilation. Homocysteine has preprothrombotic property by inhibiting thrombomodulin activity and reduction of protein C activation and thus facilitates thrombus formation. All the above mentioned events lead to formation of atheromatous plaque and sequentionally cause myocardial infarction.

Conclusion:

Total serum homocysteine increased in myocardial infarction may be due to deficiency of Vit B_{12} & Vit $_{B6}$ and folic acid and it can be prevented by supplementation of these vitamins. So, the present study will be helpful to develop awareness about reduced serum Vit B_{12} & Vit $_{B6}$ and folic acid and its relation to myocardial infarction. It also helps to develop awareness among the community about the importance of these vitamins in the prevention of myocardial infarction.

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REVIEW ARTICLE

Fetal Echocardiography

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Prenatal diagnosis of congenital heart disease is a very important aspect for both the obstetrician and neonatal specialists for optimal care to be given to the mother, fetus and the newborn baby. With advances in ultrasound technology, fetal echocardiogram has proved to be a very important diagnostic imaging test to evaluate the structural or functional abnormalities of the fetal heart. In addition, fetal cardiac intervention is becoming a field of interest for some specific lesions like semilunar valve stenosis. In taking care of a fetus with congenital or functional heart disease, obstetricians, pediatric cardiologists and neonatologists work together for optimal outcome for the mother, fetus and the newborn baby.

Fetal echocardiography should be done by fetal ultrasound transducers in the range of 5.5-10 MHz. In addition to detailed two dimensional imaging, M-Mode, Doppler, color flow Doppler and image enlarging should be used during fetal cardiac scanning.[1]

Congenital heart disease affects 6-8 per 1000 live births, at least half of which should be detectable before birth. If the fetuses are screened for cardiac malformations according to the traditional high-risk groups, only about 20% of babies with heart disease would be identified.[2] In today's advanced era of imaging, the fetal heart must be examined by all obstetric ultrasounds. The imaging of a four-chamber of heart, outflow tracts with great vessel crossing, and arches, along with cardiac function and rhythm, should be routinely done during an obstetric ultrasound. Even the smallest suspicion should direct the patient to a center with pediatric cardiologists specialized in fetal cardiac scanning and diagnosis.

Indications

Fetal and maternal factors and obstetric ultrasound findings are used to define high-risk populations for referring a fetus for detailed cardiac scanning. [3,4]

1. Fetal factors: Chromosomal abnormalities, extracardiac defects (e.g. Omphalocele, diaphragmatic hernia, duodenal atresia, tracheoeosophageal fistula, abnormal visceral situs, hydrocephalus, microcephalus, hydronephrosis, hydrops), multiple fetal pregnancy, fetal cardiac arrhythmia.
2. Family or maternal history: Previous siblings affected with CHD, familial inherited disorders (Marfan's syndrome, Noonan's syndrome etc) diabetes mellitus, autoimmune disease (SLE, Sjogren's) phenylketonuria; to decline invasive prenatal diagnosis in advanced maternal age.
3. Exposure to Teratogens: Drugs (warfarin, retinoic acid, lithium, anticonvulsants, alcohol, prostaglandin synthetase inhibitors); infections (rubella, parvovirus, coxsackie virus); high doses of ionizing radiation.
4. Ultrasound findings: Increased nuchal fold, suspicious obstetric scan, echogenic foci.

The likelihood of detecting a fetal cardiac defect is closely related to the experience of the pediatric cardiologist, the timing of the examination and the equipment used.[3]

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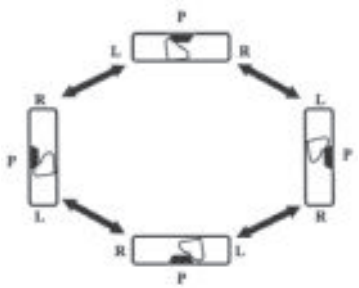
Timing of Examination

Though fetal heart images can be obtained as early as 15 weeks by trans abdominal scanning, the optimal timing for a fetal cardiac evaluation is between 18-22 weeks gestation.[4]

Equipment

Fetal ultrasound transducers must be in the range of 5.5 MHz transmitted frequency and may be sector or linear array.[1] With wider near-field view, curvilinear probes may be more helpful.[4] In addition to detailed two dimensional imaging, M-Mode, Doppler, color flow Doppler and image enlarging should be used during fetal cardiac scanning.[1]



P: Posterior; L: Left; R: Right

Examination

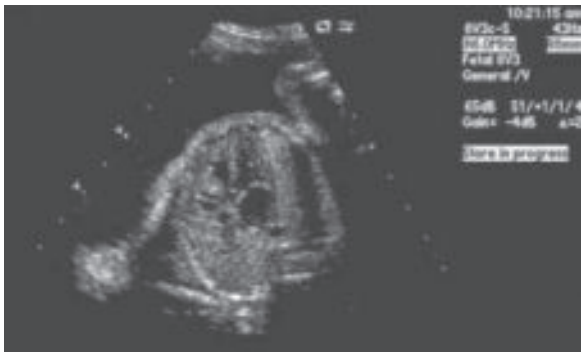
An uncomplicated, complete fetal cardiac exam can be performed in 30-60 minutes.

The scan should include but not be limited to the examination of.[1]

- fetal heart rate and rhythm
- Biparietal diameter for estimation of gestational age
- fetal lie and position
- fetal visceral situs
- cardiac position
- four-chamber anatomy
- great vessels and their relationships
- atrioventricular and semilunar valves
- aortic and ductal arches
- shunting at foramen ovale and ductus
- systemic and pulmonary veins
- cardiac chamber dimensions /cardiothoracic index
- wall thicknesses
- valve/vessel dimensions
- umbilical cord
- pericardial and extracardiac spaces for fluid accumulation

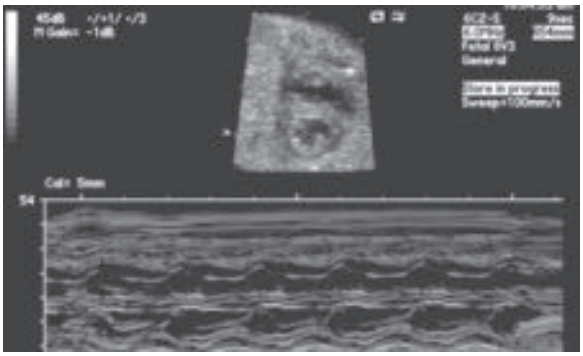
In addition to 2D images from four chamber view, five chamber view, long axis views (from LV and RV outflow tracts), short axis view/ sweep (3 vessel view), caval long axis view, ductal arch and aortic arch views along with systematic Doppler examination of atrio-ventricular and semilunar valves, systemic and pulmonary veins, ductus venosus, foramen ovale, ductus arteriosus, aortic arch, and umbilical vessels should be a part of a routine fetal cardiac examination.[4]

Although it is often not very easy to follow a sequence of scanning secondary to fetal (e.g.fetal lie) and maternal (e.g. obesity, previous intraabdominal surgery) factors, every effort should be made to evaluate the fetal heart according to the above recommendations in which order they may be best obtained.



Four chamber- crossing of great arteries-aorta

In an fetal ultrasound at least a four chamber heart along with five chamber view, outflow tracts with crossing over of the great vessels, and aortic and ductal arches should be visualized. The three-vessel view will also be an added asset in determination of fetal cardiac abnormalities. In this way, most of the cardiac abnormalities will be seen or suspected to have the patient evaluated in detail by Pediatric Cardiologist.

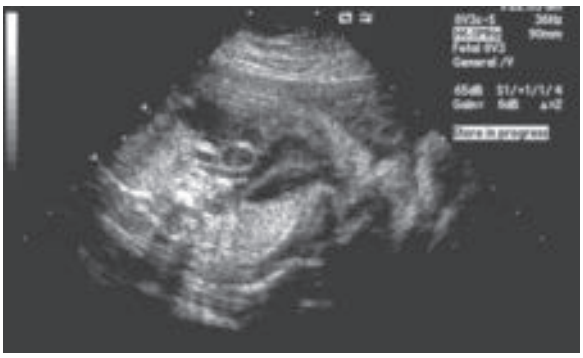


M-Mode of RV/LV to measure wall thickness

A fetal cardiac scan should start with the number of fetuses and how they are positioned in the uterus. Cardiac position and visceral situs should be determined before starting a detailed scanning. Differentiating the fetal right side from the left may be challenging in some cases. Cordes et al have proposed a simple way of determination of fetal right and left sides [5]. During initial orientation, the fetal head is placed to the right side of the screen. From this sagittal plane, the transducer is rotated 90 degrees clockwise to get the fetus in transverse image. In this image, the fetus will always be visualized from caudal to cranial. Depending on the fetal lie (face up/down, left side/right side down), the fetal side can then be determined with a simple technique. If the left hand is assumed as the letter L with the tips of fingers pointing towards the sternum and the palm is placed on the spine, wherever the thumb is directed will be the left side (letter L) of the fetus. Once the cardiac position and visceral situs is determined, then one can move to further delineation of anatomy. Four-chamber view of the heart is the most widely recognized view by the non-fetal echocardiographer. It is usually easy to get and gives the operator an idea about the chambers (atria and ventricles) with respect to their size and function, atrial and ventricular septums and atrioventricular valves. From thisview, with minimal movement of the transducer, the heart should be scanned from posterior to anterior to see the coronary sinus and pulmonary veins posteriorly, and the aorta anteriorly. Moderator band and lower insertion of the TV leaflets to the crux of the heart compared to the insertionof mitral valve leaflets are hints fordetermination of the right ventricle.

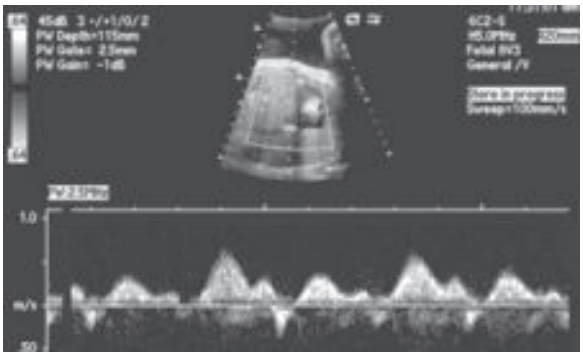
The long axis view of the fetal heart will show the aortic mitral continuity and the ascending aorta. With further sweeping at this level, pulmonary arterial and aortic connections as well as ductus arteriosus will be seen.

When scanned perpendicularly from the long axis view, fetal cardiac short axis view can be obtained. Cranial and inferior sweeps of fetal cardiac short axis will help with delineation of pulmonary veins, short axis of both ventricles, relationship of great arteries relative to their respective ventricles, pulmonary artery and its branches, inferior and superior vena cava and the 3-vessel view (SVC, AO, PA), ductus arteriosus and aortic arch with its branches.



Aorta, PA Branches, SVC

The ductal and aortic arches can be visualized from the ductal/aortic arch view. In this view, the RVOT, MPA and the branch PAs can easily be seen. Aortic arch with its head and neck vessels, ascending/ transverse and descending aorta as well as the entrance of ductus at isthmus with its flow normally directed towards the isthmus/ aorta (right to left flow) are findings that are observed sweeping from anterior right side of fetus to posterior left side.



IVC Doppler

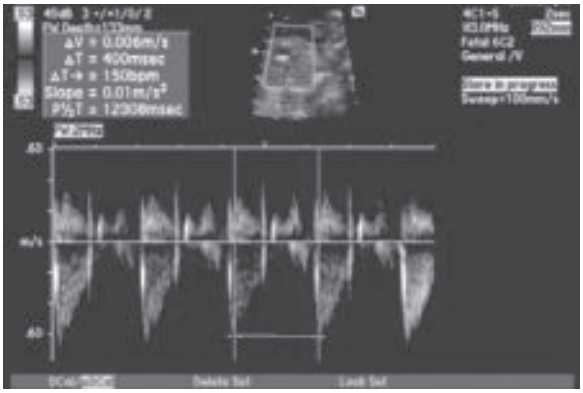
The best view of the PFO/atrial septum is from caval long-axis view where long axis of SVC and IVC and their continuity is also seen.

During visualization of the above mentioned cardiac structures, chamber, vessel, semilunar and atrioventricular valve annulus sizes should be measured and incorporated into the report. In addition to 2D measurements, Doppler interrogation of valves, systemic and pulmonary veins, aorta and ductusarteriosus, PFO, and umbilical vein and artery should be performed.

Cardiothoracic ratio should be measured from an optimal four-chamber view.

Different techniques have been studied to evaluate heart rate and rhythm. M mode, pulsed Doppler, pulsed tissue Doppler and recently tissue velocity imaging (TVI) are most commonly used modalities.[6] In a normally conducting rhythm, calculation of baseline rate can be easily done from Doppler interrogation of the outflow tracts..

For additional information, during M mode evaluation, simultaneous recordings of atrial and ventricular wall motion are done. Pulsed wave Doppler of ventricular outflow tract, along with the ventricular inflow where the"A" wave of atrial contraction can be differentiated, gives information about the type of arrhythmia (premature beats, etc). Extrasystoles, especially premature atrial contractions (PAC) (conducted or blocked) are the most common arrhythmias encountered in a fetus. Though 1-3% of PACs may result in intermittent supraventricular tachycardias, usually PACs are benign findings that resolve by the time the patient seeks the attention of a fetal echocardiographer.[6] Premature ventricular contractions (PVC) are rarely seen in fetuses, and may be benign findings though myocardial disease, cardiac tumors and decreased cardiac function should be ruled out. PVCs may require further postnatal evaluation.



Heart rate calculation

Fetal tachyarrhythmias are usually SVTs that have a rate over 180 bpm. These arrhythmias warrant immediate attention, since as a result of this, cardiac compromise and hydrops can develop. Usually these arrhythmias are controlled by medical management but in rare instances may require early delivery.[6] Ventricular tachyarrhythmias are very rare and, as mentioned before, may be the consequence of myocardial compromise or cardiac tumors and need immediate attention for treatment.

Any fetus with tachyarrhythmias, even though hemodynamically stable, requires frequent follow-up imaging to evaluate the cardiac function and fetal hydrops.

Bradyarrhythmias (HR less than 110 bpm) are usually encountered during episodes of vagal stimulation, fetal distress or systemic disease. During cardiac ultrasound examination, short periods of self-recovering bradycardia are commonly encountered. Nonconducted PACs are also a reason for bradycardia though these are not deemed hemodynamically significant. Maternal autoimmune diseases (SLE or Jorgen Syndrome) are the main reasons for fetal bradycardia, usually fetal atrio-ventricular block. Any AV block in the fetus warrants maternal investigation since maternal autoimmune disease may not be symptomatic at the time of fetalbradyarrhythmia diagnosis. Certain medical treatments (maternal plasmapheresis, dexamatehasone, sympatho-mimetic treatment) are being tried in mothers of fetuses with AV block. Where there is evidence of cardiac dysfunction or fetal distress, early delivery should be thought as an option.

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REVIEW ARTICLE

Idiopathic Interstitial Pneumonia - An Update

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Introduction:

The idiopathic interstitial pneumonias comprise a group of diffuse lung diseases of unknown etiology that primarily involve the pulmonary interstitium. Fibrous framework of the lung, the area between the alveolar epithelium and capillary endothelium is the main target. However, frequently the airways, vasculature, and alveolar airspaces also involve. The underlying pathological process is one of varying degrees of inflammation and fibrosis.

The diagnosis and management of idiopathic interstitial pneumonia have challenged physicians since its initial description more than a century ago. When faced with a patient suspected of having idiopathic interstitial pneumonia, physicians must have a rigorous and organized approach to its diagnosis, as therapy and prognosis depend on the patient's underlying histopathological pattern. This fact remains unappreciated by many physicians, and as a result, patients often undergo incomplete evaluation and empirical treatment.

Defining the Interstitial Pneumonia

Interstitial pneumonia has been recognized as a chronic progressive lung disease for more than a century. In 1892, Osler described chronic interstitial pneumonia, also called *cirrhosis of the lung*.[1] In 1944, Hamman and Rich described 4 cases of acute diffuse interstitial fibrosis.[2] Although all 4 of these cases were acute in onset and rapidly progressive, the term *Hamman-Rich syndrome* was used for some time to describe any diffuse idiopathic fibrotic lung disease.Those conditions that remained idiopathic were collectively called by various names, including *chronic idiopathic interstitial fibrosis*, *diffuse interstitial fibrosis*, *diffuse fibrosing alveolitis*, *Hamman-Rich syndrome*, *diffuse pulmonary alveolar fibrosis*, *idiopathic pulmonary fibrosis*, and *idiopathic interstitial pneumonia*. The preferred term at present is *idiopathic interstitial pneumonia*.In 1969, Liebow and Carrington initially described five histo-pathological subgroups of chronic idiopathic interstitial pneumonia but recently the American Thoracic Society and the European Respiratory Society recommend four histo-pathological pattern seen on lung biopsy findings with clinical information to arrive at a final clinicopathological diagnosis.[3,4] When the terms are the same for the histopathological pattern and the clinical diagnosis (eg, desquamative interstitial pneumonia), it was recommended that the pathologist use the addendum *pattern* when referring to the appearance on lung biopsy findings (eg, desquamative interstitial pneumonia pattern) and reserve the initial term for the final clinicopathological diagnosis.

Clinical Presentation

The various histopathological subgroups are often clinically indistinguishable (with the exception of acute interstitial pneumonia).

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Although patients with UIP are generally older (two thirds are older than 60 years at diagnosis) than those with other forms of idiopathic interstitial pneumonia, age is not a reliable predictor of histopathology. Symptoms are identical for all subgroups, with the typical patient reporting progressive dyspnea for months to years and a chronic, nonproductive cough. Physical examination will often reveal digital clubbing and the presence of bibasilar fine inspiratory crackles ("Velcro" crackles). Results of pulmonary function testing reveal restrictive lung disease (decreased forced vital capacity and total lung capacity [TLC]) and abnormal gas exchange (decreased diffusion capacity of carbon dioxide and resting or exercise PaO2). The most useful clinical tool for distinguishing between subclasses is high-resolution computed tomography (HRCT) of the chest. Acute interstitial pneumonia presents much differently, with the acute onset of dyspnea and cough and the rapid development of respiratory failure.

Histopathological Subgroups

The histopathological subgroups are:

Usual interstitial pneumonia pattern (UIP)

Nonspecific interstitial pneumonia pattern (NSIP)

Desquamqtive interstitial pneumonia / Respiratory bronchiolitis-associated interstitial lung disease pattern (RBILD)

Acute interstitial pneumonia pattern

The relative distribution of the histopathological subgroups suggest that UIP is the most common (50%-60%), with NSIP (14%-36%) and desquamative interstitial pneumonia/RBILD (10%-17%) less common, and acute interstitial pneumonia quite rare (0-2%).[4] The histo-pathological patterns described herein can be seen in conditions other than idiopathic interstitial pneumonia.[5] This is especially true of NSIP, which has been described in a variety of conditions, including collagen-vascular disease, hypersensitivity pneumonitis, recent acute lung injury, and drug reactions. Therefore, before the diagnosis of idiopathic interstitial pneumonia is made, a careful clinical evaluation to rule out such associated conditions is paramount.

Usual interstitial pneumonia is characterized by a heterogeneous, predominantly subpleural distribution of involvement, Temporal heterogeneity is seen, with areas of end-stage fibrosis and honeycombing abutting areas of active proliferation of fibroblasts and myofibroblasts.

Nonspecific interstitial pneumonia evolved as a categorization reserved for idiopathic interstitial pneumonia that did not meet the criteria for UIP, desquamative interstitial pneumonia/ RBILD, or acute interstitial pneumonia. It is characterized by varying degrees of inflammation and fibrosis, with some forms primarily inflammatory (cellular NSIP) and others primarily fibrotic (fibrotic NSIP).

Desquamative interstitial pneumonia/RBILD is quite distinct in histopathological appearance from UIP, The most striking feature of these two conditions is the filling of alveoli by pigment-laden macrophages. These macrophages were originally and incorrectly thought to be desquamated alveolar epithelial cells; thus the name *desquamative interstitial pneumonia.*

Acute interstitial pneumonia is a diffuse,fibroproliferative process. The fibrotic changes are temporally homogeneous and may be accompanied by the presence of hyaline membranes. With time, end-stage fibrosis develops, and large cystic airspaces resembling honeycomb form.

Response to Therapy

Corticosteroids

Corticosteroids have been the mainstay of therapy since their initial release for clinical use in 1948.[6] Unfortunately, no prospective randomized placebo-controlled trial has examined the role of corticosteroids for idiopathic interstitial pneumonia.Attempts to predict who will respond to treatment have been largely disappointing. Clinical factors possibly associated with responsiveness to corticosteroid therapy include younger age, lesser degree of dyspnea, and female sex. A stronger association has been suggested with the degree of inflammation on open lung biopsy findings. More recent studies have found poor response rates to corticosteroids for patients with UIP (8%-17%).[7] No prospective

treatment studies exist for NSIP or RBILD. However, retrospective reviews of observational studies in which most patients received corticosteroids have suggested excellent responsiveness for these diseases. Respiratory bronchiolitis– associated interstitial lung disease appears to resolve in most patients with smoking cessation alone.

Immunomodulatory Agents

Because of the often poor responsiveness of idiopathic interstitial pneumonia to corticosteroids, immunomodulatory agents have been tried with mixed results. A randomized controlled trial of 43 patients with idiopathic interstitial pneumonia compared cyclophosphamide (anhydrous) plus low-dose prednisolone with standard-dose prednisolone alone and also showed no statistically significant difference in improvement or survival between the 2 groups, although a combined end point of time to change of treatment and survival was better for the cyclophosphamide group.[8]

Antifibrotic Agents

Recently, antifibrotic agents have been tried alone or in combination with corticosteroids in patients with UIP. Colchicine and pirfenidone were compared with prednisone in 26 patients with biopsy-proved UIP who were followed up for 1 year.[9] Although improvement was not directly reported, a trend was found toward a lower failure rate (eg, clinical decline, drug intolerance) and a lower incidence of serious adverse effects with colchicine. A recent study of another agent, interferon gamma-1b, showed significantly better lung function (total lung capacity and PaO2 at rest and with exercise) at 12 months in patients treated with interferon gamma-1b and prednisolone compared with prednisolone alone.[10]

Lung Transplantation

Lung transplantation should be considered in all patients with progressive disease who are unresponsive to medical treatment. Single lung transplantation is equal to bilateral lung transplantation[11] and leads to improvement in exercise capacity, pulmonary function, and gas exchange.

Survival

Excluding acute interstitial pneumonia, which is usually clinically distinct and has a poor prognosis (less than half of patients survive), the most important prognostic information is the presence or absence of UIP.

Idiopathic interstitial pneumonias: summary of key features

Idiopathic pulmonary fibrosis (IPF): This is the commonest Idiopathic interstitial pneumonia. Previously it was called cryptogenic fibrosing alveolitis. The histological appearance of Idiopathic pulmonary fibrosis is usual interstitial pneumonia (UIP),

It is now clear that distinguishing UIP from the other histopathological subgroups of idiopathic interstitial pneumonia has important therapeutic and prognostic implications.

UIP appears to be a distinct pathophysiological entity characterized by minimal inflammation and chronic fibroproliferation due to abnormal parenchymal wound healing.Recent hypothesis that UIP is a result of ongoing diffuse microscopic alveolar epithelial injury and abnormal wound healing.[12] The American Thoracic Society and the European Respiratory Society have recommended reserving the term *idiopathic pulmonary fibrosis* (IPF) for the clinical condition characterized by progressive dyspnea, cough, restrictive lung disease, and the histopathological pattern of UIP.

Approach to Diagnosis

The clinically important distinction to be made when diagnosing idiopathic interstitial pneumonia is whether the patient has IPF (as defined by the presence of UIP).

Clinical characteristics

The history and results of physical and laboratory evaluations have little diagnostic accuracy for IPF.

Bronchoscopic Technique

Unfortunately, no bronchoalveolar lavage findings are specific to IPF. Using the cellular constituency of the bronchoalveolar lavage fluid from patients with idiopathic interstitial pneumonia to predict the underlying histopathological features has been of little

clinical utility. Patients with IPF demonstrate a nonspecific increase in bronchoalveolar lavage levels of neutrophils, eosinophils, and, less commonly, lymphocytes. Several studies have suggested that a predominance of bronchoalveolar lavage lymphocytes predicts corticosteroid responsiveness and improved survival. Transbronchial biopsy is limited by the small size of the specimen obtained and the lack of histological preservation due to mechanical crushing of the tissue. Because of these factors, transbronchial biopsy specimens have poor diagnostic accuracy for IPF.[12]

Chest Radiograph

The chest radiograph lacks diagnostic specificity in interstitial lung disease, with a correct diagnosis made in less than 50% of cases.

High-resolution CT

High-resolution computed tomography (HRCT) is significantly more sensitive and specific for the diagnosis of IPF and has replaced conventional chest radiography as the preferred imaging method.[13] The characteristic radiographic features of IPF include patchy, predominantly basilar, subpleural reticular opacities absent or limited ground-glass opacities; traction bronchiectasis and bronchiolectasis, and honeycombing. Thus, the presence of significant ground-glass opacities on HRCT should bring in to question the radiographic diagnosis of IPF. The most recent studies of HRCT have reported sensitivities of 43% to 78% and specificities of 90% to 97% for the confident radiographic diagnosis of IPF[14]. HRCT can be used to make a confident, highly specific diagnosis of IPF in half to two thirds of patients with idiopathic interstitial pneumonia.

Combined Clinical and Radiographic Diagnosis

A clinical diagnosis of IPF was made if a patient met all of the following criteria: (1) absence of clinical features suggestive of infectious, neoplastic, collagen-vascular, occupational, environmental, or drug related conditions or hereditary diseases known to be associated with IPF; (2) age greater than 50 years; (3) insidious onset of exertional dyspnea of greater than 6 months' duration; (4) bibasilar end-expiratory crackles; (5) restrictive lung defect without coexisting airflow obstruction, decreased diffusing capacity, and increased alveolar-arterial oxygen gradient at rest or with exercise; (6) chest radiograph or HRCT with characteristic findings of IPF; and (7) transbronchial biopsy findings or bronchoalveolar lavage cellular profile lacking features to support a specific alternative diagnosis. When the clinical and radiographic diagnoses are consistent, IPF can be confidently diagnosed.

Diagnosing IPF without Surgical Lung Biopsy

The American Thoracic Society and the European Respiratory Society recently published a consensus statement describing major and minor criteria for the clinical diagnosis of IPF.

Major and Minor Criteria Supporting the Clinical Diagnosis of Idiopathic

Pulmonary Fibrosis*

Major criteria

1. Exclusion of other known causes of ILD, such as certain drug toxicities, environmental exposures, and connective tissue diseases.
2. Abnormal findings of pulmonary function studies that include evidence of restriction (reduced VC often with an increased FEV1/FVC ratio) and impaired gas exchange (increased alveolar-arterial oxygen gradient with rest or exercise, or decreased DLCO).
3. Bibasilar reticular abnormalities with minimal ground-glass opacities on HRCT.
4. Transbronchial lung biopsy or bronchoalveolar lavage showing no features to support an alternative diagnosis.[13]

Minor criteria

1. Age _50 years.
2. Insidious onset of otherwise unexplained dyspnea on exertion.
3. Duration of illness of 3 or more months.
4. Bibasilar, inspiratory dry crackles (Velcro type).

Abbreviations: DLCO, diffusion capacity for carbon monoxide; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; HRCT, high-resolution computed tomography; ILD, interstitial lung disease; VC, vital capacity.

*Adapted from American Thoracic Society.[13]

For major criteria, all 4 must be present; for minor, at least 3 of 4 must be present.

The presence of all 4 major criteria and at least 3 of 4 minor criteria increases the likelihood of a correct clinical diagnosis. If patients do not meet these major and minor criteria, we believe that surgical lung biopsy should be pursued in all patients except those too frail or ill to tolerate it.

Surgical Lung Biopsy.

It can be done by video-assisted thoracoscopic surgery or open- lung biopsy.

The choice between video-assisted thoracoscopic surgery and open-lung biopsy should generally be made by the thoracic surgeon on the basis of individual patient characteristics, but most patients today undergo video-assisted thoracoscopic surgery

IPF management

There is currently no evidence that any drug treatment improves survival or quality of life.drugs should not be used routinely,but may be considered in a closely observed trial of therapy.

In general,decisions regarding treatment are based on severity and rate of progression of symptoms,changes in pulmonary function,and HRCT appearance.Predominant ground glass appearance on HRCT suggests an IIP other than IPF,and may be associated with steroid responsiveness.Predominantly reticular pattern are usually less steroid responsive.[12,13]

2)Non specific interstitial pneumonia NSIP

The term NSIP is a description of a histological pattern rather than a specific clinical entity.NSIP may be idiopathic or occur in association with other systemic conditions, most notably connective tissue diseases.Typically affects younger patients than IPF.Onset gradual or subacute,typical symptom duration before diagnosis varies 0.5-3 years. HRCT frequently shows diffuse symmetrical ground-glass change,with or without reticulation and traction bronchiectasis.Histology is variable, ranging from a predominantly cellular pattern to a fibrotic pattern.Cellular pattern on biopsy responds well to corticosteroids and is associated with a good prognosis.[13]

3) Cryptogenic organizing pneumonia (COP)

Formerly it was called bronchiolitis obliterans organizing pneumonia,BOOP.Cryptogenic organizing pneumonia is a disease of unknown cause characterized by plugging of alveolar spaces with granulation tissue that may also extend up into the bronchioles.In addition to the cryptogenic pneumonia form, organizing pneumonia also occur in the context of other diseases.More common in non-smokers.Often presents as a slow to resolve chest infection;frequently after several courses of antibiotics.HRCT shows areas of consolidation with air bronchograms,often basal, subpleural, and peribronchial.Most patients respond to steroids,and improve within a week of starting treatment.Prognosis is generally good.[11,12]

4) Acute interstitial pneumonia(AIP)

Rapidly progressive form of interstitial pneumonia characterized histologically by diffuse alveolar damage.Formerly known as Hamman-Rich syndrome.May be considered as an idiopathic form of ARDS.Rapid onset of breathlessness;usually presents <3 weeks after symptom onset.HRCT shows diffuse ground glass and patchy consolidation.Histology shows diffuse alveolar damage;interstitial oedema,intra-alveolar hyaline membranes,followed by fibroblast proliferation and interstitial fibrosis.No treatment is of beneficial and overall mortality is more than 50%.[11-13]

5) Respiratory bronchiolitis-associated interstitial lung disease(RB-ILD)

Respiratory bronchiolitis is a pathological term referring to the accumulation of bronchiolar pigmented macrophages in cigarette smokers.Smoking cessation is the mainstay of treatment.Prognosis is good.[13]

6)Desquamative interstitial pneumonia(DIP)

Perhaps it is an extensive form of RB-ILD.It occurs in smokers and associated with the pathological finding of abundant pigmented macrophages located diffusely throughout alveolar air spaces.The term DIP is misleading,as desquamation of epithelial cells is not responsible for the histological findings as previously thought ;a more accurate term is alveolar macrophage pneumonia.Smoking cessation is the key.Prognosis is usually good.[13,14]

7) Lymphoid interstitial pneumonia(LIP)

Interstitial pneumonia characterized by diffuse lymphoid infiltrates and often lymphoid hyperplasia.It is idiopathic or may be associated with auto-immune condition,infection or connective tissue disease.HRCT shows ground-

glass change often with reticulation.Prognosis is variable.[14]

Conclusion:

All patients with suspected idiopathic interstitial pneumonia should undergo careful evaluation, with an in-depth history and physical examination, pulmonary function testing, bronchoscopy, and HRCT by physicians experienced in the care of patients with idiopathic interstitial pneumonia. Many patients can be classified as having IPF with a high degree of specificity without the need for surgical lung biopsy. The American Thoracic Society and the European Respiratory Society have recommended that initial therapy for IPF involve corticosteroids and immunomodulatory agents (cyclophosphamide or azathioprine) for 6 months, with progressive clinical decline or substantial adverse effects of treatment prompting cessation or modification of therapy.42 Physicians need to counsel their patients with IPF early with regard to prognosis, as it is distinct from the other forms of idiopathic interstitial pneumonia. Referral for lung transplantation should be pursued early in those patients with progressive disease that is unresponsive to therapy.

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REVIEW ARTICLE

Update on Idiopathic Pulmonary Hypertension: Advances in Management and Applicability of Sildenafil

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Abstract

Pulmonary arterial hypertension (PAH) is a rare debilitating disease characterized by progressive elevation of pulmonary arterial pressure and pulmonary vascular resistance that leads to right ventricular failure and death. Because there is no definite cure for the disease, the primary goal of management is to alleviate symptoms and prolong survival. PAH is a progressive disorder carrying a poor prognosis; however, dramatic progress has occurred in our knowledge of its pathogenesis and consequently, its treatment over the last two decades. Patients suspected to have PAH should be submitted to a battery of investigations which help in establishing the diagnosis, identifying the etiology, guiding in treatment and informing the prognosis. In this article, we attempt to provide an overview of the etiology, pathophysiology, and current therapeutic modalities with role of sildenafil in the treatment of PAH.

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Introduction:

Pulmonary hypertension (PH) is defined as a mean pulmonary artery pressure (mPAP) more than 25 mmHg at rest or 30 mmHg with exercise. Pulmonary arterial hypertension (PAH) also requires the presence of a pulmonary capillary wedge pressure (PCWP) d" 15 mmHg and a pulmonary vascular resistance (PVR) e" 240 dynes/s/cm^5.[1] Idiopathic pulmonary arterial hypertension (IPAH), which was formerly known as primary pulmonary hypertension (PPH), is characterized by clinical, radiological and electrocardiographic evidence of pulmonary hypertension and increased pulmonary arterial pressure (PAP) and PVR with normal PCWP.[2] A patient is said to be suffering from IPAH when there is no identifiable etiology that are known to elevate PAP. The etiology of secondary PAH

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includes a wide spectrum of factors like drugs, toxins, portal hypertension, HIV, collagen vascular diseases, and persistent pulmonary hypertension of newborn, etc. The geographic distribution and economic diversity along with significant regional variations in human development and healthcare infrastructure make the estimation of the disease prevalence very difficult.[3] Untreated, it is characterized by progressive dyspnea, a rapid downhill course, and an invariably fatal outcome.

Scenario in the Developing World in Contrast to the Developed

Bangladesh is currently in the grip of an epidemic of cardiovascular disease (CVD) secondary to diabetes, hypertension, and atherosclerosis. With most of the public health attention being focused on atherosclerotic cardiovascular disease, the problem of pulmonary hypertension is largely overlooked. The etiology of pulmonary hypertension is diverse and all the identifying causes of PAH are prevalent in the developing world in a much larger magnitude as compared to the western world. No published estimates are available on the expected magnitude of the incidence of IPAH in Bangladesh; however, it is estimated that one to two individuals per million per year are diagnosed with PPH compared to five to six individuals per million per year with pulmonary hypertension secondary to rheumatic autoimmune disease in the western world. There is an unexplained predominance of females (approximately a 3 : 1 ratio) with women mainly presenting in the third decade and men in the fourth. Approximately 6–12% of cases are believed to have a familial origin with inheritance in an autosomal dominant fashion.[2]

Pathophysiology

There has been extraordinary progress in the past 10 to 20 years in understanding the pathogenesis and development of pulmonary hypertension.[4] Detailed discussion is beyond the topic of this article. In short, pulmonary hypertension is associated with obstruction to the vasculature caused by proliferation of endothelial, smooth muscle, and intimal cells accompanied by concentric laminar intimal fibrosis. All these changes are brought due to the mutations in the bone morphogenetic protein receptor type 2 (BMPR2) gene signaling pathway. [5]

Essentials of Diagnosis[6]

- Most frequently seen in younger women.
- Dyspnea, and often cyanosis, with no evidence of left heart disease.
- Enlarged pulmonary arteries on chest radiograph.
- Elevated JVP and RV heave.
- Echocardiography is often diagnostic.

Diagnostic workup

Patients of PAH must undergo a complete evaluation to help establish a diagnosis (to rule out secondary causes), to assess the severity, as a guide to treatment modalities and for determining the prognosis. Followings should be done:

- Electrocardiogram (ECG): PAH suspected if an ECG show a right ventricular 'strain' pattern.
- Chest X-rays: May show enlarged pulmonary arteries peripheral pruning and right ventricle enlargement
- A complete blood profile including liver, renal and thyroid function tests are recommended.[7,8]
- Confirmation is by transthoracic echocardiography; Doppler assessment of the tricuspid regurgitant jet provides a non-invasive estimate of the pulmonary artery pressure.[1]

Elevated levels of N-terminal pro-brain natriuretic peptide and serum uric acid correlate with adverse right ventricular (RV) function and prognosis.[9-11]

As connective tissue and collagen vascular diseases have a strong association with PAH, immunological tests may be done to rule out the same if the index of suspicion is high.

HIV infection should be ruled out in all patients.

Spiral CT chest has been successfully used in diagnosing chronic thromboembolic pulmonary arterial hypertension (CTEPH).

MRI can help assess RV mass and volume and the presence of septal delayed contrast

enhancement at the RV enhancement points correlates with the severity of PAH.[12]

Right heart catheterization helps in confirming the diagnosis of PAH, exclusion of other causes, assessing the severity of the disease and establishing its prognosis.

Acute vasodilatory testing may be done with drugs including adenosine, epoprostenol, and nitric oxide to assess pulmonary vasoreactivity which serves as a guideline while initiating treatment.[1]

The six minute walk test helps in staging the disease, estimating prognosis and is used as an endpoint for calculating the efficacy of therapy.[13]

Mangement

Pulmonary hypertension is incurable but new treatments have delivered significant improvements in exercise performance, symptoms and prognosis.

Goals of Therapy

The goals of therapy include promoting vasorelaxation, suppressing cellular proliferation, and inducing apoptosis within the pulmonary-artery wall. Furthermore, because PAH is associated with right heart failure, another goal is to increase cardiac output by decreasing afterload (pulmonary vascular resistance) and by enhancing ventricular inotropy. The combination of a relatively fixed pulmonary vascular resistance and a normal systemic vasculature presents a unique challenge in the treatment of pulmonary arterial hypertension, because nonselective vasodilator therapy increases the risk of hypotension due to systemic vasodilatation that cannot be compensated for by an increase in right ventricular output, which can cause cardiovascular collapse. Ideal therapies for pulmonary arterial hypertension decrease pulmonary vascular resistance, spare the systemic circulation, and increase right ventricular inotropy. Although molecular abnormalities have been identified that may have potential as future therapeutic targets, PDE 5 inhibition meets many requirements for an ideal therapy now.[14-15]

General measures

- Patients are advised to avoid heavy physical exertion and exposure to high altitude
- Low grade aerobic exercises as tolerated are recommended.
- Patients should adhere to a sodium restricted diet
- Should be immunized against influenza and pneumococcus.
- Pregnancies should be avoided or terminated early as there is a high mortality rate associated with the same.
- Many PAH patients develop anxiety and depression and require psychosocial support.
- Elective surgeries carry an increased risk and if unavoidable, these patients should be administered epidural rather than general anesthesia.[3]

Supportive treatment

All patients should be anticoagulated with warfarin. Oxygen, diuretics and digoxin should be prescribed as appropriate.[1]

Role of Calcium channel blockers

Vasoreactivity should be tested before initiating therapy with calcium channel blockers and non reactive patients should be offered other therapies.[3]

Current recommendations include the use of an oral calcium channel blocker in patients without right heart failure who have had a favorable response to acute vasodilator challenge on cardiac catheterization.[16,17]

A favorable response is defined as a fall in mean pulmonary artery pressures of e" 10 mmHg and d" 40 mmHg on acute vasodilator testing with drugs like intravenous epoprostenol, adenosine, or inhaled nitric oxide.

High doses of drugs including amlodipine (20 to 30 mg per day), nifedipine (180-240 mg per day), and diltiazem (720-960 mg per day) have to be used to realize full benefit.

Verapamil should be avoided because of its negative inotropic effect.

Patients initiated on calcium channel blockers should be closely followed up after three months

and alternative PAH therapy should be considered in non responders.

Specific treatment

Specific treatment options include prostacyclins such as epoprostenol or iloprost therapy, the phosphodiesterase 5 (PDE5) inhibitor sildenafil, and the oral endothelin antagonist bosentan. These drugs should be administered in accordance with the WHO functional classification. The functional classification system of the New York Heart Association(NYHA) has been adapted by the World Health Organization (WHO) for use in classifying symptoms in patients with pulmonary hypertension (Table 1). The beneficial effects of drug therapy should be closely monitored over six to eight weeks. Treatments which are not effective should be replaced.

Table-I

*WHO Functional Classification of Pulmonary Arterial Hypertension.**

Class	Description
Class-I	No limitations in daily physical activities. Nosymptoms of dyspnea with routine exertion.
Class-II	Mild symptoms with exertion, including dyspnea and fatigue. No symptoms at rest.
Class-III	Moderate dyspnea with routine activities andactivities of daily living. No symptoms at rest.
Class-IV	Inability to perform even minimal activities. Signs and symptoms of right heart failure may be present.Dyspnea present at rest.

*Adapted from McLaughlin and McGoon.[18]

Table-II

Drug class: Prostacyclin analogues[3]

Drug	Route	Comment	Side effects/Disadvantage
Epoprostenol	Intravenous	to improve symptoms, exercise capacity and prognosis in IPAH and also in PAH associated with scleroderma.	flushing, headache, nausea, diarrhea, jaw discomfort with eating, chronic foot pain, and gastropathy
		starting dose of the drug is 2 ng/kg/min (started in the hospital) and this is usually up titrated to the chronic therapeutic dose of 25 to 40 ng/kg/min.	must be delivered by a continuous intravenous infusion via a tunneled catheter
Treprostinil	Subcutaneous	For functional class II, III, and IV PAH	pain and erythema at infusion site, headache, diarrhea, rash, and nausea.
Iloprost	Inhalation	an adjunctive to epoprostenol for treatment of functional class III and IV patients with PAH	headache, flushing, and jaw pain
		has to be administered six to nine times a day when the patient is awake	requirement of multiple doses and absence of treatment during sleep
Beraprost	Oral	not approved by the FDA, but is approved in Japan for the treatment of PAH	loses its efficacy over a year

Prostacyclins

Prostacyclin is a product of arachidonic acid metabolism and is a potent vasodilator of pulmonary and systemic circulations and also inhibits platelet aggregation. Prostacyclin levels are low in patients with PAH and this leads to a relative rise in thromboxane levels which further is responsible for vasoconstriction and smooth muscle proliferation.

Endothelin Receptor Blockers

Endothelial cells produce endothelin-1 which is one of the most potent vasoconstrictor ever isolated. The endothelin system is hyperactive in PAH with increased endothelin levels and up regulation of endothelin receptors in pulmonary vasculature. Various endothelin receptor blockers are available for therapy.

Phosphodiesterase Inhibitors

Nitric oxide (NO) is a vasodilator and inhibits smooth muscle cell proliferation. It is produced by nitric oxide synthase, the levels of which are decreased in patients with PAH. The effects of NO are mediated through cGMP which is degraded by phosphodiesterase (PDE) especially PDE-5. Hence, PDE-5 inhibitors have been used in the treatment of PAH as they prolong and increase the vasodilating effects of cGMP.

Sildenafil: Background and Mechanism of Action

The rationale for the use of PDE 5 inhibitors in pulmonary arterial hypertension is augmentation of the cyclic guanosine mono phosphate (cGMP)

Table-III

Drug Class: Endothelin Antagonists[3]

Drug	Route	Comment	Side effects/ Disadvantage
Bosentan	Oral	non-selective endothelin antagonist blocking both ET_A and ET_B improves pulmonary hemodynamics and functional capacity in patients with PAH. Recent studies have demonstrated improved survival at one and two years post therapy. The approved dosage of bosentan is 125 mg twice a day and is the first line medication in patients who have the New York Heart Association (NYHA) class III to IV symptoms	causes a dose dependant increase in hepatic transaminases in 10% patients and dose reduction/interruption is recommended for a threefold rise.
Sitaxsentan	Oral	ET_A receptor selective antagonist administered as a once daily oral dose	a rise in prothrombin time is a frequent side effect because of the inhibition of CYP2C9 P450 enzyme which is involved in the metabolism of warfarin.
Ambrisentan	Oral	a relatively selective ET_A blocker for PAH treatment in patients with functional class II and III symptoms. given as five mg daily studies have shown improvements in functional class and quality of life indices	So far, there is no data on survival improvement with Ambrisentan therapy

Table-IV

Drug Class: Oral Phosphodiesterase inhibitors[3]

Drug	Comment	Side effects/ Disadvantage
Sildenafil	highly selective PDE–5 inhibitor which was initially approved for the treatment of erectile dysfunction	headache, flushing, dyspepsia, and epistaxis
	has a preferential effect on the pulmonary circulation and has been shown to improve significantly the six minute walk distance and functional capacity in patients with PAH	escalation above the recommended dose has not been proved to be of additional benefit.
Tadalafil	longer acting PDE-5 inhibitor	As of silfdenafil Cautiousness required in mild to moderate hepatic or renal impairment
	Tadalafil received FDA approval for PAH in 2009[15]	remains investigational as a therapeutic agent
Vardenafil	has been approved for the treatment of erectile dysfunction	not yet approved for the treatment of PAH

pathway. By inhibiting the hydrolysis of cGMP, agents in this class increase its levels, with consequent vasodilatory, antiproliferative, and proapoptotic effects that may reverse pulmonary artery remodeling.[19] PDE 5 is expressed at minimal levels in the systemic vessels, other than the penile circulation, allowing for the relative selectivity of PDE 5 inhibitors for the pulmonary circulation. In addition, there is evidence that PDE 5 inhibitors may directly enhance right ventricular contractility through cGMP–mediated inhibition of Phosphodiesterase 3.[20]

Clinical Evidence

The benefit of sildenafil in pulmonary arterial hypertension was shown in the Sildenafil Use in Pulmonary Arterial Hypertension (SUPER) study, a Pfizer-sponsored randomized trial[21]. In this trial, 278 patients (39% with WHO class II pulmonary arterial hypertension and 58% with class III) received placebo or sildenafil (20, 40, or 80 mg administered orally three times a day) for 12 weeks. The mean placebo-corrected increase in the 6-minute walking distance (the primary end point) for the three doses of sildenafil was 45, 46, and 50 m, respectively. The baseline 6-minute walking distance at enrollment was 339 to 347 m. The mean decrease in pulmonary vascular resistance was 171, 192, and 310 dyn · sec · cm”5, respectively. In a 1-year extension trial in which sildenafil was given at a dose of 80 mg three times a day, there was a sustained increase in the mean 6-minute walking distance (by 51 m).

Clinical Use: Sildenafil versus Tadalafil

Sildenafil is indicated for use in patients with pulmonary arterial hypertension who have symptoms that are mild to moderately severe

(WHO class II or III). On the basis of the exclusion criteria used in the SUPER and Pulmonary Arterial Hypertension and Response to Tadalafil (PHIRST) trials, there is no evidence supporting the use of this drug in patients who have severe symptoms (WHO class IV; 6-minute walking distance, <100 m) or who are relatively asymptomatic (WHO class I; 6-minute walking distance, >450 m). Of the two currently approved PDE 5 inhibitors, there is longer experience with the use of sildenafil than with the use of tadalafil in patients with pulmonary arterial hypertension, and data from the SUPER and PHIRST trials suggest that sildenafil may be slightly more efficacious. However, tadalafil has the advantage of once-daily administration. Both the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have recommended that sildenafil be used at a dose of 20 mg given orally three times a day. This recommendation was based on the results of the SUPER trial, in which the benefit of sildenafil with respect to the 6-minute walking distance (6MWD) was not dose-dependent.[21] However, the effect on hemodynamic variables was dose dependent, with an increasing benefit at 40 and 80 mg. Furthermore, dose-titration studies have suggested incremental improvement in functional capacity with doses up to at least 225 mg daily.[8] It is therefore our practice to begin at a dose of 20 mg given orally three times a day and to increase the dose every 2 weeks to a maximum of 80 mg given orally three times a day or until dose-limiting side effects (usually headache, nasal congestion, or dyspepsia) occur.

Drug Pharmacokinetics and Interactions

Maximum plasma concentrations of sildenafil dosed at the FDA approved schedule of 20 mg 3 times daily are achieved 1 hour after administration, with a half-life of approximately 4 hours. Bioavailability is approximately 40%, which is reduced to 29% following large meal.[22]

It should be used with caution in hepatic disease, concomitant HIV infection and in the elderly.

The pharmacokinetics of sildenafil is not altered in the setting of mild to moderate renal insufficiency.

Sildenafil is currently listed by the FDA as a category B drug in pregnancy.[23]

Drug Side Effects

Review of the pivotal SUPER 1 study demonstrate that the most frequent placebo subtracted side effects were epistaxis (8%), headache (7%), and flushing (6%).[24]

Because of a shared and common pathway of increased nitric oxide (NO) mediated effects, concomitant administration with oral nitrate medications can potentiate the effects of either agent, and their use together is contraindicated.[25] Administration of sildenafil to patients taking nitrate medications can produce dramatic reductions in blood pressure (systolic blood pressure drop in excess of 50 mmHg) and syncope.[26] Sildenafil should not be administered to patients who have taken any oral or sublingual preparation within the previous 24 hours. While larger doses of sildenafil have been associated with significant reduction in systolic blood pressure approaching 10 mmHg, dose of 20 mg by mouth 3 times daily has not been shown to significantly affect blood pressure.[27]

Blurring of vision has been described at higher doses, primarily due to minor inhibition of PDE-6 located in the eyes. Nonarteritic anterior ischemic optic neuropathy (NAION) is a common cause of acute optic neuropathy in the elderly. Anecdotal reports and cases series suggested increased risks of NAION in sildenafil-treated patients. However, pooled data from clinical trials of all three commercially available PDE-5 inhibitors (sildenafil, tadalafil, vardenafil) suggested no increased risk of NAION.[28]

Although these findings are reassuring to health care providers, it remains advisable to monitor for visual changes, and to seek prompt medical attention for sudden vision loss.

Uncommon drug effects, including a case report of thrombocytopenia, have been described.[29]

Areas of Uncertainty

The SUPER and PHIRST trials examined the use of sildenafil and tadalafil almost exclusively in patients with WHO class II or III disease. It has not yet been determined whether these agents are beneficial in patients with class I or class IV disease.[15]

In patients who do not have an adequate response to a phosphodiesterase type 5 inhibitor, the

options are to switch to another agent or try combination therapy. The available data on combination therapy are limited. In trials of brief duration, the combination of sildenafil plus inhaled iloprost has additive pulmonary vasodilatory effects.[9]

In small, unblinded studies, sildenafil (50 mg administered orally three times a day) combined with treprostinil, epoprostenol, or inhaled iloprost was safe and appeared to have additive beneficial effects.[10-12] The combination of sildenafil with endothelin-receptor antagonists is not yet supported by data.

Sildenafil in other acquired PAH

Patients with end-stage liver disease are susceptible to development of porto- pulmonary hypertension, which, if untreated, is a contraindication for liver transplantation. While epoprostenol has long been the gold standard for treatment of portopulmonary hypertension, smaller studies suggest that in milder cases, sildenafil treatment can be safely used as a bridge to liver transplantation.[30]

Combination therapy

The rational for combination therapy stems from using different classes of medications target the disease from multiple mechanisms. As a general rule, efficacy should be maximized, while minimizing drug toxicity. The largest clinical trial evaluating combination therapy studied adding sildenafil, at doses ranging from 40 mg 3 times daily to 80 mg 3 times daily, to patients on stable doses of intravenous epoprostenol[31]. The study included 267 patients with predominantly idiopathic PAH (79%), and those with WHO FC II (26%) and WHO FC III (66%) symptoms. Addition of sildenafil was associated with a significant placebo-adjusted increase in 6MWD of 26 m ($P = 0.0009$) and increased time to clinical worsening. Hemodynamic improvements were noted with addition of sildenafil, including a reduction in mPAP of 3.9 mm mg ($P = 0.00003$). Health related Quality of Life (QoL) was improved with sildenafil treatment.

A few small single center studies have reported safety in adding sildenafil in combination with inhaled iloprost. Fourteen patients were randomized to treatment with sildenafil or placebo, and the sildenafil-treated group experienced significant and durable improvements in 6MWD.[32] Coadministration of bosentan (a hepatic enzyme inducer) and sildenafil reduces plasma levels of sildenafil and increases bosentan concentrations, though the clinical significance of this remains uncertain.[33]

Sildenafil in heart failure

The most common cause of right heart failure is longstanding left heart failure and development of pulmonary venous hypertension. Over time, if left untreated, some patients can develop structural changes in the pulmonary arteries with resultant increase in pulmonary vascular resistance.[34] Sildenafil has been shown to be well tolerated among severe end-stage heart failure patients undergoing transplant evaluation and as an acute screening agent for fixed pulmonary hypertension that would otherwise be a contraindication to heart transplantation.[35]

WHO classification of PH and Sildenafil

Multiple conditions result in development of pulmonary hypertension, which are included in WHO classification that is based upon groups of diseased states (Table V).

Given the costs, unproven benefits, and potential side effects of therapy, it is generally not advisable to use sildenafil for conditions other than WHO Group I PH.[36]

Clinical response to treatment

Adequate clinical response is defined as the achievement of a stable and a satisfactory clinical state, including absence of clinical signs of RV failure, stable WHO functional class I or II without syncope, a six minute walk distance of more than 500 meters, near normal or normal BNP plasma levels, no pericardial effusion, and right atrial pressures < 8mm Hg.[38-40]

Controversies in treatment with use of ACE inhibitors:

Previous publications suggested that inhibitors of the angiotensin converting enzyme (ACE) 1 could alleviate pulmonary hypertension and reduce right heart hypertrophy.[41] However, therapeutic interventions in animal models with PAH and clinical data do not support this fact.[3]

Table V
WHO classification of pulmonary hypertension

WHO classification	Disease states
Group I: PAH	Idiopathic PAH, familial PAH, associated PAH
Group II: Pulmonary hypertension with left heart disease	Valvular heart disease, systolic or diastolic dysfunction
Group III: Pulmonary hypertension associated with lung disease or hypoxemia	OSA, ILD, COPD, chronic hypoxemia
Group IV: CTEPH	Thromboembolic occlusion of the distal or proximal pulmonary vasculature
Group V: Miscellaneous	Sarcoidosis, fibrosing mediastinitis

Adapted from McLaughlin et al.[37]
Abbreviations: PAH, pulmonary arterial hypertension; OSA, obstructive sleep apnea; ILD, interstitial lung disease; COPD, chronic obstructive pulmonary disease; CTEPH, chronic thromboembolic pulmonary hypertension.

Invasive Techniques

- *Atrial septostomy*: It has been shown to be of benefit in patients with refractory right heart failure.[42]
- *Lung and combined heart lung transplant:* improvement in pulmonary hemodynamics with reduction in pulmonary vascular resistance and improvement in right ventricular function.[43]
- *Pulmonary thromboendarterectomy* may be considered as a treatment option in patients with CTEPH if they have surgically accessible disease.[44]
- *Right ventricular assist devices* are investigational tools which may help in the control of refractory right heart failure.[45]

Future Therapies

Several case reports have suggested that *Vasoactive Intestinal Polypeptide (VIP)*,[46] *Gene Therapy*.[47] platelet derived growth factor (PDGF) inhibitor, imatinib could improve the clinical condition.[48-49]

Conclusion

Since the treatment varies with the etiology of PAH, it is important to diagnose the underlying etiology accurately. Different investigations are essential to diagnose the underlying etiology and to assess disease severity. Sildenafil has emerged as a safe and efficacious pharmacotherapy for PAH. Longer-term studies, examining the effects of therapy on disease remodeling overall survival have yet to be completed. Combination therapy is an exciting development in the treatment of PAH. A favorable side effect profile and acceptable dosing regimen make sildenafil an attractive option for combination therapy, and studies are underway examining multiple drug combinations.

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CASE REPORT

Askin's Tumour Presenting as Haemorrhagic Pleural Effusion in a School Boy – A Case Report

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Abstract:

In this article, we report a 13ys old school boy with a rare tumor- Askin's tumor involving the chest wall and Lung who had presented to NIDCH Emergency department with Chest pain for 1 year, cough & breathlessness for 1 month with occassional fever for same duration.He has significant weight loss. Patient is tachypnoeic with RR 24/min, has features consistant with left sided pleural effusion.Bedside aspiration noted haemoharrgic effusion.So the provisional diagnosis was left sided pleural effusion.But the primyary cause is not clear at this moment.D/D were Lymphoma, Pulmonary tuberculosis with pleural involvementn,Teratoma,Sarcoma and rarely other pleural or lung malignancy.Investigation reported ESR-12 mm1st hr,WBC-10,500/cmm,CXR- Dense homogenous opacity with calcification within is noted in upper and mid zone of left lung and another dense homogenous opacity in the lower zone with curvilinear upper boarder obscuring left dome of diaphragm and left CP angle with ill defined opacities in mid zone of left lung. Bone destruction is noted in left 4th rib.Pleural fluid analysis noted exudative reddish fluid with lymphocytic pleocytosis and ADA 53U/ml, C T Guided FNAC from left lung lesion shows plenty of atypical cell with few small spindle cells highly suggestive of Pleuropulmonary blastoma. Closed Lung biopsy section shows collapsed lung tissue with small round cell tumour compatible with Primitive neuroectodermal tumour/Askin's tumour.We have transferred the pationt to National Institute of Cancer Research and Hospital Mohakhali Dhaka for management.

Keywards: Askin's Tumor, Chest wall Tumor,Haemorrhaic Pleural Effusion

[Chest & Heart Journal 2012; 36(2) : 161-166]

Introduction:

Askin and Rosai in 1979 described the rare primitive neuroectodermal tumor involving the thoracopulmonary region. It is a subset of Ewing's tumor characterized histologically by the presence of small round blue cells.It is 2nd most common primary, malignancy, in children.[1] Incidence is 2.1 / million (USA) and is more in males than females,65% in 2nd decade of life and rare in blacks and Asians.[2] FNAC shows of

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a small round blue cell Immunohistochemistry confirms the diagnosis by detection of neuron specific enolase and CD99. Chromosomal study proves translocation of chromosome between the long arm of 11 and 22.[3]Cough,Chest pain,fever,breathlessness,pleural effusion, local pain and paraesthesia, pathological, fracture, metastasis,related symptoms. Investigations: CBC shows raised ESR with Leukocytosis ,Chest X-ray large soft tissue mass, rib destruction pleural effusion calcification. Pleural fluid analysis reveals exudative effusion. Malignant cell may be present. CT scan of Chest large heterogeneous mass lesion, Rib destruction, Calcification MRI : Superior than CT scan, Chest wall muscle involvement Marrow involvement. FNAC Suggestive of a small round blue cell . Immunohistochemistry neuron specific enolase CD99.Chromosomal study: Translocation of chromosome between the long arm of 11 and 22. [3,4] Options of treatment are radical surgical resection, neoadjuvant and adjuvant chemotherapy ,radiation. Patients with Askin's tumour treated with aggressive pre-resection chemotherapy have smaller tumours to resect (less than 100 cc by volume) with improved survival.In chemotherapy protocol a total 6 cycle of cyclophosphamide, vincristine and dactinomycin (CVD) are used.[4,5] Overall the prognosis is poor.The worst prognosis was seen in patients with bony metastasis. Lung metastasis alone carried a better prognosis.[5]

Case Presentation: Rashidul Hassan 13 Years male Student from Galachipa, Barisal has got himself admitted in NIDCH Mohakhali Dhaka on 17-09-12 with the complaints of Chest pain for 1 year, cough and breathlessness for 1 month and fever for same duration.The patient was in his usual health 1 year ago then he gradually experienced chest pain in his left upper chest which was mild to moderate, dull aching, increased on movement and deep inspiration, without any radiation and relieved to some extent by pain killers. Occasionally he experienced severe chest pain. Cough is usually dry but occasionally expectorated mucoid sputum without any diurnal or postural variation. He felt short of breath during hurrying on the level ground which has worsened to the point where he cannot walk for further than 50 feet on the level , becomes more breathlessness on right lateral posture but no night time awakening due to breathlessness or wheeze. His fever was low grade, intermittent, persisted all the time of the day but relieved temporarily after medication, associated with night sweats but without any rash, itching, headache, vomiting, conjunctival congestion, joint pain, mouth ulcer, loss of alertness. Maximum temperature was not recorded. On query, he admits of weight loss for about 4 kgs in 2 months and loss of appetite but no history of haemoptysis, hoarseness of voice, difficult deglutition, gum bleeding. Local doctor evaluated and referred him to Barisal Medical College Hospital . He had been admitted there and after evaluation CAT-1 antiTB drugs was prescribed and some amount of red coloured fluid was aspirated from his left chest. After 10 days of medication , he did not feel well rather experiencing more cough, shortness of breath , along with worsening chest pain. Then his guardian decided to come here at NIDCH for better management.His past medical and surgical histories were uneventful. His family history is noncontributory and has no H/O contact with tuberculosis patient. He is immunized with childhood EPI immunization schedule.He drinks arsenic free tube well water and uses sanitary latrines. On physical examination, this well cooperative boy has average body build and nutritional status, looks pale and exhausted and tachypnoeic. His pulse is 98 bpm, blood pressure is 120/70 mm of Hg. His JVP is not elevated, respiratory rate is 24 per minute, temperature is 99 degree Farenhite. Respiratory system revealed restricted chest movement on left hemithorax with diminished chest expansion with full intercostal space on left.He has local tenderness on mid thoracic level over the left posterior axillary line.Vocal fremitus is diminished in all three lines on left side. Total chest expansibility is reduced to 2cm. Left hemithorax is stony dull below in all three lines on percussion .Breath sound is diminished vesicular in all three lines in left hemithorax in the aforesaid area with no added sound.Vocal

resonance is also diminished in all three lines. Abdomen is soft, non tender and there is no organomegaly.Testicular examination is normal. Other systemic examinations were normal. Provisional diagnosis was Lymphoma with pleural effusion (Left).

Differential diagnosis was tubercular pleural effusion (Left), Germ cell tumor with pl. effusion (left)or Sarcoma or any malignancy of pleural or lung origin. CBC revealed Hb 64%, ESR 12 mm in 1st hour, TC of WBC 10,500/ cmm, AFB not found in Sputeum, Pleural fluid was found reddish with Plenty of RBC.Blood urea& serum creatinine and sugar were found normal. Chest skiogram showed dense homogenous opacity with calcification within it in upper and mid zone of left lung with another dense homogenous opacity with curvilinear upper boarder obscuring left dome of diaphragm and left CP angle. Ill defined opacities are noted in mid zone of left lung. Bony thorax showed bone destruction in 4th rib. Left dome dome was not well visualized.

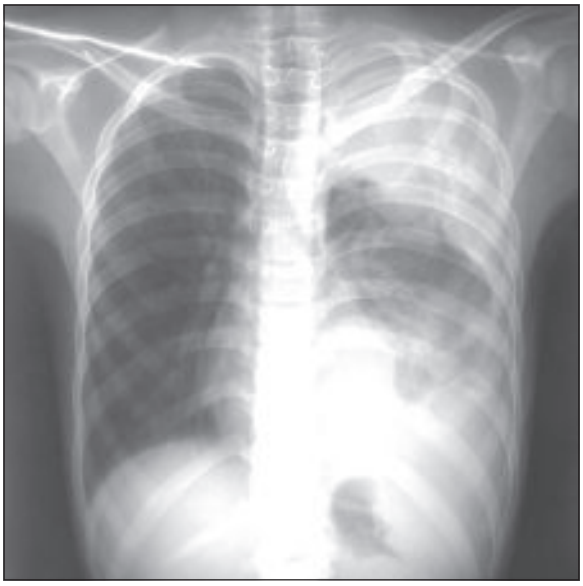

Fig.-1: *Suggestive of germ cell tumor with adjacent rib destruction with encysted pleural effusion with Inflammatory lesion (Left)*

USG of Chest: Mass lession with pleural effusion with huge internal septation is noted in left hemi thorax

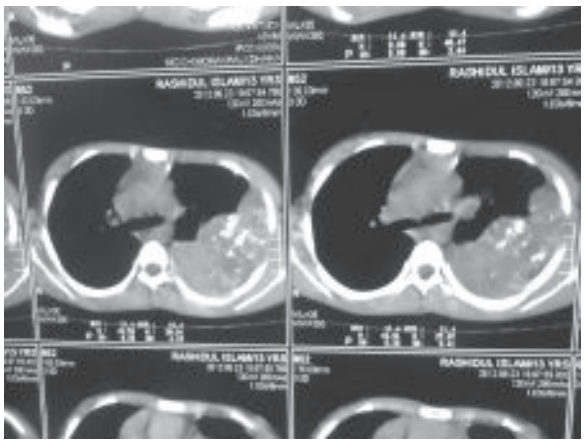

Fig.-2: *C T Scan of chest Mild heterogonous contrast enhancing mixed mass lession with internal calcification and adjacent rib erosion noted in in left hemi thorax compressing the adjacent lungs. Pleural effusion with pleural thickening is noted. Bony thorax shows rib destruction in left upper hemi thorax*

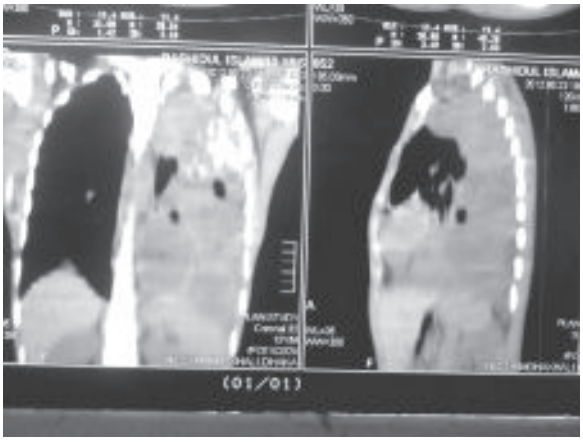

Fig.-3: *Suggestive of teratoma with adjacent rib destruction with mild pleural effusion*

USG Of whole abdomen including testis was found normal. AFP and Beta HCG were normal. Pleural fluid analysis revealed exedutive fluid with lymphocytic pleocytosis with high ADA (53U/L).CT Guided FNAC from left lung lesion revealed non Hodgkin'sLymphoma. As FNAC report was not consistent with radiological features surgical lung biopsy was performed. Smear shows plenty of atypical cell and few small spindle cells highly suggestive of pleuropulmonary blastoma

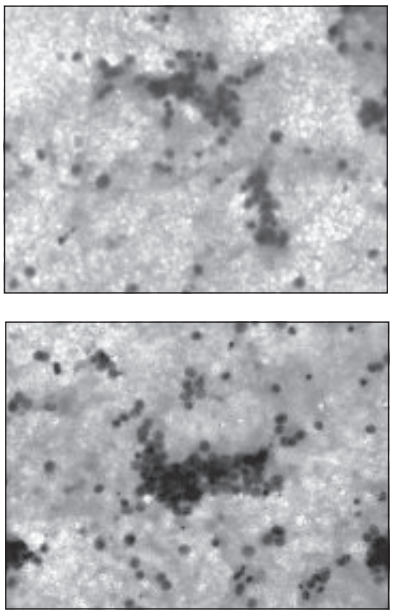

Fig.-4: *Closed Lung biopsy -Section shows collapsed lung tissue. It contains small round tumour cell compatible with Primitive neuroectodermal tumour/ Askin's tumour.*

Rashidul Hassan is now in National institute of the cancer research and hospital, Mohakhali, Dhaka under treatment for the disease since 23/ 10/2012 (about two months) with chemotherapy by Paediatric oncologist and recommanded protocol is VACIE(V-Vincristine D1,A-Adriamycin D1-D2,C-Cyclophosphamide D1,I-Iphosphamide D1-D5,E-Etoposide D1-D5) regimen 2 weekly for 14 cycles.Now with 5th cycle,his condition has improved both clinically and investigationally with wellbeing been regained,weight increased by 2Kg and CXR also showing signs of improvement,ESR has come down to 11 mmHg from 45mmHg and Hb raised to 13.3gm/dl.

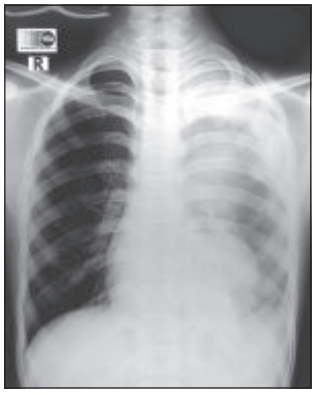

Fig.-5: *CXR PA View shows improvement of Lt.Lung Shadows with 5th Cycle of Chemotherapy*

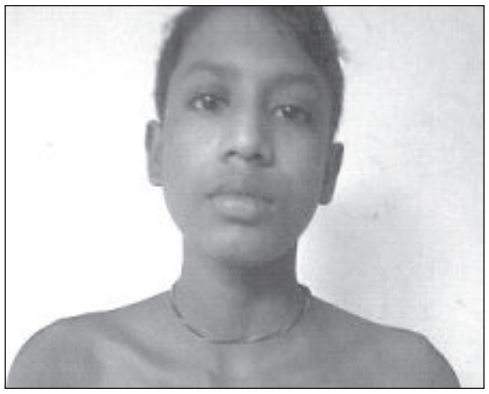

Fig.-7: *Before treatment with pale & vacant helpless look.*

Fig.-8: *Looks fresh and confident after 5th course of chemotherapy.*

Discussion:

Ewing's sarcoma (ES) was initially believed to be of perivascular endothelial origin. The Ewing's sarcoma family of tumors (EFT) includes ES of bone (ESB), extraosseous ES (EES), peripheral primitive neuroectodermal tumor of bone (PPNET), and malignant small-cell tumor of thoracopulmonary region (Askin's tumor). All of these tumors are now known to be neoplasms of neuroectodermal origin. [1,6] Askin's tumor is a rare neoplasm with a dismal prognosis and is usually observed in young subjects .The aggressive nature of Askin's tumor results in its short clinical presentation. The diagnosis of Askin's tumor is primarily by histopathologic examination.[6,7].In our case FNAC report from the lung chest lesion was not supporting the imaging suspicion. Imaging has only a complimentary role. So we have decided for lung biopsy. Closed lung boipsy showed smear with plenty of atypical cell and few small spindle cells highly suggestive of pleuropulmonary blastoma/

Askin's tumour. Establishing an accurate preoperative diagnosis of Askin's tumour poses a diagnostic challenge and is imperative both for instituting specific therapy and for prognosis.[8,9] In our case, not the fine needle aspiration cytology but biopsy conclusively proved the diagnosis. We were unable to go for immunophenotyping because of nonavailability of the tests in our institute and some other limitations too. . The differential diagnosis includes lymphoma,tuberculosis,germ cell tumor and Sarcomas and other malignancy, which were excluded by relevant investigations and tissue diagnosis. In recent times immunophenotyping has made the distinction more objective with demonstration of membrane-pattern positivity for MIC-2 (CD 99) (whereas muscle and lymphoid markers are negative).[9,10] The pattern of staining is important as CD 99 cytoplasmic positivity can be seen in small cell variant of synovial sarcoma.[11,12] A small proportion of rhabdomyosarcomas may be positive, hence positivity for a second neural marker (S-100,synaptophysin) and negativity for muscle markers makes the diagnosis more objective.[13,14] Its similarity with PNET is further established by detection of the EWS-FL1 chimeric gene.[15] CT scan is valuable for tumour diagnosis, assessing the effects of chemotherapy and recurrence.[16] Treatment includes radical surgical resection,neoadjuvant and adjuvant chemotherapy and radiation.

Patients with Askin's tumor treated with aggressive pre-resection chemotherapy have smaller tumors to resect (less than 100 cc by volume) with improved survival. In our case, there was gross reduction of the primary tumor with on going 5th cycle of chemotherapy, but multiple bony metastasis persisted hence radical surgery was not performed. Occasionally intraoperative radiotherapy has been helpful. Overall the prognosis is poor.

Conclusion:

Askin's tumour is a primitive neuroectodermal tumour presenting in children as a chest wall mass involving ribs. Accurate diagnosis of Askin's tumour poses a diagnostic challenge and is imperative both for instituting specific therapy and for prognosis. In most instances it is diagnosed as sarcoma. In our case, lung biopsy established the diagnosis. [16] Treatment includes radical surgical resection,neoadjuvant and adjuvant chemotherapy and radiation. The worst prognosis was seen in patients with bony metastasis. Lung metastasis alone carries a better prognosis.[5,16] Our case has both lung and bone involement.So prognosis may not be good but initial response to chemotherapy is encouraging.

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CASE REPORT

Common Variable Immune Deficiency (CVID) - A Rare Cause of Bronchiectasis: A Case Report

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Abstract

The possibility of an underlying immune deficiency, particularly antibody deficiency, should be considered in all children and adults with bronchiectasis. To our knowledge, no cases of common variable immune deficiency (CVID) with bronchiectasis have been reported previously in our country. The authors present the case of a 21-year-old male, diagnosed as bronchiectasis, who had recurrent fever, productive cough and frequent passage of loose stool since childhood. After exclusion of a wide range of differentials, CVID as the underlying cause was finally identified. CVID is prone to under diagnosis and may not reach relevant specialists until late in life. A high index of clinical suspicion, an early diagnosis and treatment of the disease could avoid future complications and improve the quality of life of these patients.

[Chest & Heart Journal 2012; 36(1) : 167-174]

Introduction:

Bronchiectasis represents an end-stage of a variety of pathological conditions.[1] Whereas most bronchiectasis is acquired during childhood, the condition may rarely result from a gross congenital developmental anomaly or be predisposed by some other inherited defect, be it ultra structural (as in ciliary dyskinesia), related to a generalized defect of ion transport (as in Cystic Fibrosis) or due to an immunodeficiency syndrome (e.g. hypogammaglobulinaemia).[1] Apart from the anatomical and mechanical defenses afforded by the epiglottis, the larynx, the act of coughing and mucociliary transport, the lung is also protected by bacteriostatic substances and by humoral and cellular immune mechanisms that may become defective for various reasons. Such defects sometime lead to recurrent or chronic lower respiratory tract infection, which may in turn be complicated by bronchiectasis.[1] Because the clinical features of the immunodeficiency states are not highly specific and vary from one entity to another, a definitive diagnosis is often delayed. Normally, immunodeficiency syndromes are recognized when a predisposition to unusual or recurrent infections develops in an individual. Most of these infections occur in the respiratory system and are the most frequent cause of morbidity and mortality.[2] Respiratory infection in the immunosuppressed has become a major clinical issue with the advance of human

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immunodeficiency virus (HIV) and with progress in transplant and oncology programmes. Deficiency of any arm of the immune system, may be primary or secondary; among which, secondary causes are relatively common. Hypogammaglobulinaemias are also associated with repeated respiratory tract infections. Secondary hypogammaglobulinemia can be due to a variety of conditions, which can be divided into diseases of immunoglobulin loss (e.g. protein losing enteropathy, chronic kidney disease); diseases of immunoglobulin production (e.g. chronic lymphocytic leukemia, lymphoma, and multiple myeloma); drug induced states (e.g. systemic steroids, phenytoin, disease-modifying antirheumatic drugs such as sulfasalazine and gold); and high-stress states.[3] The primary ones may present in infancy, when the protective benefit of transferred maternal immunoglobulin has waned. However, three forms of primary antibody deficiency can also present in adulthood: *Selective IgA deficiency, Common variable immune deficiency (CVID)*, & *Specific antibody deficiency or functional IgG antibody deficiency.*[4] Among these, CVID is associated with chronic sinusitis and repeated episodes of infective bronchitis leading to bronchiectasis in adult life.[1]

Case History:

A 21-year-old man was referred to NIDCH for worsening cough and sputum production with recurrent high grade fever, headache & occasional foul smelling diarrhoea since childhood. Additional symptoms included shortness of breath on exertion and fatigue. At presentation, there was high grade, continued fever for the last 7 days. Maximum recorded temperature was 103Ú F. Fever was accompanied with headache, chills & rigor and subsided with sweating after taking antipyretics. The cough was productive, aggravated in the morning & had no seasonal variation. Sputum was greenish-yellow in color, copious in amount, about 100ml per day, not foul smelling, not mixed with blood, aggravated on lying posture, and more marked in the morning. Diarrhoea was for last 5 days, which was characterized by loose, bulky , foul smelling stool , not mixed with blood, around 8-10 times a day and associated with nausea, loss of appetite, diffuse colicky abdominal pain & occasional vomiting. He was treated by local physicians several times with various antibiotics without much improvement. He was non-smoker, non-alcoholic & non-diabetic. There was no history of tuberculosis or contact with such patients, haemoptysis, foreign body inhalation, or infections like measles & whooping cough in childhood. He had no family history of such disease. He was immunized as per EPI schedule.

General examination showed moderate anaemia with digital clubbing, moderate dehydration and a weight below average for the age. Cyanosis, jaundice, oedema, bony tenderness, leukonychia, and koilonychia were absent. Neck veins were not engorged, jugular venous pressure was not raised and thyroid gland was not enlarged. There were no palpable lymph nodes. His vital parameters including pulse, blood pressure and temperature were normal. Respiratory rate was 20 breaths per minute. Respiratory system examination revealed, on palpation, his trachea was centrally placed; apex beat was located at left fifth intercostals space, just medial to the mid-clavicular line and there was bilateral maxillary tenderness . Percussion note was resonant over both sides. On auscultation, there was vesicular breath sounds with bilateral coarse crepitations on both lung fields, more marked over the bases. There were no palpable organs on abdominal examination. Other systemic examination revealed no abnormality.

Considering history and physical examination, the provisional diagnosis was bilateral bronchiectasis with sinusitis with steatorrhoea due to cystic fibrosis. The differential diagnoses included:

- Disseminated tuberculosis
- Primary ciliary dyskinesia
- Human Immunodeficiency Virus infection
- Primary hypogammaglobulinaemia

Initial blood tests showed total count of WBC: 17000/cmm, with a differential count: Neutrophils: 40%, Lymphocytes: 24%, Monocytes: 02%, Eosinophils: 34%, and Basophils: 0%.Total circulating eosinophil count

was 5780/cmm, indicating peripheral eosinophilia. Total count of RBC: 3900000/cmm, and Platelets: 512000/cm.

After observing this report, we added chronic pulmonary eosinophilia as another possibility.

Peripheral blood film study showed normochromic normocytic anaemia of moderate severity. Haemoglobin concentration was 7.7 gm/dl, ESR 28 mm in 1st hour and haematocrit was 26%. Blood biochemical tests included Plasma Glucose Fasting: 4.6mmol/l, Plasma glucose (2hrs ABF): 5.8 mmol/l, S. albumin: 4gm/dl, S.bilirubin: 0.5mg/dl, SGPT: 35 U/L, Blood urea: 25 mg/dl, S.creatinine: 0.8mg/dl, all of which were within normal limit.

A chest radiograph (Fig. - 1) indicated evidence of fibrosis in several areas of both lung fields with pleural thickening. But chest computed tomography (CT) scan (Fig. – 2) revealed bilateral traction bronchiectasis with a consolidation in right upper lobe & collapsed middle lobe. Roentgenogram of paranasal sinuses (Fig. -3) showed bilateral maxillary sinusitis.

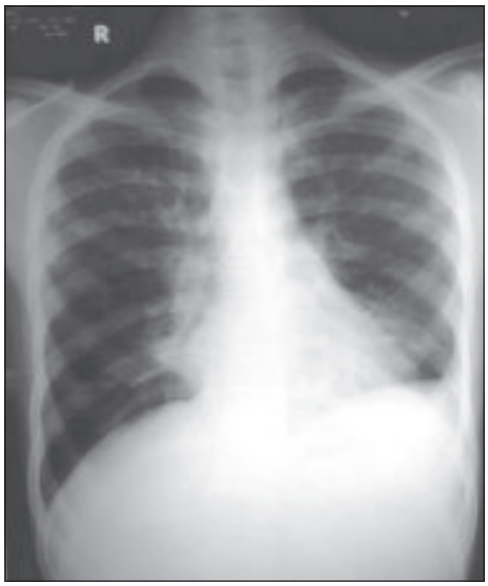

Fig.-1: *Chest X-ray (P/A): Lt. sided pleural thickening with fibrosis on both side.*

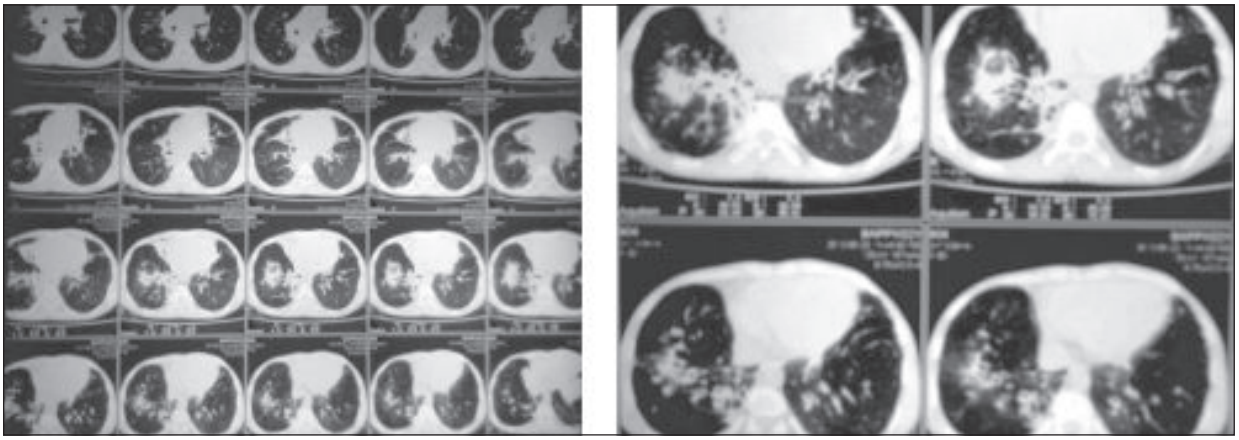

Fig.-2: *HRCT scan of chest showing, bilateral traction bronchiectasis, consolidation in right upper lobe and collapsed middle lobe.*

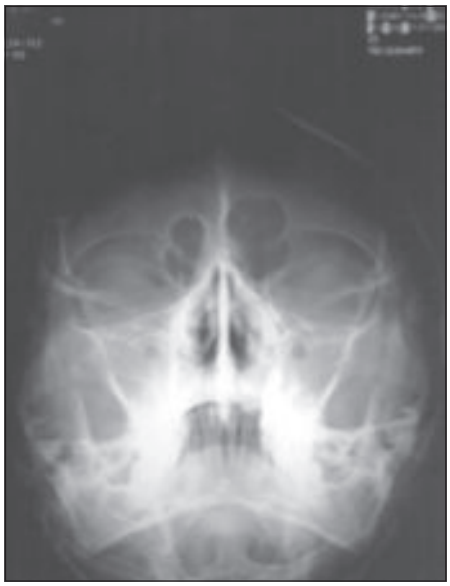

Fig.-3: *X-ray Para-nasal sinus (O/M) view showing bilateral maxillary sinusitis*

Pulmonary function testing demonstrated a decrease in lung capacity with mild airflow obstruction that significantly improved with an inhaled bronchodilator. Sputum for Gram stain and C/S showed growth of Pseudomonas aeruginosa; resistant to cefixime and ciprofloxacin.

Bronchiectasis was diagnosed & the possible causes were evaluated. The quest for tuberculosis was in vain; sputum for acid fast bacilli (AFB), broncho-alveolar lavage (BAL) for AFB (Table-I) & mantoux test was negative. Sputum for eosinophil count, radiographic appearance, and BAL study excluded chronic pulmonary eosinophilia. Sweat electrolytes (Table-II) for cystic fibrosis, saccharin test (Table-III) for primary ciliary dyskinesia & serologic testing for human immunodeficiency virus could not yield the cause. Ultra sonogram (USG) of whole abdomen, stool for routine examination and occult blood test reports were normal. Last but not the least, serum immunoglobulin measurement (Table-IV) was done, which revealed pan-hypogammaglobulinaemia. As no secondary cause depending upon the clinical picture and investigation would reflect such state, the patient was labeled as a case of common variable immune deficiency (CVID).

Table-I

Broncho-alveoler lavage (BAL) study by fiber optic bronchoscope (FOB)

BAL for	BAL for differential count
AFB: Not found	Macrophage: 87%
Malignant cells: Not found	Lymphocytes: 8%
Fungal hyphae: Not found	Neutrophils: 3%
Culture: No growth	Others: < 1%

Table-II

Sweat electrolytes

Sweat electrolytes	Result
Na^+	20.20 mmol/l *
Cl^-	14.80 mmol/l

* A raised sweat sodium concentration of 70mmol/L or more is required for cystic fibrosis[1]

Table-III

Mucociliary clearance for primary ciliary dyskinesia

Procedure*	Nasal clearance
Saccharin test	~20 th minute**

* A 1 mm cube of saccharin is placed on the inferior turbinate and the time to taste measured

**Normally less than 30 minutes[5]

Table-IV

Serum immunoglobulin measurement

Investigation	Result	Unit	Reference value
IgG	0.94	g/l	7.0-16.0 g/L
IgM	0.18	g/l	0.4-2.3 g/L
IgA	0.22	g/l	0.7-4.0 g/L
IgE	5.0	IU/ml	<100 IU/ml

Management

The patient was initiated a management strategy that included chest physiotherapy, bronchodilator, antibiotics with anti-pseudomonal coverage, anti helminthic drugs & blood transfusion with correction of dehydration. He was vaccinized against pneumonia & influenza. On discharge he was prescribed prophylactic azithromycin thrice weekly to continue with postural drainage and breathing

exercise. He was advised to have a regular three monthly follow-up visit. Over the next 3 months, his symptoms improved, although did not resolve completely. He regained a sense of well-being and was able to resume his normal lifestyle while continuing with this treatment advice.

Discussion:

CVID is a heterogeneous immune disorder characterized by frequent and recurrent infections due to decreased concentrations of multiple classes of immunoglobulins.[3] Recurrent upper and lower respiratory tract infections is typical and may progress to chronic bronchiectatic lung disease, malabsorption and diarrhoea.[5] The main feature is the hypogammaglobulinaemia where the serum level of IgG is low or absent, and the IgA and IgM levels are variably diminished; thus, antibody production is diminished. A primary defect in B-cell maturation is the problem.[2] More than 80% of patients have normal numbers of B lymphocytes, but when the lymphocytes are presented with an antigen, they fail to differentiate into antibody-secreting plasma cells[3]. Mechanisms such as abnormalities in the function of cells involved in cellular immunity (T cells, dendritic cells), and alterations in the secretion of various cytokines are also common to cases of CVID.[6] Genetic defects underlying the condition have revealed a mutation in the gene encoding ICOS-L.[5] Approximately 70–80% of patients are diagnosed based on a previous history of recurrent sinusitis with pulmonary and gastrointestinal infections. The diagnosis is made after all other known causes of humoral defects have been excluded.[6]

The estimated prevalence of CVID is 1 in 20,000 to 100,000.[3] It may be diagnosed in childhood, but more often presents in adults.[7] Common variable immunodeficiency occur in both sexes. A bimodal distribution of incidence by age has been noted, with the major peak between 25 to 45 years and a significant second peak between 5 and 15 years, although the onset may be at any age.[8-10] The diagnosis may be delayed considerably.[7] Pulmonary disease is more frequent and more severe than in patients with X-linked agammaglobulinemia.[2] Sinopulmonary infections begin in the second or third decade.[7] Bronchiectasis and obstructive airways disease occur in up to 40% of patients.[2] Roentgenographic features may include atelectasis, bronchiectasis, and homogeneous or heterogeneous segmental opacities.[2] Patients generally have recurrent and frequent upper and lower respiratory tract infections (e.g. sinusitis, otitis, bronchitis, pneumonia) from encapsulated organisms.[11] In several series of patients with either recurrent sinusitis or pneumonia, the prevalence of hypogammaglobulinemia is greater than in the general population.[12] About 25% to 48% of patients have splenomegaly.[13]

Patients with CVID are also at increased risk for a number of non-infectious diseases and should periodically undergo a thorough history and physical examination to evaluate for their presence. In 1999, Cunningham-Rundles and Bodian found that patients with CVID had a 20-year life expectancy of only 65%, compared with more than 90% in age matched controls.[14] The risk of non-Hodgkin B-cell lymphoma and gastric cancer is particularly high.[14] Hypogammaglobulinemia-associated thymoma (Good syndrome) has also been reported.[3] It is important that lymphoma not be confused with benign lymphoid hyperplasia, which is also seen in patients with CVID.[3]

CVID is associated with systemic lupus erythematosus, juvenile rheumatoid arthritis, idiopathic thrombocytopenia purpura, and autoimmune hemolytic anemia.[15,16] The relationship between connective tissue diseases and CVID is not fully understood. Some patients initially present with an immune cytopenia or other autoimmune disease that eventually progresses to CVID.[17]

Our case of interest did not present with cytopenia rather, there was peripheral eosinophilia. Based on clinical and haematological evidence, we considered chronic pulmonary eosinophilia (CEP) as another likelihood. CEP is also a rare disorder of unknown cause with subacute or chronic respiratory and general symptoms. There is alveolar and/or blood eosinophilia. The classical chest X-ray appearance has been likened to the photographic negative of pulmonary oedema with bilateral, peripheral and predominantly upper lobe

parenchymal shadowing.[4] The peripheral blood eosinophil count is almost always very high, and the ESR and total serum IgE are elevated. BAL reveals a high proportion of eosinophils in the lavage fluid. Diagnosis is usually based on the association of.[18]

1) respiratory symptoms of usually more than 2 weeks duration;
2) alveolar and/or blood eosinophilia (alveolar eosinophilia e" 40% at broncho-alveolar lavage (BAL) differential cell count; blood eosinophilia e" 1000/mm^3);
3) pulmonary infiltrates with usually a peripheral predominance on chest imaging; and
4) exclusion of any known cause of eosinophilic lung disease.

BAL findings (Table-I) and chest imaging (Fig.-2) excluded the possibility.

CVID patients may develop chronic diarrhea, with or without *Giardia* infection.[3] In our case, though stool examination finding was normal, peripheral eosinophilia might be due to giardiasis. The anaemia in this patient could be explained by the consequence of the chronic disease process.

Intravenous immunoglobulin (IVIG) is the cornerstone of managing CVID. Immunoglobulins are pooled from the sera of thousands of screened donors and typically given through a peripheral catheter either at home or in a physician's office—at a cost of $10,000 to $15,000 per infusion. A dose of 400 mg/kg is recommended every 3 to 4 weeks.[19] The dosage is adjusted on the basis of symptomatic improvement and IgG trough levels, which should be measured every 6 months or more often if infections persist. Serum IgG levels should be maintained above 500 mg/dL to help eliminate serious infections and preserve pulmonary function.[3]

Since IVIG is a blood product, its administration may raise concerns of viral transmission. Although no case of human immunodeficiency virus transmission through IVIG has been reported, hepatitis C transmission occurred in the early 1990s.[20] Donor screening and IVIG purification techniques have since improved,[21] and no known transmission of viral or other infection has since been reported. Reactions to treatment with IVIG include headache in up to 50% of patients, and chills, nausea, fatigue, or myalgia in 5% to 10%. Other reported reactions include increased blood pressure,[22] aseptic meningitis 24 to 72 hours after the infusion,[23] and acute renal failure in older, diabetic patients after receiving high-glucose, high-osmolar preparations.[24] Infusion-related side effects may diminish with slower infusion rates. Anaphylaxis to IgA in the IVIG preparation can also occur: patients who are IgA-deficient and are exposed to IgA in pooled sera may develop IgE antibodies against IgA. The use of IgA-depleted IVIG has greatly reduced this risk and is safe for patients who are IgA deficient, even after long-term use of IVIG.[25] Because the frequency of IgA deficiency is relatively high in the population, one should check the IgA level prior to initiating IVIG therapy. If low, one should utilize IgA-depleted IVIG, with the first dose given in a monitored, controlled setting.[3]

Regularly scheduled treatment with high doses of intravenous immunoglobulins (IVIG) leads to improved outcomes, including fewer hospitalizations and severe infections.[3] A clinical evaluation of 12 patients with common variable immunodeficiency followed for a mean of 10.5 years revealed few cases of pneumonia among those treated with intramuscular gamma globulin and long-term oral antibiotics.[26] The survival rate 20 years after the diagnosis of common variable immunodeficiency was 64% for men and 67% for women, versus the expected 92% survival for men and 94% for women in the general population.[15]

Limitations of the study:

Following are the investigations that could not be done in this case:

— Quantification of B & T Lymphocytes number by flow cytometry
— Specific antibody response to known pathogens
— Serum & urinary protein electrophoresis
— Blood DNA analysis of gene defect
— Blood immunoreactive trypsin levels
— Nasal mucosal biopsy for ultrastructural study

Conclusion:

Bronchiectasis is progressive when associated with ciliary dysfunction and cystic fibrosis and eventually causes respiratory failure. In other patients, as in CVID, the prognosis can be relatively good with early diagnosis and if physiotherapy and IVIG is provided regularly along with aggressive use of proper antibiotics.

Learning points:

1. Patients with frequent and recurrent respiratory infections should be tested for immune system abnormalities.
2. CVID though rare, is prevalent in our country and mostly under diagnosed. The estimated prevalence of CVID is 1 in 20,000 to 100,000 in western countries.
3. Mere bronchiectasis should not only be treated; aim should be to find out and treat the cause along with management of complications.

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CASE REPORT

Child with Sick Sinus Syndrome – A Case Report

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Abstract:

Sinatrial diseases can occur at any age but it is most common in older people.The underlying pathology involves fibrosis,degenerative changes or ischaemia of the SA node.The condtion is characterised by a variety of arrhythmias and may present with palpition,dizzy spells or syncope due to intermittant tachyacardia,bradycardia or pauses with no atrial or ventricular activity(SA block or Sinus arrest).As Sick sinus syndrome is very rare in children and immediate diagnosis was done by ECG and through presentation. The rarity of the case and life saving immediate measures saving the boy inspired us to report the case.

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Introduction:

Sick sinus syndrome is a clinical state in which there is a primary disorder of the normal Pacemaker, the SA node. This term was first used by Lowen (1967) as a defect in elaboration or conduction of sinus impulses characterized by chaotic atrial activity,changing p-wave contour and bradycardia interspersed with multiple and recurrent ectopic beats and runs of atrial and nodal tachycardia.[1]The diagnosis is essentially an electrographic one. Using Easeley and Golstein,s (1971) subclassification, type-1 sick sinus syndrome is diagnosed in patients exhibiting inappropriate sinus bradycardia or sinus arrest and type-2 in those showing a bradycardia-tachycardia combination.[2] Reports of s.s.s have been of adult patients, mostly elderly, and recordings of cases in children are few.[3,4]It has been reported to occur after intra-atrial operations with injury to the sinuatrial node or its blood supply, particularly after the Mustard operation[5-7] and also in children with various congenital cardiac malformations,[8-10] but occasionally it occurs in children and adolescents with no other evidence of heart disease.[10,11] However, the condition occurs in children and manifests as syncope, dizziness, convulsion, breath holding attack, life threatening arrhythmia or sudden death so its, recognition and treatment are important.

Case Report:

A two and half year old boy attended at physicians chamber with the complaint of preceded by sudden shrill cry which was associated with self injurious bleeding for last two month. On physicians chamber he developed that attack while he was playing.

Suddenly the boy started to scream followed by breath holding, he lacerated his gum which started bleeding and simultaneously he became cyanosed. The family history was unremarkable. There are no history of epilepsy, structural heart disease and operative procedure as well as no recent history of fever. Physical examination showed heart rate 120/m, R/R- 38/m, temp-normal, BP- 70/55 mm Hg, heart sound- normal and neurological examination showed no abnormality. He was investigated for cardiac, neurological evaluation and also evaluated for bleeding disorder. Echocardiogram, electro-cardiogram, bleeding time, clotting time, platelet count, APTT all were normal except ECG which was consistent with sick sinus syndrome.

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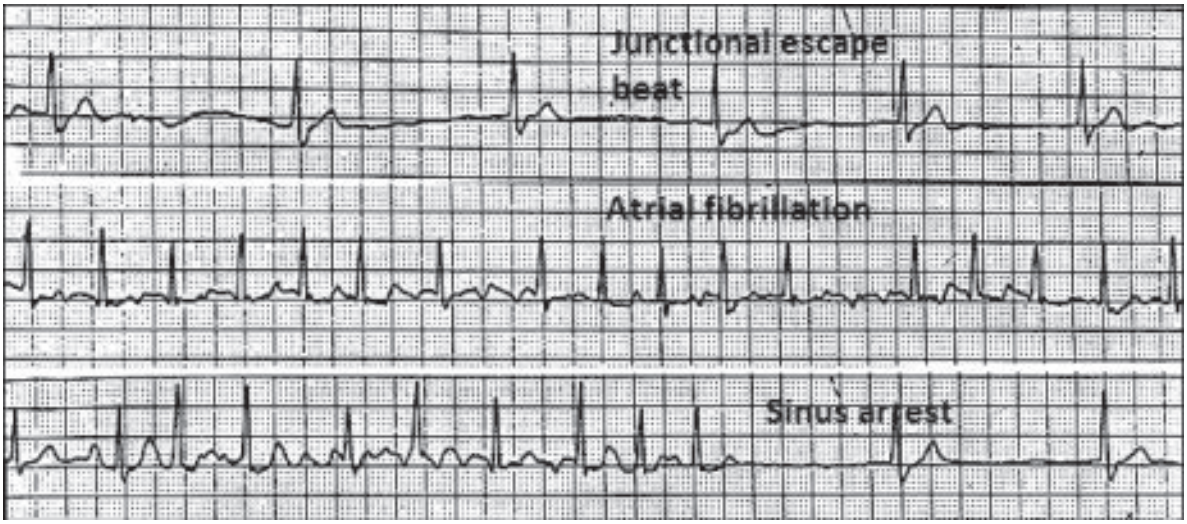

ECG shows both bradyarrythmia and tachyarrythmia.

Discussion:

There have been many reports of sick sinus syndrome (Ferrer, 1973.Rubenstein et.al 1972.It is often referred to as the brady-tachycardia syndrome because of alternating slow and rapid rates in some cases. The sick sinus syndrome is a well known complication of cardiac surgery.[5,6] It's association with cardiac malformation[8-10] and with myocarditis[7,10] is equally documented. However, no underlying or associated heart disease could be detected on ECHO or CXR in the case report here. Similar 20 cases have been published , a few well documented case reports.[12] There was no history of similar symptoms in the relative of our patient nor there was any history of illness in the boy to suggest recent myocarditis or other infection. So, the etiology was unknown. The age of onset of symptoms in our patient at two and half years or case is younger than in most of those previously reported. All the patients reported by Scott et.al 4 for instance were athletic boys between 10-15 years. The presenting symptom in our case was breath holding attack cyanosis (fainting spell) while playing. There is no such history before this attack or no history of epilepsy. Such clinical presentation matches partially with study by ECTOR et.al.[17] & Dorothy [13] . Actually the variability and vagueness if the symptoms make diagnosis difficult in the young children. So, ECG monitoring can help in this condition.ECG criteria of sick sinus syndrome apply to the presence of one or more of the following:1)Low voltage broad P-wave which at times may be bifid. 2) P-waves which alter shape and direction during recording. 3) Episodes of sinus arrest of three second or longer. 4) Episodes of 2:1 or 3:1 sinu-atrial block. 5)Slow escape rhythms that originate within the atria, His bundle, or ventricles. 6) Presence of both bradyrrythmias and tachyarrythmias (ie, SN reentry tachycardia, atrial tachycardias from an ectopic focus, atrial flutter, atrial fibrillation)

The case of our study had the ECG change of Junctional escape beat, Atrial fibrillation,

Sinus arrest which match with the ECG of sick sinus syndrome.

Conclusion:

Sick Sinus Syndrome may present with varied symptoms like breath holding attack, cyanosis, syncope, convulsion etc. but need ECG to confirm S.S.S. Diagnosis and treatment is important to reduce morbidity and mortality specially sudden death.

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