

**THE USEFULNESS OF PLEURAL FLUID ALKALINE
PHOSPHATASE AND ITS RATIO TO SERUM ALKALINE
PHOSPHATASE LEVELS IN CLASSIFYING PLEURAL
EFFUSIONS AS EXUDATES AND TRANSUDATES AND ITS
CORRELATION WITH LIGHT'S CRITERIA**

DISSERTATION SUBMITTED FOR

MD DEGREE (BRANCH 1) GENERAL MEDICINE

APRIL 2017



THE TAMILNADU DR.M.G.R

MEDICAL UNIVERSITY

CHENNAI – TAMILNADU

CERTIFICATE FROM THE DEAN

This is to certify that this dissertation entitled “**THE USEFULNESS OF PLEURAL FLUID ALKALINE PHOSPHATASE AND ITS RATIO TO SERUM ALKALINE PHOSPHATASE LEVELS IN CLASSIFYING PLEURAL EFFUSIONS AS EXUDATES AND TRANSUDATES AND ITS CORRELATION WITH LIGHT’S CRITERIA**” is the bonafide work of **DR. P.SHANMUGANATHAN**, in partial fulfilment of the university regulations of the Tamil Nadu Dr. M.G.R. Medical University, Chennai, for M.D General Medicine, Branch I examination to be held in April 2017.

Dr. M.R. VAIRAMUTHU RAJU MD.

THE DEAN,

Madurai Medical College

Madurai.

CERTIFICATE FROM THE HOD

This is to certify that this dissertation entitled “**THE USEFULNESS OF PLEURAL FLUID ALKALINE PHOSPHATASE AND ITS RATIO TO SERUM ALKALINE PHOSPHATASE LEVELS IN CLASSIFYING PLEURAL EFFUSIONS AS EXUDATES AND TRANSUDATES AND ITS CORRELATION WITH LIGHT’S CRITERIA**” is the bonafide work of **DR. P.SHANMUGANATHAN**, in partial fulfilment of the university regulations of the Tamil Nadu Dr. M.G.R. Medical University, Chennai, for M.D General Medicine, Branch I examination to be held in April 2017.

PROF. DR. V.T. PREMKUMAR M.D.,

Professor and HOD,

Department Of Medicine,

Government Rajaji Hospital,

Madurai Medical College, Madurai.

CERTIFICATE FROM THE GUIDE

This is to certify that this dissertation entitled “**THE USEFULNESS OF PLEURAL FLUID ALKALINE PHOSPHATASE AND ITS RATIO TO SERUM ALKALINE PHOSPHATASE LEVELS IN CLASSIFYING PLEURAL EFFUSIONS AS EXUDATES AND TRANSUDATES AND ITS CORRELATION WITH LIGHT’S CRITERIA**” is the bonafide work of **DR. P.SHANMUGANATHAN**, in partial fulfilment of the university regulations of the Tamil Nadu Dr. M.G.R. Medical University, Chennai, for M.D General Medicine, Branch I examination to be held in April 2017.

DR.J.SANGUMANI M.D, D.DIAB

Professor of Medicine

Chief, Vth Medical Unit

Madurai Medical College & Govt. Rajaji Hospital

Madurai.

DECLARATION

I, **DR.P.SHANMUGANATHAN**, solemnly declare that this dissertation titled **“THE USEFULNESS OF PLEURAL FLUID ALKALINE PHOSPHATASE AND ITS RATIO TO SERUM ALKALINE PHOSPHATASE LEVELS IN CLASSIFYING PLEURAL EFFUSIONS AS EXUDATES AND TRANSUDATES AND ITS CORRELATION WITH LIGHT’S CRITERIA”** is a bonafide record of work done by me at the Department Of General Medicine, Government Rajaji Hospital, Madurai, under the guidance of **Dr.J.SANGUMANI M.D, D.DIAB.**, Professor, Department of General Medicine , Madurai Medical college , Madurai.

This dissertation is submitted to The Tamil Nadu Dr. M.G.R Medical University, Chennai in partial fulfilment of the rules and regulations for the award of M.D Degree General Medicine Branch- I examination to be held in April 2017.

Place: Madurai

Dr.P.SHANMUGANATHAN

Date:

ACKNOWLEDGEMENT

Above all I thank the Lord Almighty for His grace and guidance.

My sincere thanks to our **Prof. DR.VAIRAMUTHURAJU. MD.**, Dean, Madurai Medical College and Government Rajaji Hospital, for permitting me to utilize the clinical materials from this hospital to conduct the study.

My respect and sincere gratitude to my beloved HOD **Prof. Dr.V.T.PREMKUMAR,M.D.**, Head of the Department of Medicine, Government Rajaji Hospital, Madurai Medical College for his valuable guidance and encouragement during the study and also throughout my course period.

I extend my gratitude and sincere thanks to my beloved teacher, my guide and my Unit Chief **Prof. Dr. J.SANGUMANI, M.D., D.DIAB.**, for his valuable suggestions, patience, guidance and support throughout the study and also throughout my course period.

I am greatly indebted to my beloved Professors, **Dr. R. BALAJINATHAN, M.D., Dr. M. NATRAJAN, M.D., Dr. G. BAGYALAKSHMI, M.D., Dr. C. DHARMARAJ, M.D., Dr.R.PRABHAKARAN, M.D.**, for their valuable suggestions throughout the course of the study.

I am extremely thankful to the Assistant Professors of Medicine of my Unit, **DR.R.SUNDARAM M.D., Dr.K.S.RAGHAVAN M.D., D.DIAB.,** for their valid guidance, encouragement and suggestions.

I extend my sincere thanks to **Prof. Dr. PRABHAKARAN, M.D,** HOD Department of THORACIC MEDICINE , Government Rajaji Hospital and Madurai Medical College for his unstinted support and valuable guidance throughout the study period.

I am extremely thankful to **Prof. Dr. MOHANKUMARESAN, MD.,** Head of the Department of Bio-chemistry for their constant support, guidance, cooperation and to complete this study.

My special thanks and love for my wife **Dr.Rohiniya BDS,** my daughters **Megha** and **Harshini,** my colleagues **Dr.Sundarnathan, Dr.Sridhar, Dr.Dinesh** for their support throughout the study.

Finally, I thank all the patients, the most integral part of the work, who were always kind and cooperative. I pray for their speedy recovery, comfort and strength.

CONTENTS

S.NO	TOPICS	PAGE.NO.
1.	INTRODUCTION	1
2.	AIMS AND OBJECTIVES	3
3.	REVIEW OF LITERATURE	4
4.	MATERIALS AND METHODS	62
5.	RESULTS AND INTERPRETATION	68
6.	DISCUSSION	78
7.	CONCLUSION	82
8	LIMITATIONS OF THE STUDY	85
9	ANNEXURES	
	BIBILIOGRAPHY	
	PROFORMA	
	ABBREVIATIONS	
	MASTER CHART	
	ETHICAL COMMITTEE APPROVAL LETTER	
	ANTI PLAGIARISM CERTIFICATE	

INTRODUCTION

Pleural effusion is a very common clinical presentation of diseases. A correct diagnosis of the underlying disease is essential for the management of pleural effusion. A limited number of diseases cause Transudative Pleural Effusion, whereas exudative effusions require more extensive diagnostic investigations. Therefore, the first step is to classify them as transudates or exudates, even if this differentiation does not contribute to the etiological diagnosis.

Many criteria have been used to distinguish them, but none of them have been found to be satisfactory. Light's criteria is the most commonly used method

The criteria is one or more of the following to diagnose exudates.

1. Pleural fluid protein / Serum protein > 0.5
2. Pleural fluid LDH / Serum LDH > 0.6
3. Pleural fluid LDH more than 2/3rd of the upper limit of serum

LDH.

It was found that even Light's criteria misclassified a large number of effusions - 25% of transudates as exudates.

Hence, there is a need to probe into new parameters which will prove to be superior or supportive to the various investigations available at present. Many other biochemical markers like bilirubin, cholesterol, alkaline phosphatase etc. can be taken into consideration.

Hence, this study is done to evaluate the efficacy of Total Pleural fluid Alkaline Phosphatase (ALP) and its ratio to Serum Alkaline Phosphatase levels in classifying the Pleural Effusion as Exudate or Transudate and its correlation with Light's criteria.

AIMS AND OBJECTIVES

To evaluate the advantages of Total Pleural fluid Alkaline Phosphatase(ALP) and its ratio to Serum Alkaline Phosphatase levels in classifying Pleural Effusions as Exudates or Transudates.

REVIEW OF LITERATURE

Definition

Pleural effusion is defined as the abnormal accumulation of pleural fluid within the pleural cavity. Crucial feature of the breathing apparatus is the pleural space. “This is a potential space between the parietal pleura and the visceral pleura. It is the coupling system between the lung and the chest wall.”

ANATOMY OF PLEURA

The lung parenchyma, the diaphragm, the mediastinum and the rib cage are covered by a serous membrane called the Pleura. Pleura is divided into visceral pleura and parietal pleura. Both these layers meet at the lung root.

Visceral pleura

“It covers the lung parenchyma in its points of contact with the diaphragm, the mediastinum and the chest wall and also in the inter-lobar fissures”

Parietal pleura

“It lines the inside of the thoracic cavities.

It is subdivided on the basis of intra-thoracic structures that it lines into

1. Costal parietal pleura
2. Mediastinal parietal pleura
3. Diaphragmatic parietal pleura”.

Pulmonary ligament

This is a thin double fold of pleura formed due to the downward extension of the pleura, posterior to the lung root.

Pleural space

This is a potential space present between the visceral and parietal pleura.

Pleural fluid

“This is a thin film of fluid normally present in between the visceral pleura and parietal pleura i.e., pleural space”

Functions of pleural fluid: It acts as a lubricant. During the respiratory movements the pleural fluid facilitates the visceral pleura which is covering the lung to slide along the parietal pleura which lines the thoracic cavity.

HISTOLOGY OF PLEURA

“Parietal pleura and visceral pleura are composed of two layers, namely the mesothelium and the connective tissue.”

Functions of Connective tissue layer

1. Contributes to elastic recoil of lung and helps in expelling air from the lung
2. Restricts the inflatable volume of lung and thereby protects the lung.

Functions of Mesothelial cells

It forms a monolayer of pavement like cells lining the pleural surfaces.

1. Movement and transport of particulate matter and fluid across the pleural surfaces.
2. Migration of leucocytes in response to inflammation.
3. Synthesis of cytokines, growth factors, extracellular matrix proteins.
4. Antigen presentation and transformation to myofibroblasts.

Blood supply

“Parietal pleura receives blood supply from systemic capillaries namely intercostal artery, pericardiophrenic artery, superior phrenic and musculophrenic artery and drained by intercostal veins and phrenic veins.

Visceral pleura: Pulmonary circulation supplies thin pleura and Bronchial arteries supply thick pleura. Venous drainage is through the pulmonary veins.”

Lymphatic drainage

Lymphatic plexus in the parietal pleura drains into intercostal, mediastinal, tracheobronchial, parasternal and phrenic nodes.

In the parietal pleura the lymphatic vessels are in communication with the stomas, the diameter of which ranges between 2 to 6 microns. The main pathway for the elimination of particulate matter is the stomas with lacuna and lymphatic vessels.

In the visceral pleura there are abundant lymphatic vessels which join bronchial lymph vessels.

Nerve supply

Intercostal nerves supply the costal and peripheral part of diaphragmatic pleura. So the pain sensation due to inflammation of this part of pleura is perceived in the chest wall.

Phrenic nerve supplies the central part of diaphragmatic pleura. So when this part of pleura is irritated or inflamed the pain is felt in the ipsilateral shoulder.

PHYSIOLOGY OF PLEURA

Formation of the Pleural Fluid:

“Pleural fluid can originate in the

- pleural capillaries
- intra-thoracic lymphatics
- intrathoracic blood vessels
- peritoneal cavity or
- interstitial spaces of the lung.”

Pleural Capillaries

The movement of fluid between the pleural capillaries and the pleural space obeys the Starling’s law of transcapillary exchange.

Hydrostatic pressure

In the parietal pleura, the hydrostatic pressure is approximately 30 cm H₂O, but the pleural pressure is approximately -5 cm H₂O. The net hydrostatic pressure is therefore $30 - (-5) = 35$ cm H₂O. This pressure favours the movement of fluid from the capillaries in the parietal pleura to the pleural space.

Oncotic pressure

The hydrostatic pressure gradient is opposed by oncotic pressure gradient. Plasma oncotic pressure is approximately 34 cm H₂O.

Normally, the pleural fluid has an oncotic pressure of approximately 5 cm H₂O, as it contains a small amount of protein. The net oncotic pressure gradient is $34 - 5 = 29$ cm H₂O. Thus, the net gradient is $35 - 29 = 6$ cm H₂O. It favours the movement of fluid to the pleural space from the capillaries present in the parietal pleura.

The net gradient for fluid movement across the visceral pleura in humans is probably close to zero, which has not been demonstrated. The pressure in the parietal pleural capillaries is approximately 6 cm H₂O more than that in the visceral pleural capillaries.

This is because capillaries in the visceral pleural are drained by the pulmonary veins. This is the only pressure that differs from the pressure affecting fluid movement across the parietal pleura. The net gradient for the

parietal pleura is 6 cm H₂O. So the net gradient is approximately zero for fluid movement across the visceral pleura.

The capillaries in the visceral pleura are much farther from the pleural space when compared to the capillaries in the parietal pleura. Hence the filtration coefficient (L^P) for the visceral pleura is substantially less than that for the parietal pleura.

The fluid formation is more across the parietal pleura over the ribs than the pleura over the intercostal spaces,. Also fluid formation was more over the caudal ribs than over the cranial ribs. But in contrast, pleural liquid absorption was more primarily in the parietal pleura adjacent to the intercostal space rather than that overlying the ribs. The formation of pleural fluid was more, if the breathing frequency was increased.

Interstitial Origin

“It has been demonstrated that the interstitial spaces of the lungs is the origin of much of the fluid that enters the pleural space. Pleural fluid accumulates if there is either high-pressure or high-permeability pulmonary edema. The elevation in the wedge pressure is directly related to the amount of pleural fluid formed. But increased pleural fluid accumulation occur only after the development of pulmonary edema. The origin of the pleural effusion is probably the pulmonary interstitial space in patients with congestive heart failure,.”

“It is likely that in many conditions associated with lung injury, such as lung transplantation and pulmonary embolisation, the origin of the pleural fluid is also the interstitial spaces of the lung.

It has been shown that the subpleural interstitial pressure increases with increasing levels of interstitial fluid. Even though the visceral pleura is thin, the barrier to the movement of fluid across the visceral pleura appears to be weak. Hence, once there is increase in subpleural interstitial pressure, the fluid will enter to the pleural space through the visceral pleura.”

Peritoneal Cavity

“If there is free fluid in the peritoneal cavity, pleural fluid accumulation can occur. Peritoneal fluid enters the pleural space through the openings in the diaphragm. Since the pressure in the pleural cavity is less than the pressure in the peritoneal cavity the fluid will flow from the peritoneal space to the pleural space. In conditions like hepatic hydrothorax, Meigs' syndrome, and peritoneal dialysis, the peritoneal cavity is the origin of the pleural fluid.”

Thoracic Duct or Blood Vessel Disruption

If there is disruption of thoracic duct, there is accumulation of lymph in the pleural space. This will produce a chylothorax. The rate of fluid accumulation can be more than 1,000 mL/day in chylothorax.

Origin of Normal Pleural Fluid

Pleural fluid is formed from the parietal pleural capillaries. The amount of pleural fluid formed daily is approximately 15 mL in a 50-kg individual. Since the protein level in the interstitial spaces is normally approximately 4.5 g/dL, and the protein level in normal pleural fluid is only approximately 1 to 1.5 g/dL, the origin of the fluid does not appear to be the interstitial spaces of the lung. Pleural fluid with lower protein levels are produced by higher vascular pressures. Evans blue dyed albumin studies with rabbits have demonstrated that most fluid originates in the parietal pleura over the ribs.

Pleural Fluid Absorption

Lymphatic Clearance

The lack of fluid accumulation in normal individuals is due to the clearance of fluid through the pleural lymphatics. The pleural space communicates with the lymphatic vessels in the parietal pleura via stomas in the parietal pleura. Visceral pleura lacks such stomas. The lymphatics in the parietal pleura removes proteins, cells and all other particulate matter from the pleural space. The carbon particles exit the pleural space through the stomas where the mesothelial cells are small and not flattened. Increased levels of nitric oxide in the pleural space cause increase in diameter of the stomas.

In a 60-kg individual the lymphatic drainage from each pleural space is on the order of 20 mL/hr or 500 mL/day.

Once the volume of the pleural liquid exceeds a particular threshold, the lymphatics operate at maximum capacity.

Clearance through Capillaries in Visceral Pleura

Until the mid-1980s, it was thought that the capillaries in the visceral pleura in humans were the primary route for the exit of fluid from the pleural space.

Through the lymphatics in the parietal pleura almost all the pleural fluid is removed. Several hundred millilitres of water probably traverse the pleural membranes each day. The net movement is of only a few millilitres as the osmolarity is nearly identical on each side of the membrane.

Alternative Mechanisms for Pleural Fluid Removal

Transcytosis plays a role in the removal of protein from the pleural space. Only 29% of the overall removal of albumin occurred through the stoma with small hydrothoraces, while 64% of the albumin from large hydrothoraces was removed through the stoma.

Pathogenesis of Pleural Effusions

Pleural effusion occurs whenever “the rate of pleural fluid formation exceeds the rate of pleural fluid absorption.”

“Normally, a small amount (0.01 mL/kg/hour) of fluid constantly enters the pleural space from the capillaries in the parietal pleura. The lymphatics in

the parietal pleura remove almost all of this fluid. Lymphatics have a capacity to remove at least 0.20 mL/kg/hour. The lymphatics remove the fluid exceeding the normal rate of fluid formation by a factor of 20.”

GENERAL CAUSES OF PLEURAL EFFUSION

A. Increased pleural fluid formation :

1. “Increased interstitial fluid in lungs

- Left ventricular failure
- Pneumonia
- Pulmonary embolism

2. Decreased pleural pressure

- Lung atelectasis
- Elastic recoil of lung is increased

3. Increased permeability of pleural capillaries

- Pleural inflammation
- Elevated vascular endothelial growth factor (VEGF) levels

4. Increased levels of protein in the pleural fluid

5. Increased intravascular pressure in pleura

- Right or left ventricular pressure
- Superior vena cava syndrome

6. Disruption of thoracic blood vessels

7. Thoracic duct disruption

8. Increased fluid in the peritoneal cavity

- Peritoneal dialysis
- Ascites“

B. Decreased pleural fluid absorption

1. “Obstruction of pleural lymphatic drainage
2. Disruption of Aquaporin system in the pleura
3. Elevated systemic vascular pressure
 - Superior vena cava syndrome
 - Right ventricular failure”

1. Increased Pleural Fluid Formation

Whenever there is increased pulmonary interstitial fluid or when one of the terms in Starling's equation is changed, there is increased pleural fluid formation.

a) Increased Interstitial Fluid

“Increased interstitial fluid in the lungs is the most common cause of increased pleural fluid formation.” Irrespective of whether the edema is due to low-protein or high-protein fluid, pleural fluid accumulates whenever the amount of edema in the lung exceeds 5g/gram of dry lung weight. In conditions like congestive heart failure, parapneumonic effusions, acute respiratory distress syndrome, and

in those who have undergone lung transplantation, increased interstitial fluid appears to be the predominant mechanism for the accumulation of pleural fluid.

b) Increased Hydrostatic Pressure Gradient

According to Starling's equation, there will be an increase in the rate of pleural fluid formation if there is an increase in the gradient between the intravascular pressure and the pleural pressure.

In conditions like right ventricular failure, left ventricular failure, pericardial effusion or superior vena cava syndrome, there is increase in the intravascular pressure. Atelectasis of the lower lobe or complete lung due to bronchial obstruction is the most common situation producing a decrease in the pleural pressure. “A decrease in the pleural pressure also occurs when the visceral pleura becomes coated with a collagenous peel and the lung becomes trapped.” The pleural pressure can become very negative, in these instances i.e., it goes below $-50 \text{ cm H}_2\text{O}$. “The decreased pleural pressures can also contribute to pleural fluid accumulation in diseases where the elastic recoil of the lung is increased.”

c) Increased Capillary Permeability

If the pleural surfaces become inflamed, the permeability of the capillaries may be increased. High levels of vascular endothelial growth factor (VEGF) increases the capillary permeability .This may be at least partially responsible for the accumulation of pleural fluid. It has been demonstrated that

mesothelial cells have VEGF receptors on their surface. The levels of VEGF are higher in exudative than transudative pleural effusion.

d) Decreased Oncotic Pressure Gradient

In conditions like hemothorax, increased permeability pulmonary edema and with conditions in which the pleural capillary permeability is increased, the level of pleural fluid protein is increased. The capacity to remove pleural fluid by the lymphatics is approximately equal to the rate of formation of pleural fluid. Hypoproteinemia is a very uncommon cause of pleural effusion.

e) Presence of Free Peritoneal Fluid, or Disruption of the Thoracic Duct or an Intrathoracic Blood Vessel :

The free fluid in the peritoneal cavity traverse through the holes in the diaphragm and it leads to pleural fluid accumulation and pleural effusion. Similarly, if the thoracic duct disrupts, chyle will accumulate in the pleural space. And if there is a disruption of a blood vessel in the thorax, blood will accumulate in the pleural space .

2. Decreased Pleural Fluid Absorption

a) Normal Pleural fluid absorption by lymphatics

Normally, “the lymphatic flow from the pleural space is approximately 0.01 mL/kg/hour or 15 mL/day as this is the amount of pleural fluid formed.

However, the capacity of the lymphatics is approximately 0.20 mL/kg/hour or 300 mL/day.”

b) Obstruction of Lymphatics

“Obstruction of the lymphatics draining the parietal pleura is the most common cause of decrease in pleural fluid absorption.” Lymphatic blockade is an important factor in the development of a malignant pleural effusion.

c) Elevation of Systemic Venous Pressures

Lymphatic flow will be reduced when there is elevation of pressure in the central veins. This is because the lymphatics drain into the systemic venous circulation.

“The pleural effusions developed because of (a) leakage of lymph out of the lymphatics that pass through the chest (these include the diaphragmatic and pulmonary lymphatics and thoracic duct) ; or (b) leakage of interstitial fluid into the pleural space due to obstruction of lung or chest wall lymphatics .”

CLINICAL MANIFESTATIONS OF PLEURAL EFFUSION

Normally, the pleural space contains only a few millilitres of pleural fluid. If fluid in the pleural space is detected on a radiologic examination, it is abnormal. Pleural fluid accumulation is associated with many conditions. When pleural fluid is detected, an effort should be made to determine the etiology.

1. Symptoms

“In a patient with pleural effusion, symptoms mainly depends on the underlying process causing the effusion. Many patients have no symptoms referable to the effusion. When symptoms are related to the effusion, they arise either from inflammation of the pleura, compromise of pulmonary mechanics, interference with gas exchange, or rarely decreased cardiac output.”

a) Pleuritic chest pain

“Normally visceral pleura does not have pain fibres, only the parietal pleura contains pain fibres. In a patient with pleural effusion, pleuritic chest pain always indicates inflammation of the parietal pleura. Some patients with pleural effusions experience a dull aching chest pain rather than pleuritic chest pain.

The parietal pleura is innervated mostly by the intercostal nerves. So, the pain associated with pleural disease is well localized and it coincides with the area of the pleura which is affected by disease. Since the intercostal nerves are also distributed to the abdomen, pleuritic pain is referred to the abdomen .When the central portion of the diaphragmatic pleura is involved, there are exceptions to the localization of the pain. Phrenic nerve supplies this portion of the parietal pleura. Pain is referred to the tip of the ipsilateral shoulder if the central portion of the diaphragm is inflamed. Pleuritic pain felt simultaneously in the lower chest and ipsilateral shoulder points to diaphragmatic involvement.”

b) Cough

“A dry, non-productive cough is the second symptom of pleural effusion. Although it may be related to pleural inflammation, the exact mechanism producing the cough is not clear. Alternately, cough reflex is stimulated by the pleural fluid compressing the lung, bringing the opposing bronchial walls into contact.”

c) Dyspnea

“Dyspnea is the third symptom of pleural effusion. As pleural effusion acts as a space-occupying process in the thoracic cavity, it reduces all subdivisions of lung volumes leading to dyspnea.

This explains the small increase in pulmonary function following therapeutic thoracocentesis if pleural effusion is associated with parenchymal disease. The degree of dyspnea is frequently out of proportion to the size of the pleural effusion. Due to the weight of fluid on the diaphragm, the diaphragmatic function is compromised and this results in dyspnea .”

2. Physical Examination

a) Inspection

Clinical findings vary according to the pleural pressure. The ipsilateral hemithorax will be “larger and the usual concavity of the intercostal spaces will be blunted or even convex, if the pleural pressure on the side of the effusion is increased”. In contrast, the ipsilateral hemithorax will be “smaller and the

normal concavity of the intercostal spaces will be exaggerated if the pleural pressure on the side of the effusion is decreased.” This occurs with obstruction of a major bronchus or a trapped lung. In addition, the intercostal spaces retract with inspiratory efforts.

An indication of therapeutic thoracocentesis is enlargement of the hemithorax with bulging of the intercostal spaces. It is done to relieve the increased pleural pressure. It is also found that the hemithoraces are equal in size and the intercostal spaces are normal, in many patients with pleural effusions.

b) Palpation

Palpation is useful to determine the extent of the effusion. “Vocal fremitus is absent or attenuated in areas of the chest where pleural fluid separates the lung from the chest wall.” This is because the vibrations emanating from the lung are absorbed by the fluid.

To identify the upper limit of the pleural fluid, vocal fremitus is much more reliable than percussion. It is also useful to identify a proper site to attempt a thoracocentesis. Vocal fremitus is much more reliable than percussion, because with a thin rim of fluid, the tactile fremitus is diminished, but the percussion note may still be resonant.

Apical impulse

Palpation may also reveal that the apical impulse is shifted to one side or the other. The apical impulse may not be palpable in patients with large left pleural effusions.

Position of trachea

The position of the trachea in patients with pleural effusion always indicates the relationship between the pleural pressures in the two hemithoraces.

c) Percussion

In a patient with pleural effusion the percussion note over the area of involvement is dull or flat. For identifying small amounts of pleural fluid, light percussion is better than heavy percussion.

d) Auscultation

Auscultation reveals decreased or absent breath sounds. However, breath sounds may be accentuated and take on a bronchial characteristic, near the superior border of the fluid. This accentuation of breath sounds denotes a passively collapsed lung with a communicating bronchus.

Systemic cause and clinical findings

1. If the patient has cardiomegaly, neck vein distension, or peripheral edema, the effusion is probably due to congestive heart failure (CHF).

2. The pleural effusion is due to rheumatoid disease or systemic lupus erythematosus (SLE) if the patient has signs of joint disease or subcutaneous nodules.
3. Metastatic disease such as breast masses should be suspected as the cause of pleural effusion if there is an enlarged, nontender nodular liver or the presence of hypertrophic osteoarthropathy.
4. In patients with subdiaphragmatic pathology there will be abdominal tenderness.
5. Tense ascites suggests cirrhosis and a hepatic hydrothorax.
6. Lymphoma, sarcoidosis or metastatic disease should be suspected if there is lymphadenopathy.

DIFFERENTIAL DIAGNOSIS OF PLEURAL EFFUSION

1. Transudative pleural effusions

- A. “Congestive heart failure
- B. Cirrhosis
- C. Nephrotic syndrome
- D. Cerebrospinal fluid leaks to pleura
- E. Hypoalbuminemia
- F. Sarcoidosis
- G. Peritoneal dialysis
- H. Glomerulonephritis

- I. Myxoedema
- J. Superior vena cava obstruction
- K. Fontan procedure
- L. Urinothorax”

2. Exudative pleural effusions

- A. “Neoplastic diseases
 - 1. Metastatic disease
 - 2. Mesothelioma
 - 3. Pyothorax-associated lymphoma
 - 4. Body cavity lymphoma “
- B. “Infectious diseases
 - 1. Bacterial
 - 2. Tuberculosis
 - 3. Viral
 - 4. Parasitic
 - 5. Fungal “
- C. Pulmonary embolization
- D. “Gastrointestinal disease
 - 1. Pancreatic disease
 - 2. Subphrenic abscess
 - 3. Intrahepatic abscess”

E. Obstetric and gynecologic disease

1. Ovarian hyperstimulation syndrome
2. Fetal pleural effusion
3. Endometriosis
4. Postpartum pleural effusion
5. Meigs' syndrome

F. “Collagen vascular diseases

1. Rheumatoid pleuritis
2. Systemic lupus erythematosus”

G. Drug-induced pleural disease

1. Ergot drugs
2. Amiodarone
3. Interleukin 2
4. Nitrofurantoin
5. Dantrolene
6. Methysergide

I. Hemothorax

J. Chylothorax”

GENERAL TESTS TO DIFFERENTIATE THE CAUSES OF EXUDATIVE PLEURAL EFFUSION:

1. Appearance of the fluid

“Most pleural effusions are clear, straw colored, nonviscid and odourless.”

The red colour of the fluid indicates the presence of blood. To confirm hemothorax, a hematocrit should be done. If the hematocrit of the pleural fluid was more than 50 % of the peripheral blood hematocrit, then it is a hemothorax. When the pleural fluid is blood tinged the RBC count is 5000 to 10000 / mm³ . If the pleural fluid macrophages contain haemoglobin inclusions, then it indicates that the blood was present before thoracocentesis and the blood is not due to traumatic tap.

Increased lipid content or increased cellular content both can make pleural fluid to appear turbid. If after centrifuge the supernatant fluid remains turbid then it is due to lipid content.

Amebiasis with a hepato-pleural fistula – chocolate sauce or anchovy sauce pus is seen. The mixture of blood, cytolysed and normal liver tissue make this appearance.

Malignant mesothelioma	–	High viscosity due to elevated hyaluronic acid
.Anaerobic bacterial infection	–	Faeculent odour
Urinothorax	–	Smell of urine

2.WBC count

“Most transudates have WBC count below 1,000/mm³ and exudates have more than 1,000/mm³.”

WBC count > 10,000/mm³ – parapneumonic effusions

WBC count > 50,000/mm³ – pancreatic disease and pulmonary embolism

Neutrophils predominate – suggests acute inflammation. It is seen in “pneumonia, pancreatitis, pulmonary embolism, subphrenic abscess and early tuberculosis”.

Eosinophils predominate – indicates air or fluid in the pleural space. It is seen in patients with spontaneous pneumothorax who had undergone thoracotomy, introduction of air during thoracentesis into pleural space, traumatic hemothorax, pulmonary embolization, CABG, asbestos related effusion, drugs like dantrolene, bromocriptine, parasitic disease like amebiasis, ascariasis .

Basophils predominate – pneumothorax, pneumonia, leukemic pleural involvement .

Pleural fluid lymphocytosis - malignancy, TB, CABG, leukemia or lymphomas.

Mesothelial cells – Tuberculosis in HIV patients. Whereas it is absent in complicated parapneumonic effusions, malignancy after pleurodesis.

3. Glucose levels

“Glucose level < 60 mg / dL – malignancy, parapneumonic effusions, rheumatoid pleuritis, tuberculosis”. Other causes include hemothorax, lupus pleuritis, paragonimiasis, Churg-Strauss syndrome.

4. Amylase level

It is elevated in pancreatic disease, malignancy, esophageal rupture. In the latter two cases the amylase is of salivary type.

5. Lactate dehydrogenase level

“LDH in the pleural fluid is a reliable indicator of degree of inflammation of the pleura. More the inflamed surfaces, higher the LDH levels. The most common causes of elevated LDH levels are parapneumonic effusions and malignancy. These two conditions mostly meet the light’s criteria on the basis of levels of LDH than the protein levels .The iso-enzymes elevated in these conditions are LDH – 4 and LDH – 5. They are thought to arise from the inflammatory WBCs”.

Usually LDH isoenzyme is not used routinely. This is done in conditions where there is a bloody pleural fluid tap in a patient who has transudative pleural effusion clinically. The pleural fluid protein meets the criteria for transudative pleural effusion but LDH levels meet the criteria for exudative

pleural effusion. In these conditions iso-enzyme LDH – 1 confirms that the rise in LDH was due to blood .

6. AdenosineDeaminase

ADA has two isoenzymes – ADA 1 and ADA 2

ADA 1 is produced by lymphocytes, neutrophils, monocytes, macrophages

ADA 2 is produced by macrophages and monocytes .

“The cut off level for ADA level to diagnose tuberculous pleural effusion is 40 to 45 U/L . The diagnosis of TB pleural effusion is more likely if the level is higher i.e., more than 70 U/L”.

7. **C–Reactive proteins** more than 50 mg /L, high levels of **lysozyme** are also used to diagnose tuberculous pleuritis.

8. Lipids

Chylothorax –“ Accumulation of chyle in the pleural space due to disruption of the thoracic duct. In these situations the triglyceride levels are increased”.

Chyliform pleural effusions – This is characterised by high levels of lecithin globulin levels.

Pseudo chylous effusions – “There is increased levels of cholesterol crystals. Triglyceride levels more than 110 mg / dL – Chylothorax is confirmed.

But if the levels are less than 50 mg / dL then the patient does not have chylothorax”.

“If triglyceride level is between 50 to 110 mg / dL then a lipoprotein analysis should be done. Presence of chylomicrons in the lipoprotein analysis of pleural fluid is diagnostic of Chylothorax”.

Alkaline Phosphatase

“Alkaline phosphatase is a hydrolase enzyme which catalyze the removal of phosphate groups from nucleotides, proteins, alkaloids etc. It is mostly produced by liver and bone and these are the predominant forms. Other sites of production include kidney, intestine, placenta, pleura etc. Alkaline phosphatase levels are also used to differentiate transudative and exudative pleural effusion. A cut off value of 60 IU for Pleural fluid ALP and Pleural fluid/Serum ALP ratio of 0.35 is applied to classify pleural effusion into transudate or exudates.”

RADIOGRAPHIC EXAMINATION OF PLEURAL EFFUSION

Typical Arrangement of Free Pleural Fluid

“The distribution of free fluid in the pleural space” is governed by two important factors.

First, accumulation of the pleural fluid occurs in “the most dependent part of the thoracic cavity since the lung is less dense than pleural fluid”.

Second, the distribution of fluid within the free pleural space obeys the law of gravity. The lung also maintains its shape when compressed”.

Bearing these 2 factors in mind, it is easy to predict the distribution of excess pleural fluid.

“The fluid first gravitates to the base of the hemithorax and comes to rest between the inferior surface of the lung and the diaphragm, where the pleural sinus is the most inferior, particularly posteriorly. The fluid spills out into the costophrenic sinuses posteriorly, laterally and anteriorly when the fluid accumulation is higher. Additional fluid assumes a higher position in the thorax as it spreads upward in a mantle-like manner around the convexity of the lung and gradually tapers”.

“The lateral costophrenic angle is obliterated in the posteroanterior projection. The density of the fluid is high laterally and curves gently medially and downward, to terminate at the mediastinum with a smooth, meniscus-shaped upper border. At the mediastinal border the layer of fluid is narrower than at the costal border”.

The upper surface of the pleural fluid density is semicircular in the lateral projection. It is high in the anterior and posterior regions. It curves smoothly downward to its lowest point approximately midway between the posterior chest wall and the sternum.

Frequently, in the lateral chest radiograph a middle lobe step is observed. The explanation for the middle lobe step is that the most dependent and the first affected lobe is the lower lobe, the pleural fluid starts to accumulate here. Therefore, it starts to float and shrink but maintains its shape. So the middle

lobe is unaffected and its full volume is maintained. Hence, the result is a middle lobe that retains its usual size and shrunken lower lobe. The fluid accumulation is mostly in the posterior part of the chest on radiograph. The height of the pleural fluid is greater laterally, based on the radiologic appearance. When viewed en face, this layer of fluid is of insufficient depth to cast a discernible shadow, so it assumes a meniscus shape.

Radiologic Signs

The fluid first accumulates “between the inferior surface of the lower lobe and the diaphragm, when the patient is in the upright position”. The pleural fluid occupies this position if the amount of fluid is small (approximately 75 mL) and without spilling into the costophrenic sinuses. The normal configuration of the diaphragm is maintained, with this small amount of fluid.

The chest radiograph when viewed in the lateral projection, accumulation of more fluid obliterates the costophrenic angle as it “spills over into the posterior costophrenic angle”. The posterior costophrenic angle is normally sharp. It is obliterated by a homogeneous, shallow shadow with a meniscus-shaped upper surface. There is also widening of the pleura that lines the posterior thoracic wall .

If the posterior part of one or both diaphragms is obscured or the posterior costophrenic angle is obliterated, it indicates the presence of pleural fluid.

Then we should be do further diagnostic tests.

Moreover, “the presence of clinically significant amounts of free pleural fluid can be nearly excluded, if both posterior costophrenic angles are clear and sharp. In the postero - anterior chest radiograph, lateral costophrenic angle is blunted with increasing amounts of fluid. The entire outline of the diaphragm is lost on the affected side,” as more fluid accumulates. The fluid then extends upwards around the posterior, anterior and lateral thoracic walls. At the lung base, this fluid produces opacification which is the typical meniscus shape.

Supine Position

There are three characteristics that serve to differentiate the increased density due to parenchymal infiltrate from that due to a pleural fluid.

First, in a properly exposed film, “the vascular structures of the lung will be readily visible through the density, if the density is caused by pleural fluid”. However, vascular structures are obliterated by the silhouette effect, if a similar density is produced by any intrapulmonary process. •

Secondly, the density is usually completely homogenous, if it is due to pleural fluid. Whereas, the infiltrates are usually less homogenous, if it is caused by an intrapulmonary processes. Third, “the presence of air bronchograms”. They are present only if the “increased density is due to a parenchymal infiltrate and not due to a pleural fluid.”

Ultrasound

In a pleural effusion , the ultrasound can be used for the following purposes.

They are

1. To determine the presence of pleural fluid;
2. To identify an appropriate location for the attempted thoracocentesis, chest tube placement, or pleural biopsy;
3. To identify loculated pleural effusion;
4. To distinguish pleural thickening from pleural fluid;
5. To semi-quantify the amount of pleural fluid;
6. To differentiate a lung abscess from a pyopneumothorax;
7. to assess whether pleurodesis is present; and
8. To evaluate the trauma patient for the presence of a pneumothorax or a hemothorax.

FIGURE

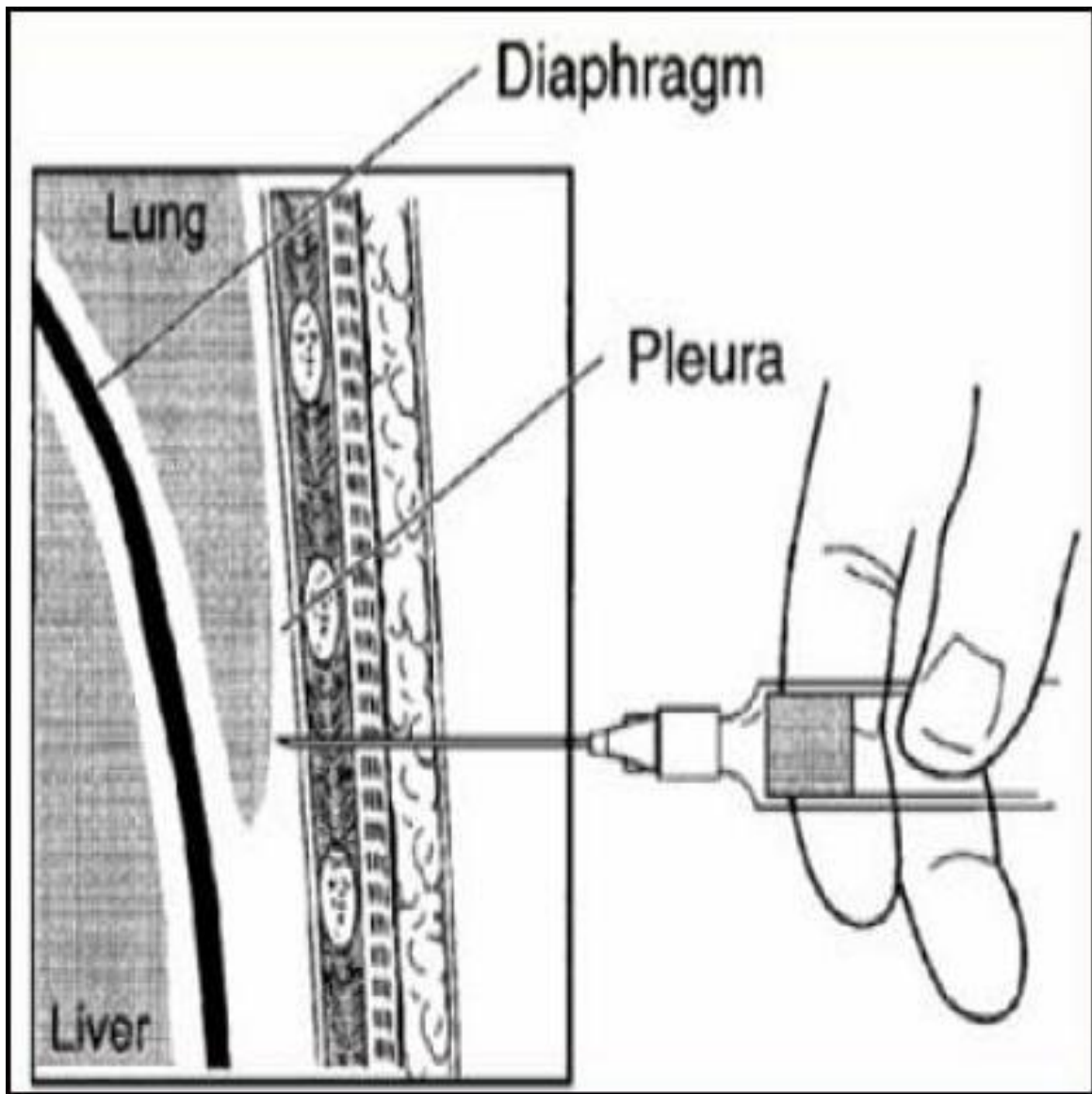
**CHEST X RAY – POSTERIOR ANTERIOR VIEW SHOWING RIGHT
SIDED PLEURAL EFFUSION**



FIGURE
DIAGNOSTIC OR THERAPEUTIC THORACENTESIS
RECOMMENDED POSITION OF THE PATIENT



FIGURE
DIAGNOSTIC THORACENTESIS: THE PLEURAL SPACE IS
ENTERED AND PLEURAL FLUID IS OBTAINED.



FIGURE

CT CHEST PLAIN SHOWING PLEURAL EFFUSION



SEPARATION OF TRANSUDATIVE FROM EXUDATIVE EFFUSIONS

The “accumulation of clinically detectable quantities of pleural fluid is distinctly abnormal”.

Indications of diagnostic thoracentesis:

1. “Whenever the thickness of pleural fluid on ultrasound or the decubitus radiograph is greater than 10 mm” or
2. Whenever “loculated pleural fluid is demonstrated with ultrasound”
3. Etiology of the effusion is unknown.

A diagnostic thoracentesis takes less than 10 minutes. It should not cause any morbidity more than a venipuncture. The information available from examination of the pleural fluid is invaluable in the management of the patient with pleural effusion.

Transudative pleural effusion

“If the systemic factors influencing the absorption or formation of pleural fluid are altered, transudative pleural effusion develops”.

“The permeability of the capillaries to proteins, ALP, cholesterol is normal in the area where the fluid is formed”.

Examples of conditions producing transudative pleural effusions :

1. Increased pulmonary interstitial fluid and a resulting pleural effusion - left ventricular failure.
2. Movement of fluid across the diaphragm from ascites due to cirrhosis.

3. Decreased serum oncotic pressure with hypoproteinemia.

Exudative pleural effusion

In contrast, “when the pleural surfaces or the capillaries in the location where the fluid originates are altered such that fluid accumulates, an exudative pleural effusion develops”.

The common causes of exudative pleural effusions are :

1. Pleural malignancy,
2. Parapneumonic effusions,
3. Tuberculosis and
4. Pulmonary embolism.

Total protein

Earlier to separate between transudate and exudates, a pleural fluid protein of 3gms was used. This test misclassified about 10% of pleural effusions.

Light’s criteria:

Light demonstrated the following criteria for diagnosing exudate.

Exudative pleural effusions meet at least one of the following criteria

- “Pleural fluid protein divided by serum protein greater than 0.5”
- “Pleural fluid LDH divided by serum LDH greater than 0.6”
- “Pleural fluid LDH greater than two thirds of the upper limit of normal serum LDH”

Other tests to differentiate exudates and transudate

In recent years, following are the other tests for the separation of transudates from exudates.

1. Pleural fluid ALP > 60 IU
2. Pleural fluid serum ALP ratio > 0.35
3. Pleural fluid serum albumin gradient of <1.2
4. Pleural fluid protein gradient <3.1

When a pleural fluid shows above findings on analysis then it indicates an exudative effusion.

Light's criteria identify approximately 20% of transudative effusions as exudates. This “mislabeling occurs most commonly in patients with CHF”. When they are treated with diuretics before thoracentesis is performed, these mislabeled transudates barely meet the exudative criteria. “The mislabeled transudate can be identified by examining the gradient between the serum and the pleural fluid protein levels. If this gradient is greater than 3.1 g/dL, one can presume that the fluid is actually a transudate. An albumin gradient of 1.2 g/dL rather than the protein gradient of 3.1 g/dL can be used”. However, the protein gradient is equally effective as the albumin gradient. Also the pleural fluid bilirubin and cholesterol can be used to correctly identify the transudates and exudates.

“If the pleural fluid ALP is more than 60IU and pleural fluid to serum ALP ratio is more than 0.45, then it is an exudate”.

Approach to diagnose a transudative or exudative pleural effusion

First assess the fluid for Light's criteria. The fluid is more likely an exudate if there is “higher the value for the protein ratio, the LDH ratio, and the absolute value of the LDH. If the fluid meets the criteria for a transudative effusion, it is a transudate”.

“If the fluid meets the criteria for an exudative effusion by only a small margin and the clinical picture is compatible with a transudative effusion, measure the protein gradient between the serum and pleural fluid. If this value is greater than 3.1 g/dL, then the fluid can be relabelled a transudate”.

And if the “pleural fluid ALP is more than 60IU and pleural fluid to serum ALP ratio is more than 0.45,” then it is an exudate.

Other Characteristics of Transudates

Most transudates are clear, straw coloured, non - viscid, and odourless. The discovery of blood-tinged pleural fluid does not mean that the fluid is not a transudate. To give the pleural fluid a pinkish tinge, pleural fluid red blood cell (RBC) count should be more than $10,000/\text{mm}^3$. Approximately 15% have RBC counts above this level. RBCs contain a large amount of LDH. So elevated LDH level in a blood-tinged or bloody transudative pleural effusion would meet the criteria for an exudative pleural effusion.

White blood cell (WBC) count

White blood cell (WBC) count in the pleural fluid of most transudates is less than $1,000/\text{mm}^3$, but approximately 20% have WBC counts that exceed $1,000/\text{mm}^3$. WBC counts in pleural fluid above $10,000/\text{mm}^3$ are rare in transudative pleural effusions. The differential WBC count may be dominated by polymorphonuclear leukocytes, small lymphocytes, or other mononuclear cells in transudative pleural effusions.

In a series of 51 transudative effusions, 7 (13%) had more than 50% polymorphonuclear leukocytes, whereas 17 (34%) had predominantly small lymphocytes, 23 (47%) had predominantly other mononuclear cells, and 4(6%) had no single predominant cell type .

“The glucose level in pleural fluid is similar to the serum glucose level, but the level of pleural fluid amylase is low. Because of active transport of bicarbonate from the blood into the pleural space, there is always higher pleural fluid pH in patients with transudative pleural effusions than the pH in simultaneously obtained blood”.

Diagnostic Thoracentesis

If the decubitus film demonstrates presence of free pleural fluid, then one should consider performing a diagnostic thoracentesis with the aid of ultrasound or with a CT scan. The thickness of the fluid is important in performing the diagnostic thoracentesis. It is difficult to perform a diagnostic

thoracocentesis if “the thickness of the fluid on the decubitus radiograph, ultrasound, or the CT scan is less than 10 mm”. However, “if the thickness of the fluid is greater than 10 mm, we have to consider performing a diagnostic thoracocentesis”.

There is no need to perform diagnostic thoracentesis if the patient has congestive heart failure. But in a patient with congestive heart failure if any of the following three conditions are met: “ (a) the patient is febrile (b) the effusions are not bilateral and comparably sized (c) the patient has pleuritic chest pain”, a diagnostic thoracocentesis is done later, “if the pleural effusions do not rapidly disappear. Otherwise, treatment of the congestive heart failure is initiated”.

To sum up, the main aim of performing a diagnostic thoracentesis is to determine whether the patient has an exudative or a transudative pleural effusion.

TRANSUDATIVE PLEURAL EFFUSION

Alteration in the “systemic factors influencing the formation and absorption of the pleural fluids leads to accumulation of the pleural fluid and formation of transudative pleural effusions”.

The major causes are:

1. Congestive Heart Failure:

The most common cause of pleural effusion is probably the congestive heart failure (CHF). The incidence of pleural effusions in patients with CHF is high.

Pathophysiology

According to Starling's equation, “the increased pressures result in a decreased removal of fluid through the visceral pleura and an increased entry of fluid into the pleural space from the parietal pleura”. In patients with CHF, according to current theories on pleural fluid formation and reabsorption, there is “a different entry pathway and a different exit pathway for pleural fluid”.

“It is believed that almost all fluid exits the pleural space through the lymphatics in the parietal pleura rather than by passively diffusing across the visceral pleura. In patients with CHF, pleural effusion occurs when the rate of entry of fluid into the pleural space exceeds the capability of the lymphatics in the parietal pleura to remove the fluid”.

Clinical Manifestations

“In patients with pleural effusions due to CHF they are usually associated with other manifestations of that disease. The patient has a history of increasing dyspnea on exertion, orthopnea or paroxysmal nocturnal dyspnea, increasing peripheral edema. The dyspnea is frequently out of proportion to the size of the effusion”.

Physical examination

Physical examination usually reveals “signs of the pleural effusions as well as signs of both left-sided heart failure with an S₃ ventricular gallop and rales and right-sided heart failure with peripheral edema and distended neck veins”.

Investigations

The chest radiograph almost always reveals usually bilateral pleural effusion and cardiomegaly. “Congestive heart failure is the most common cause of bilateral pleural effusion. But only 88% of the patients studied had bilateral pleural effusion, if cardiomegaly is not present”.

“The mean volume of pleural fluid in the right pleural space (1,084 mL) when compared to the mean volume of pleural fluid in the left pleural space (913 mL) was only slightly greater. Also mediastinal lymphadenopathy is common in patients with pleural effusions that are secondary to CHF”.

Diagnosis

If the patient has bilateral pleural effusions and cardiomegaly, not febrile and no history of pleuritic chest pain, we have to initiate treatment of CHF. Then we have to observe the patient and determine whether the pleural fluid is reabsorbed. A diagnostic thoracocentesis should then be done if the effusions do not disappear within a few days.

One problem with this approach is that “the characteristics of the pleural fluid may change from those of a transudate to those of an exudate, since the patients are on diuretics”.

Serum pleural fluid albumin or protein gradient

“The serum to pleural fluid protein gradient should be examined if the pleural fluid meets exudative criteria but the effusion is thought to be due to CHF. If this gradient is greater than 3.1 g/dL, additional diagnostic studies are not indicated because the pleural effusion is probably due to the CHF. Currently, as the protein gradient is already available when Light's criteria are measured, the protein gradient of 3.1 g/dL is preferred to the albumin gradient.”

Pro-brain natriuretic peptide:

“The measurement of the serum or pleural fluid pro-brain natriuretic peptide (pro-BNP) is another test that should be considered for establishing the diagnosis of CHF. The level of NT pro-brain natriuretic peptide (NT pro-BNP) considered diagnostic of CHF is 1500pg/mL”.

Treatment

In a patient with pleural effusion secondary to heart failure the preferred treatment is to treat the heart failure with the following drugs:

- digitalis
- diuretics – to reduce preload and
- dilators - to reduce afterload .

The pleural effusion disappears if we manage heart failure successfully. In most patients with heart failure, the pleural effusion is effectively managed only with above management.

Occasionally, the patients tend to be very dyspneic, if large pleural effusion is present. Such persons may get rapid relief from the dyspnea if about 0.5L to 1.0L of pleural fluid is removed. Sometimes therapeutic thoracentesis is indicated to get symptomatic relief in patients with heart failure and large pleural effusions that are refractory to treatment. So consider interventions to control the pleural effusions in such patients.

2. Hepatic Hydrothorax

One of the complications of hepatic cirrhosis is pleural effusion. But only when ascitic fluid is present, pleural effusion occurs which is called as hepatic hydrothorax.

Pathophysiology

It is evident from the foregoing studies that “ascitic fluid is the origin of pleural fluid in these patients”.

“The fluid in the peritoneal cavity passes directly through the defects in the diaphragm to the pleural space”. The diaphragm may be stretched in patients with tense ascites, causing microscopic defects. This is because of the “Increased intraabdominal pressure”. There is always a “one-way transfer of

fluid from the peritoneal to the pleural cavity in patients with ascites”. This is because of increased hydrostatic pressure in the ascitic fluid.

In some patients, “the lymphatics play an important role in the production of the pleural effusion. The mechanism behind this is the transfer of ascitic fluid across the diaphragm by the lymphatic vessels”.

Therefore, the dominant mechanism of hepatic hydrothorax is the direct movement of fluid across the diaphragm.

Clinical Manifestations

The clinical pictures of cirrhosis and ascites dominate in patients with pleural effusion secondary to cirrhosis. At times, in association with large pleural effusions, these patients develop acute dyspnea. “Although the pleural effusions may be small to moderate in size, they are frequently large and occupy the entire hemithorax. The diaphragmatic defect permits fluid to flow into the pleural cavity from the peritoneal cavity until the pleural pressure approaches the peritoneal pressure and this results in development of large pleural effusion”.

Diagnosis

It is usually easy to diagnose the pleural effusion that is secondary to cirrhosis with ascites. We should perform both a paracentesis and a thoracentesis. This is to confirm that the ascites and pleural fluid are

compatible with the diagnosis. Also to ascertain that they do not have high polymorphonuclear cell counts.

The pleural fluid is occasionally blood tinged or is frankly bloody. But such findings have no significance due to the poor coagulation status of the patient. The differential cell count is dominated by polymorphonuclear leukocytes, small lymphocytes, or other mononuclear cells.

To rule out pancreatic ascites amylase levels should be determined. Also a cytologic examination should be performed to rule out malignant disease. This should be done in both pleural fluid and ascitic fluid.

Treatment

“Since the hydrothorax is an extension of the peritoneal fluid in patients with cirrhosis and ascites, the management of pleural effusion should always be directed towards the treatment of ascites”.

The patient should be put on a “low-salt diet and moderate fluid restriction. Then diuretics should be administered. The combination of furosemide and spironolactone is the best diuretic therapy. The initial starting dose is 40 mg of furosemide and 100 mg of spironolactone and they can be titrated upto a maximum dose of 160 mg of furosemide and 400 mg of spironolactone”.

3. Nephrotic Syndrome

Nephrotic syndrome is common in patients with pleural effusion.

Mechanism

“The combination of increased hydrostatic pressure and decreased plasma oncotic pressure is the mechanism responsible for the transudative pleural effusion in patients associated with the nephrotic syndrome”.

Diagnosis

In the typical clinical situation, “it is not difficult to diagnose pleural effusion secondary to nephrotic syndrome. But to confirm that the pleural fluid is indeed a transudate, a diagnostic thoracentesis should be performed”.

“In patients with the pleural effusion and nephrotic syndrome, the possibility of pulmonary embolism should always be considered. In all patients with the pleural effusion and nephritic syndrome , one should always obtain a lung scan or a CT angiogram”. It is important that evidence of deep venous thrombosis should be sought with venogram, pulmonary arteriogram or impedance plethysmogram, if the lung scan or spiral CT scan is equivocal.

Treatment

The main aim of treatment is to decrease the protein loss in the urine of patients with pleural effusion and associated with nephrotic syndrome. This is done to decrease the increased extracellular volume and to increase the plasma protein.

This is best accomplished by administering

- diuretics in conjunction with a low-sodium diet,
- angiotensin-converting enzyme inhibitors.

As serial therapeutic thoracocentesis only deplete the protein stores, it should not be performed. We should consider “pleurodesis with a sclerosing agent in selected patients who are symptomatic”.

EXUDATIVE PLEURAL EFFUSION

MOST COMMON CAUSES ARE

1. Parapneumonic pleural effusion
2. Pleural effusion related to metastatic malignancies
3. Tuberculous pleural effusion

1. METASTATIC MALIGNANCIES AND PLEURAL EFFUSION:

“The exudative pleural effusion secondary to malignant disease involving the pleura is the second leading cause of exudative pleural effusion. Parapneumonic effusion ranks first in this category”.

Common carcinomas associated with malignant pleural effusions are:

1. “Lung carcinoma
2. Breast carcinoma
3. Lymphoma”
4. Ovarian carcinoma
5. Sarcoma

Rarely carcinoma of uterus, cervix, stomach , colon , pancreas , bladder

MECHANISM

1. Direct mechanism:

- a) Increased permeability due to pleural metastasis
- b) Obstruction of the pleural lymphatic vessels caused by pleural metastasis
- c) Decreased pleural lymphatic drainage and mediastinal node involvement
- d) Chylothorax – thoracic duct interruption
- e) Decreased pleural pressure – bronchial obstruction
- f) Due to involvement of pericardium

2. Indirect mechanism:

- a) Pulmonary embolism
- b) Postobstructive pneumonitis
- c) Hypoproteinemia
- d) Postradiation therapy

CLINICAL MANIFESTATIONS

The most common symptom in patients with malignant pleural effusion is dyspnea. Also the symptoms due to the underlying disease will predominate. The symptoms due to underlying malignancy are weight loss, malaise, anorexia. The other manifestations are chest pain, hemoptysis, cough in patients with lung malignancy, breast mass in carcinoma breast, swelling in neck, axilla inguinal regions with mass in the abdomen in case of lymphomas .

Chest radiograph: Besides the pleural effusion, pulmonary abnormalities are demonstrated in patients with pleural effusion secondary to carcinomas. Also there is involvement of mediastinal lymphadenopathy .

The pulmonary abnormalities are:

- a) pleural nodularity ,
- b) pleural rind ,
- c) mediastinal pleura involvement ,
- d) pleural thickening > 1 cm

Pleural fluid analysis

- “Grossly bloody with RBC count > 100,000/mm³.
- WBC count between 1,000 to 10,000 / mm³ with lymphocytes 45 % other mononuclear cells > 40% , polymorphonuclear cells 15 % .
- Reduced pleural fluid glucose level less than 60 mg/ dl.
- Pleural fluid pH below 7.3
- Cytology: It is used to classify the histological subtype like adenocarcinoma but not the primary site of tumour.
- Immunohistochemical tests: Carcinoembryonic antigen is detected in metastatic adenocarcinoma and also stains MOC 3,1,B72.3,Ber – EP4 and BG – 8. Malignant mesothelial cells stain positive for cytokeratin and calretin.

- Tumormarkers: Carcinoembryonic antigen (CEA), carbohydrate antigen (CA) 15 – 3, 19 – 9, 549 and 72. Neuron specific enolase, SCC antigen, SSEA – sialyl state specific mouse embryonic antigen, cytokeratin 19 fragments” .

Non-invasive test

This includes measurement of oncogenes, lectin binding, FISH, flow cytometry, proteomics, chromosomal analysis and hyaluronic acid.

But the only test that is advised is flow cytometry. This is done when a lymphoma is suspected. The diagnosis of lymphoma is done by showing the clonality of lymphocytes in pleural fluid.

Pleural biopsy – CT guided or via thoracoscopy

TREATMENT:

In the management of pleural effusion due to metastatic disease the important thing is to identify the site of primary. This is to decide whether the primary tumor responds to systemic chemotherapy or not. Because some tumours like breast carcinoma, lymphoma, small cell carcinoma respond to systemic chemotherapy very well.

Also intrapleural chemotherapy with cisplatin, staphylococcus aureus super antigen (SSAg), rituximab, interferon – gamma, tumour necrosis factor, interleukin IL -2 has been tried with varying results.

In patients with malignant pleural effusion and a chylothorax, malignancy usually involves the thoracic duct. So in these patients it is good to administer radiotherapy to the mediastinum.

We have to consider removal of the pleural fluid if the tumor is not responding to chemotherapy or fails to respond to treatment. This is done mainly to relieve the dyspnea.

The procedures available for the chemotherapy resistant pleural effusion are:

1. Indwelling pleural catheter (pleur X)
2. Pleurodesis
3. Intercostal drainage
4. Pleuroperitoneal shunt
5. Repeated thoracentesis
6. Pleurectomy

2. TUBERCULOUS PLEURAL EFFUSION

The development of pleural effusion in a patient with absence of radiologically apparent TB indicates that it would be a sequelae to the primary infection that occurred 6 to 12 weeks before or it may be due to reactivation of TB .

Pathogenesis

In tuberculous patients there are subpleural caseous foci. Tuberculous pleural effusion occurs due to” rupture of the subpleural caseous focus in the lung to the pleural space”.

“In the development of tuberculous pleural effusion the delayed hypersensitivity plays a major role”. There is clonal expansion of lymphocytes sensitised to the tuberculous protein. “Initially the macrophages predominate in the pleural fluid from day 2 to day 6 and then the lymphocytes predominate in the pleural fluid”.

“It is clear that the delayed hypersensitivity increases the permeability of pleural capillaries to protein. There is higher rate of pleural fluid formation due to the increased levels of pleural fluid protein. Also there is increased level of VEGF, which also increases the permeability. This leads to the accumulation of pleural fluid and development of pleural effusion”.

Also there is decrease in the clearance of proteins in the pleural space. This is because of the impedance to the clearance of proteins by the lymphatics as a result of delayed hypersensitivity reactions.

Clinical manifestation:

“Patients with pleural TB have symptoms such as fever, dry cough, pleuritic chest pain and dyspnea.

Physical findings are those of pleural effusion such as dullness on percussion and absence of breath sounds.

In HIV individuals there will be longer duration of illness. The incidence of chest pain is low, but night sweats, fatigue, diarrhoea, hepatomegaly, lymphadenopathy, splenomegaly are more common.

They have associated parenchymal lesions, smear for acid fast bacilli positive and also culture positive for AFB”.

DIAGNOSIS

Tuberculin skin testing: “Tuberculin skin testing is almost always positive if performed after 8 weeks of development of symptoms. So a negative skin testing after 8 weeks of development of symptoms can be used to rule out TB. However in malnourished individuals or HIV patients the test remains negative”.

Pleural fluid analysis

1. Pleural fluid protein elevated and usually above 5 g/dL
2. Differential WBC count has more than 50% lymphocytes. If there are eosinophils, it suggests previous thoracentesis or associated pneumothorax .
3. Mesothelial cells not more than 5 %
4. Adenosine deaminase levels more than 70 U/L
5. Interferon gamma levels more than 3.7IU/ml

6. Low pleural fluid pH and CRP levels more than 30 mg/dl
7. Pleural biopsy – demonstration of parietal pleura granuloma, AFB, caseous necrosis.
8. Pleural fluid AFB staining and culture for mycobacteria

3. Parapneumonic effusion:

“When any pleural effusion is associated with bacterial pneumonia, lung abscess or bronchiectasis, it is called as parapneumonic effusion”.

“An empyema is defined as pus in the pleural space. Many complicated parapneumonic effusions are usually in the form of empyema.”

According to Weese et al. empyema is characterised by specific gravity greater than 1.018, protein more than 2.5 g/dL, WBC count more than 500 cells/mm³. But according to Vianna empyema is defined as pleural fluid protein more than 3.0 g/dL, WBC greater than 15000 / mm³ or positive bacterial cultures.

Pathogenesis

1. Exudative stage

“This stage is characterised by rapid accumulation of sterile pleural effusion. Due to increased capillary permeability, the fluid originates from the interstitial spaces of lung and also from the visceral pleural capillaries. There is low WBC count, low LDH level and a normal glucose level in the pleural fluid at this stage. This stage resolves if appropriate antibiotics are instituted”.

2. Fibropurulent stage

The pleural space is invaded by the bacteria if antibiotics are not initiated. In this stage there is accumulation of large amounts of pleural fluid which is rich in bacteria, polymorphonuclear leucocytes and cellular debris. A continuous sheet of fibrin covers the visceral and parietal pleura. This leads to the loculation and prevents the spread of pus. But this makes the insertion of chest tube difficult. In this stage there is higher pleural fluid LDH and lower pleural fluid glucose and pH

3. Organisation stage

This stage is characterised by pleural peel. The fibroblasts grow in to the exudates and an inelastic membrane is produced. The lung is encased by this inelastic pleural peel and makes it functionless. The exudate is thick at this stage and it may spontaneously drain through the chest wall called as empyema necessitans or into the lung producing a broncho-pleural fistula.

The most common organisms are Staphylococcal aureus, Escherichia coli and anaerobic Bacterioids .

Clinical features

Fever, cough with expectoration, chest pain are the major symptoms. Fever may be absent in immune-compromised patients. If the fever is present for more than 48 hours after the institution of antibiotics it is called as

parapneumonic effusion. It is important to elicit history of alcoholism, seizures or an episode of unconsciousness as it leads to aspiration.

Light's classification for parapneumonic effusions and empyema:

1. "Non-significant pleural effusion
2. Typical parapneumonic pleural effusion
3. Borderline complicated pleural effusion
4. Simple complicated pleural effusion
5. Complex complicated pleural effusion
6. Simple empyema
7. Complex empyema"

Diagnosis

1. During thoracocentesis, there is frank pus.
2. The pleural fluid will be positive for Gram stain & culture.
3. Pleural fluid glucose less than 40 mg / dL , pH < 7.0 , LDH > 3 times the upper limit.

The above findings along with loculations constitute bad prognostic factors for both empyema and parapneumonic effusions.

Management

Antibiotics

Community acquired pneumonia:

- Fluroquinolones such as levofloxacin, moxifloxacin, gatifloxacin or a macrolide such as azithromycin, clarithromycin plus beta lactams such as cefotaxime, ceftriaxone, ampicillin – sulfbactam .
- If pseudomonas is suspected anti pseudomonas antibiotics like meropenem, imipenem, piperacillin-tazobactam or cefepime is used.

Anaerobes – metronidazole or clindamycin.

MRSA – vancomycin

Management for pleural effusions

1. Therapeutic thoracocentesis
2. Tube thoracostomy
3. Intrapleural fibrinolytics like streptokinase, streptodornase, tissue plasminogen activator
4. Video assisted thoracoscopy with lysis of adhesions and / or decortication
5. Decortication
6. Open drainage

MATERIALS AND METHODS

STUDY POPULATION

This study is to be conducted among 60 patients with pleural Effusion , attending the Department of Medicine & Department of Thoracic Medicine in Govt. Rajaji Hospital, Madurai.

Inclusion criteria

- “In Patients with clinical and radiological evidence of pleural effusion irrespective of etiology, both sex
- Age > 12 years”

Exclusion criteria

- “Age less than 12 years
- Prgnancy
- Jaundice
- Bone lesions”

ANTICIPATED OUTCOME:

“Pleural fluid alkaline phosphatase and ratio to serum levels is superior or supportive to Light’s criteria in differentiating transudates and exudates”.

DATA COLLECTION

- “A Brief history with clinical examination will be done.
- Detailed Clinical Examination ,
- Pleural fluid alkaline phosphatase, Serum alkaline phosphatase ,
Pleural fluid total protein, Serum total protein , Pleural & Serum
LDH are estimated.”

LABORATORY INVESTIGATIONS

1. “Pleural fluid alkaline phosphatase & Serum alkaline phosphatase “
2. “Pleural fluid total protein & Serum Protein”
3. “Pleural fluid LDH & Serum LDH”

STUDY PROTOCOL

- “Patients with clinical and radiological evidence of pleural effusion are to be included in the study.
- Then they are classified in to exudates and transudates on the basis of the clinical , radiological and biochemical evaluation .
- In all the patients following investigation are done to classify them as exudates and transudates
- Pleural fluid alkaline phosphatase & Serum alkaline phosphatase, Pleural fluid total protein are estimated and the patients are classified in to exudates and transudates.

- Then the patients are classified in to exudates and transudates on the basis of Light's criteria”
3. “Now the classification of exudates and transudates done on the basis of Pleural fluid alkaline phosphatase & Serum alkaline phosphatase is compared with results of the classification of exudates and transudates done on the basis of Light's criteria.”
- “Sensitivity, specificity , Positive predictive value , negative predictive value , diagnostic accuracy of each tests are calculated”.

DESIGN OF STUDY

Prospective analytical study

PERIOD OF STUDY

MAY 2016 TO NOVEMBER 2016

COLLABORATING DEPARTMENTS:

Department of Medicine, Thoracic medicine , Biochemistry

CONSENT: Individual written and informed consent.

ANALYSIS: Statistical analysis

CONFLICT OF INTEREST: Nil

Method of study

This study was conducted in Govt. Rajaji Hospital, Madurai which is affiliated to Madurai Medical College. This study subjects were selected from the patients admitted in Department of Medicine and Department of Medicine , Govt. Rajaji Hospital.

The study was conducted in 60 patients; the patients had pleural effusion with clinical background of congestive cardiac failure, chronic liver disease , chronic kidney disease ,tuberculosis , parapneumonic effusions , malignancy. The patients are examined clinically with the following parameters and only 60 patients are taken for study.

Clinical criteria to classify patients as exudates and transudates

“If the patient had oedema legs, ascites, cardiac enlargement, radiological evidence of congested lungs and responded to treatment for congestive cardiac failure , then the diagnosis of congestive cardiac failure was made”.

When there were raised serum urea and creatinine levels along with signs and symptoms indicating volume overload, chronic kidney disease was diagnosed.

If the patient had features of liver cell failure,ascites, splenomegaly and evidence of volume overload status , chronic liver disease was diagnosed.

The diagnosis of tuberculosis was made if there is cough , fever with evening rise of temperature, loss of weight and appetite ,sputum showing AFB, ADA in pleural fluid ,chest x ray showing pleural effusion ,response to ATT.

The diagnosis of parapneumonic effusion was made if there is cough with expectoration, fever with chills & rigors, chest x-ray showing pleural effusion, bacteria in pleural fluid/sputum.

The diagnosis of malignant pleural effusion was made if there is Pleural fluid cytology, Pleural biopsy, demonstration of primary sites.

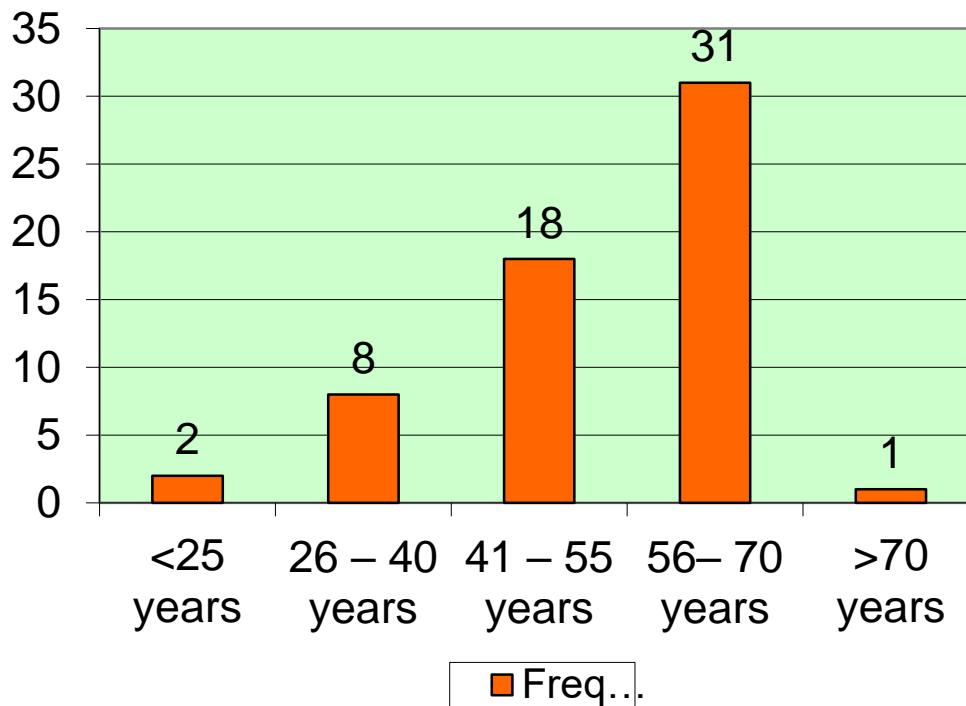
Study protocol

- “Patients with clinical and radiological evidence of pleural effusion are to be included in the study”
- Then they are classified in to exudates and transudates on the basis of the clinical , radiological and biochemical evaluation .
- In all the patients following investigation are done to classify them as exudates and transudates
- Pleural fluid alkaline phosphatase & Serum alkaline phosphatase , Pleural fluid total protein are estimated and the patients are classified in to exudates and transudates.
- “Then the patients are classified in to exudates and transudates on the basis of Light’s criteria”.
- “Now the classification of exudates and transudates done on the basis of Total Pleural fluid alkaline phosphatase and its ratio to serum , Pleural fluid Total protein are compared with results of the classification of exudates and transudates done on the basis of Light’s criteria”.
- “Sensitivity , specificity , Positive predictive value , negative predictive value , diagnostic accuracy of each tests are calculated” .

RESULTS AND INTERPRETATION

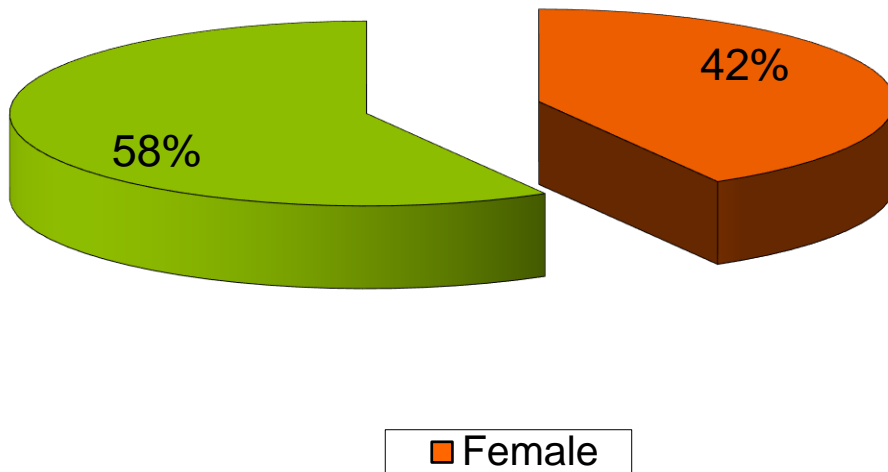
Age group	Frequency	Percent
<25 years	2	3.33
26 – 40 years	8	13.33
41 – 55 years	18	30.00
56– 70 years	31	51.67
>70 years	1	1.67
Total	60	100.00

AGE DISTRIBUTION

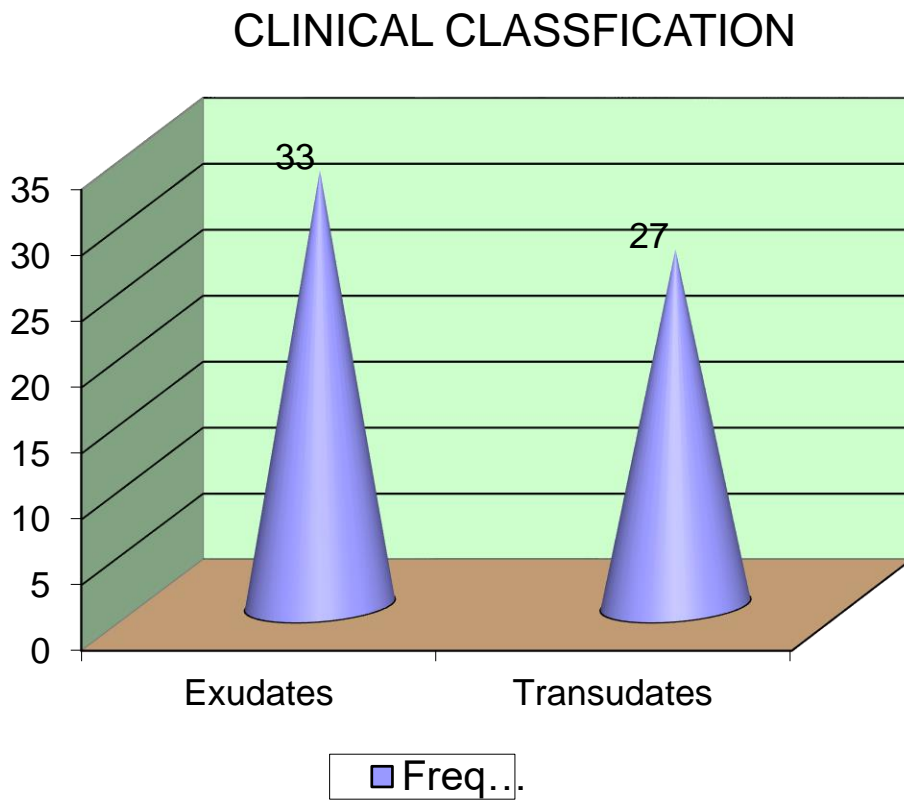


Gender	Frequency	Percent
Female	25	41.67
Male	35	58.33
Total	60	100.00

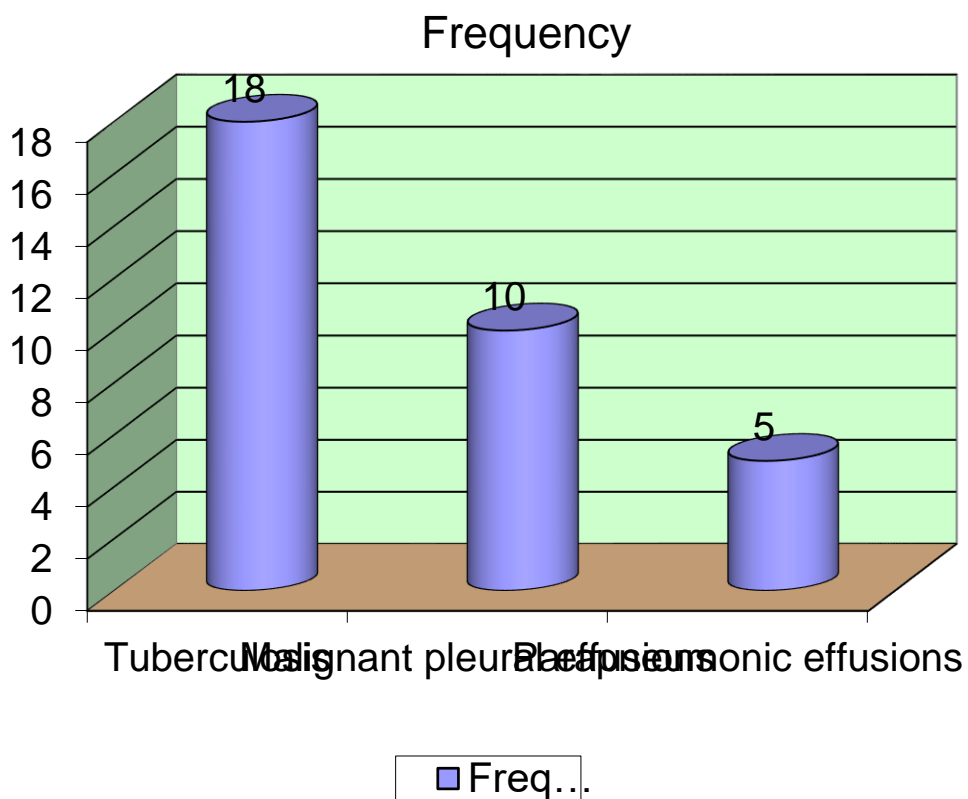
SEX DISTRIBUTION



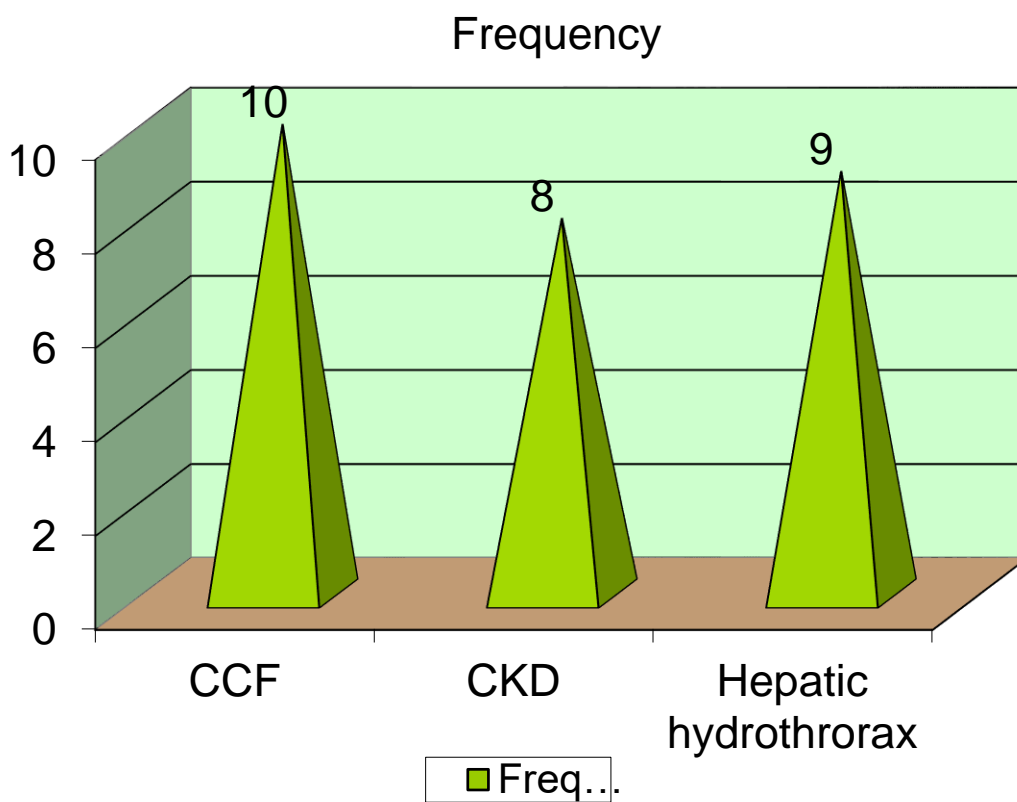
Clinical classification	Frequency	Percent
Exudates	33	55.00
Transudates	27	45.00
Total	60	100.00



Etiology	Frequency	Percent
Tuberculosis	18	30.00
Malignant pleural effusions	10	16.67
Parapneumonic effusions	5	8.33



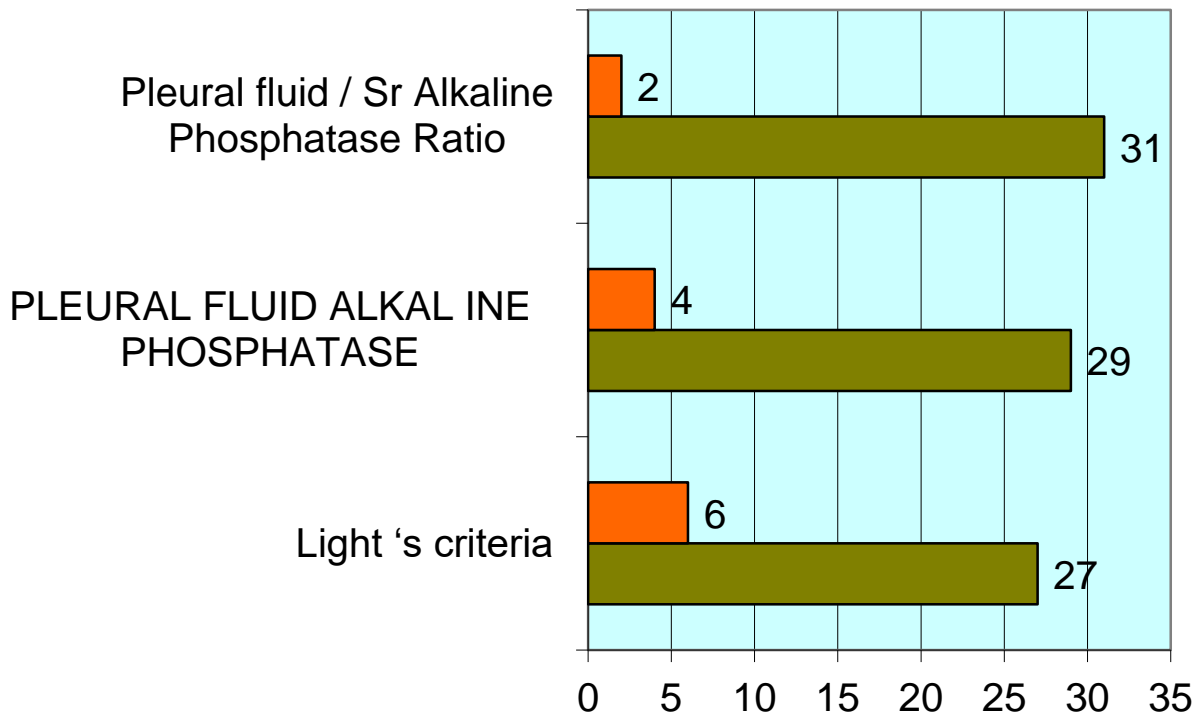
Etiology	Frequency	Percent
CCF	10	16.67
CKD	8	13.33
Hepatic hydrothrorax	9	15.00
Total	60	100.00



Descriptive statistics	Pleural Fluid Protein (gm/dl)	PLEURAL FLUID ALKALINE PHOSPHATASE mg/dl	0.61	49.98
		0.43		
Mean	3.04	0.43	0.61	49.98
Standard Deviation	0.53	0.121	0.14	19.69
Minimum	2.1	0.2	0.32	16
Maximum	4.4	0.61	0.9	80

Criteria	Correctly classified as transudate N (%)	Wrongly classified as exudate N (%)
Light 's criteria	24 (88.8%)	3 (11.2%)
PLEURAL FLUID ALKALINE PHOSPHATASE	25 (92.5%)	2 (7.5%)
Pleural fluid / Sr Alkaline Phosphatase Ratio	24 (88.8%)	3 (11.2%)

Criteria	Correctly classified as Exudate N (%)	Wrongly classified as Transudate N (%)
Light 's criteria	27	6
PLEURAL FLUID ALKAL INE PHOSPHATASE	29	4
Pleural fluid / Sr Alkaline Phosphatase Ratio	31	2



Age and sex distribution of the population in our study is as follows

51% of the study subjects were in the age group of 56-70yrs, 30% were in the age group of 41-55yrs, 16.66% were less than 40 years and 1.67% above 70 years.

Majority of the study subjects were males 58% while remaining 42% were females.

Exudates and transudates distribution in our study is as follows:

In our study about 55% of the study subjects were exudates while 45% were transudates .

Among the exudates, about 30 % of study groups have tuberculosis , 17 % have malignancy and 8 % have parapneumonic effusions.

Among the transudates, about 17% were CCF, 13% were CKD and the remaining 15% were Hepatic hydrothorax.

“Pleural fluid Alkaline phosphatase, Serum Alkaline phosphatase, Pleural fluid total protein , Serum total protein , Pleural fluid LDH , Serum LDH are estimated”.

Pleural fluid Total protein

Any serous membrane inflammation often leads to increased capillary permeability and this enables the diffusion of protein.

The permeability of pleura is increased due to “serum leakage” and this leads to the accumulation of ALP in exudative pleural effusion .

In our study to diagnose exudates the following parameters are used :

A pleural fluid alkaline phosphatase of more than 60 IU

“A pleural fluid alkaline phosphatase to serum alkaline phosphatase ratio of more than 0.45”

RESULTS

“By applying Light’s criteria in patients with exudative pleural effusion classified clinically, 81.8% % of the cases were correctly diagnosed as exudative pleural effusion.

By applying Pleural fluid Alkaline phosphatase in patients with exudative pleural effusion classified clinically, 87.8% of the cases were correctly diagnosed as exudative pleural effusion.

According to Pleural fluid/Serum Alkaline phosphatase ratio, patients with exudative pleural effusion classified clinically, 93.9% of the cases were correctly diagnosed as exudative pleural effusion.

In our study by applying the Lights criteria, about 18.28 % of exudative pleural effusion was misclassified as transudative, and by applying Pleural fluid alkaline phosphatase and Pleural fluid , the misclassification was 12.2% and 25 % respectively . Whereas by Pleural fluid / Serum alkaline phosphatase ratio , the misclassification was only 3.58 %.

By applying Light's criteria in patients with transudative pleural effusion classified clinically , 90.90 % of the cases were correctly diagnosed as transudative pleural effusion.

By applying Pleural fluid alkaline phosphatase in patients with transudative pleural effusion classified clinically , 86.36 % of the cases were correctly diagnosed as transudative pleural effusion.

According to Pleural fluid / Serum alkaline phosphatase ratio , in patients with transudative pleural effusion classified clinically, 90.90 % of the cases were correctly diagnosed as transudative pleural effusion.

Among the parameters used most specific test to classify an exudative pleural effusion from a transudative pleural effusion is pleural fluid total protein which is 95.45 % and most sensitive test is pleural fluid / serum alkaline phosphatase ratio which is 93.90 %. The positive predictive value, negative predictive value and diagnostic accuracy to classify an exudative pleural effusion from a transudative pleural effusion is higher for pleural fluid total protein which is 96.29 % , 95.23 % , 94 % respectively .

The sensitivity , specificity , positive predictive value, negative predictive value and diagnostic accuracy of Light's criteria are 85.71 % , 90.90 % , 92.30 % , 83.33 % , 88 % respectively .”

DISCUSSION

“One of the most common disease entity encountered by physicians worldwide is pleural effusion . In a situation where undiagnosed pleural effusion has come upon, the first and foremost thing to be resolved is whether the fluid is a transudate or exudate. The most frequently used Light's criteria, though still considered as a gold standard, often misclassify a transudate as an exudates. The present study was undertaken to evaluate the efficacy of pleural fluid alkaline phosphatase and its ratio to serum levels, and pleural fluid total protein in distinguishing pleural fluid transudates and exudates and its correlation with Light’s criteria“.

SUMMARY OF PRIOR PUBLICATIONS

1) **“The following persons namely K.B. Gupta, Veena Ghalaut, Prem Parkash Gupta, Puneet Arora, S. Tandon of Pt. B.D.Sharma Postgraduate Institute of Medical Sciences, Rohtak have conducted the study to evaluate the efficacy of pleural fluid alkaline phosphatase and its ratio to serum levels to classify pleural fluids as exudates.”**

Methods and results

“A total of 80 patients were divided into transudates and exudates on the basis of extensive clinical, radiological and biochemical evaluation. Up to 89% transudates misclassified by Light’s criteria were correctly classified by pleural fluid alkaline phosphatase (P ALP) and pleural fluid/serum alkaline phosphatase ratio (P/S ALP) evaluation. Similarly 92% exudates misclassified by Light’s criteria were correctly classified by pleural fluid alkaline phosphatase (P ALP) and pleural fluid/serum alkaline phosphatase ratio (P/S ALP) evaluation.”

2) ***“Ashish Anantrao Jadhav, Jayashree Suhas Bardapurkar¹, Anuradha Jain of Department of Biochemistry, People’s College of Medical Sciences and Research Centre, Bhopal, MP, 1Government Medical College, Aurangabad, Maharashtra, India have done a study on 60 patients to test the significance of pleural fluid alkaline phosphatase and pleural fluid/serum alkaline***

phosphatase ratio in differentiating exudative from transudative pleural effusion”.

Results

“The mean pleural alkaline phosphatase and pleural fluid/serum alkaline phosphatase ratio was significantly higher in exudates compared to transudates. ($P < 0.0001$). Sensitivity and specificity values were 90% and 80% for a cut-off value of 71 IU/L for pleural alkaline phosphatase activity; and were 90% and 86.66% for a cut-off value of 0.51 for pleural fluid/serum alkaline phosphatase ratio.”

DEFINITIONS

Diagnostic accuracy : “This is the probability that a randomly selected subject is correctly diagnosed by the test” .

Negative Predictive Value : “The probability that a person who has tested negative on a diagnostic test (T⁻) actually does not have the disease (D⁻)”

Positive Predictive Value : “This is the probability that a person who has tested positive on a diagnostic test (T⁺) actually has the disease(D⁺)”.

Sensitivity : “This is the probability that a person with disease (D⁺) will correctly test positive based on the diagnostic test (T⁺)”

Specificity: “This is the probability that a person without disease (D⁻) will correctly test negative based on the diagnostic test (T⁻)”

D – Disease ., **T** – Test

CONCLUSION

For many decades Light's criteria had been used widely to differentiate exudative from transudative pleural effusion. But it also misclassified 25 % of transudates as exudates, so there was a need to identify new parameters which would prove to be superior or supportive to the array of tests at present.

From our study we came to know that there was no statistically significant difference among various criteria in classifying pleural effusion as exudates and transudates.

The misclassification of exudates and transudates by various criteria when compared to Light's criteria is not statistically significant as p value is <0.05 .

From our study we came to a conclusion that to classify an exudative pleural effusion from a transudative pleural effusion

- most specific test is pleural fluid total protein and
- most sensitive test is pleural fluid / serum alkaline phosphatase ratio .

The “positive predictive value, negative predictive value and diagnostic accuracy is higher for pleural fluid total protein”.

To conclude, “though Light's criteria remains as gold standard to differentiate transudates and exudates, in cases where there is a mismatch

between clinical diagnosis and the outcome from Light's criteria, pleural fluid alkaline phosphatase / serum alkaline phosphatase ratio and pleural fluid total protein evaluation may add to the diagnostic accuracy”.

SUMMARY

The classic criteria of differentiating an exudate from a transudate is Light's criteria. Over the last few years, "it has been noted that even Light's criteria may misclassify a significant percentage of pleural effusions."

"The objective of the present study was to evaluate the usefulness of Total Pleural fluid Alkaline phosphatase and its ratio to serum levels and Pleural fluid Total Protein level in classifying pleural effusions as exudates and transudates with Light's criteria as the gold standard ".

From our study it is evident that most specific test to classify an exudative pleural effusion from a transudative pleural effusion is pleural fluid total protein which is 95.45 % and most sensitive test is pleural fluid / serum alkaline phosphatase ratio which is 93.90 %. "The positive predictive value, negative predictive value and diagnostic accuracy is higher for pleural fluid total protein which are 96.29 % , 95.23 % , 94 % respectively".

"The sensitivity , specificity , positive predictive value, negative predictive value and diagnostic accuracy of pleural fluid alkaline phosphatase was not superior to Light 's criteria" .

The pleural fluid/serum alkaline phosphatase ratio, pleural fluid total protein are very effective in differentiating exudative and transudative pleural effusion.

Limitations of the study

1. Shorter study period and smaller study sample.
2. The various parameters studied are neither combined with others nor with the Light's criteria .
3. Different levels of the “Pleural fluid alkaline phosphatase , Pleural fluid / Serum alkaline phosphatase ratio, Pleural fluid total protein are not tried in this study” .

Further recommendations

1. “A longer study period and a larger study sample should be considered in the future”.
2. “Combination of Pleural fluid alkaline phosphatase, Pleural fluid / Serum Alkaline phosphatase ratio, Pleural fluid total protein with other parameters of the Light's criteria”.
3. “Another study on varying levels of Pleural fluid Alkaline phosphatase, Pleural fluid / Serum Alkaline phosphatase ratio, Pleural fluid total protein which will give the highest accuracy in detecting exudative effusions”.

BIBLIOGRAPHY

- I. R.W. Light, M.I. Macgregor, P.C. Luchsinger, W.E. Ball, Pleural effusions: the separation of transudates and exudates, *Ann. Intern. Med.* 77 (1972) 506–513
- II. R.W. Light, Update on tuberculous pleural effusion, *Respirology* 15 (2010) 451–458.
- III. A. Lone Mushtaq, Abdul Wahid, S.M. Saleem, Alkaline phosphatase in pleural effusions, *Indian J. Chest Dis. Allied Sci.* 45 (2003) 161–163.
- IV. Isabel Gazquez, Jose Manuel Porcel, Manuel Vives, et al, Pleural alkaline phosphatase in separation of transudative and exudative pleural effusions, *Chest* 112 (1997) 569–570.
- V. K. Tahaoglu, O. Kizkin, R. El, Alkaline phosphatase: distinguishing between pleural exudates and transudates, *Chest* 105 (1994) 1912–1913.
- VI. N.C. Syabbalo, Use of pleural alkaline phosphatase content to diagnose tuberculous effusions, *Chest* 99 (1991) 522–523.
- VII. A.A. Jadhav, J.S. Bardapurkar, A. Jain, Alkaline phosphatase: distinguishing between tuberculous and nontuberculous pleural effusion, *Lung India* 26 (3) (2009) 77–80
- VIII. M. Matinas, O. Alatas, F. Alatas, et al, Comparative analysis of biochemical parameters for differentiation of pleural exudates from transudates; Light criteria, cholesterol, bilirubin, albumin gradient, alkaline

phosphatase, creatine kinase and uric acid, Clin. Chem. Acta 264 (1997) 149–162.

- IX. F. Carrion, M. Perpina, Use of pleural alkaline phosphatase content to diagnose tuberculous effusions, Chest 104 (1993) 646– 647.
- X. Storey DD, Dines DE, Coles DT. Pleural effusion : a diagnostic dilemma. JAMA 1976 ; 236 : 2183-6
- XI. McLean AN, Bicknell SR, McAlpine LG, Peacock AJ. Investigation of pleural effusion. Chest 1998 ; 114 : 150-3
- XII. Heffner JE, Sahn SA, Brown LK. Multilevel likelihood ratios for identifying exudative pleural effusion. Chest 2002; 121 : 1916-20
- XIII. Burgess LJ, Martiz FJ, Taljaard JF, et al. Comparative analysis of the biochemical parameters used to distinguish between pleural transudates and exudates. Chest 1995; 107 : 1604-09
- XIV. Porcel JM, Vives M, de Vera MCV, et al. Useful tests on pleural fluids that distinguish transudates from exudates. Ann Clin Biochem 2001; 38 : 671-5
15) Porcel NK, Vives M. Classic, abbreviated, and modified Light's criteria: the end of the story ? Chest 1999 ; 116 : 1833-34
- XV. King EJ, Armstrong AR. Estimation of alkaline phosphatase. Canad Assoc J 1934 ; 311 : 152-56
- XVI. Gupta KB, Sindhwani G, Gahlaut VS, Parkash Prem, Tandon S, et al. Evaluation of pleural fluid and serum MDA levels in differentiating

transudative from exudative pleural effusions. Indian J Tub 2002 ; 49 : 97
– 102

- XVII. Gupta KB, Ghaluat V, Gupta R, Tandon S, Parkash P, et al. Estimation of serum and pleural fluid amylase and isoenzymes in cases of malignant pleural effusion. Indian J Tub 2001; 48: 87-89
- XVIII. Roth BT, O' Meara TF, Cragun WH, et al. The serum effusion albumin gradient in the evaluation of pleural effusion. Chest 1990; 98 : 546-49
- XIX. Moss DW, Handersson AR. Teitz text book of clinical chemistry. 3rd ed. Philadelphia : WB Saunders Co. 1999 ; p 617-721
- XX. Sarojini B, Ramakrishan R. Enzymes in biofluids for diagnosis of diseases. Indian J Clin Biochem 1991; 6 : 143- 48
- XXI. Syablo NC. Use of pleural alkaline phosphatase content to diagnose tubercular effusions. Chest 1991; 99 : 522-3

PROFORMA

Name :

Age/Sex/Occupation:

Presenting complaints:

H/o Fever, chest pain , cough & expectoration, hemoptysis ,dyspnea, Loss of weight, Loss of Appetite. Etc.

Past history:

H/o Tuberculosis, Chronic liver disease, coronary artery disease, chronic kidney disease

Clinical examination:

General examination:

Consciousness, Pallor, jaundice, Clubbing, Lymphadenopathy,

Vitals: PR, BP, RR, SpO2, Temperature

Systemic examination:

CVS:

RS:

Abdomen :

CNS:

LABORATORY INVESTIGATIONS :

1.Pleural fluid alkaline phosphatase & serum alkaline phosphatase

3.Pleural fluid total protein & Serum Protein

4.Pleural fluid LDH & Serum LDH

S.No	NAME	AGE	SEX	DIAGNOSIS	PLEURAL FLUID PROTEIN g/ dl	SERUM PROTEIN N g/dl	PLEURAL FLUID PROTEIN / SERUM PROTEIN RATIO	PLEURAL FLUID LDH	SERUM LDH	PLEURAL FLUID / SERUM LDH RATIO	PLEURAL FLUID ALKALINE PHOSPHATASE	Ratio
1		45	M	CCF	2.7	6.1	0.44	156	306	0.51	30	0.21
2	PANDIARAJAN	46	M	CCF	2.9	5.6	0.51	132	288	0.45	35	0.25
3	IYYAMMAL	43	F	CCF	2.9	6.4	0.45	45	159	0.28	36	0.26
4	AYYAVU	52	M	CCF	2.5	6.2	0.4	116	250	0.46	38	0.27
5	LAKSHMANAN	62	M	CCF	2.3	6.4	0.35	129	296	0.43	40	0.29
6	CHANDRAN	57	M	CCF	2.9	6.5	0.44	112	220	0.51	42	0.30
7	KANAGA VALLI	55	F	CCF	2.2	6.5	0.34	28	91	0.31	42	0.30
8	JAMUNA	53	F	CCF	2.6	6.2	0.42	59	146	0.4	46	0.33
9	SELVA RANI	49	F	CCF	2.8	5.2	0.53	98	189	0.51	38	0.27
10	NEHRU	65	M	CCF	2.6	6.1	0.42	57	110	0.51	40	0.29
11	BAGHAYA LAKSHMI	57	F	Hepatic hydrothorax	2.9	6.4	0.45	69	156	0.44	30	0.21
12	MUTHU MANI	38	M	Hepatic hydrothorax	2.8	6.5	0.43	116	216	0.53	38	0.27
13	JAYA LAKSHMI	63	F	Hepatic hydrothorax	3.2	6.5	0.49	97	193	0.5	36	0.26
14	SIVA SANKARI	49	F	Hepatic hydrothorax	2.6	6.7	0.38	149	320	0.46	34	0.24
15	BASHEER AHMEED	57	M	Hepatic hydrothorax	2.3	6.4	0.35	133	287	0.46	35	0.25
16	MANIKANDAN	58	M	Hepatic hydrothorax	2.6	5.9	0.44	41	142	0.28	36	0.26

	17	IRULAYI	35	F	Hepatic hydrothorax	2.6	5.8	0.43	26	98	0.26	40	0.29
	18	MARI MUTHU	63	M	Hepatic hydrothorax	2.5	5.7	0.44	35	116	0.31	46	0.33
	19	SONAI MUTHU	59	M	CKD	2.5	5.9	0.45	19	85	0.22	41	0.29
	20	ARJUNAN	60	M	CKD	2.1	6.5	0.31	56	132	0.42	40	0.29
	21	ANGARYARKANNI	55	F	CKD	2.1	6.6	0.32	48	124	0.38	46	0.33
	22	ESHWAR LAL	65	M	CKD	2.3	6.7	0.34	38	106	0.35	38	0.27
	23	RAJAMMAL	63	F	Tuberculosis	3.8	6.1	0.62	79	165	0.47	60	0.43
	24	PONAMBALAM	59	M	Tuberculosis	3.5	6.1	0.39	100	133	0.38	65	0.46
	25	RAGHAVAN	54	M	Tuberculosis	4.4	6.1	0.72	45	95	0.47	62	0.44
	26	MALAIKANI	64	M	Tuberculosis	3.2	5.9	0.54	106	190	0.55	63	0.45
	27	JAYAKUMAR	21	M	Tuberculosis	3.6	6.1	0.59	98	172	0.56	78	0.56
	28	PREMAVATHI	52	F	Tuberculosis	3.2	5.6	0.57	94	166	0.56	70	0.50
	29	RAJENDRAN	56	M	Tuberculosis	3.3	5.5	0.6	69	124	0.55	76	0.54
	30	GURUVAMMAL	53	F	Tuberculosis	4.1	5.9	0.69	71	137	0.51	75	0.54
	31	KUMAR	25	M	Tuberculosis	3.2	6.8	0.43	58	101	0.42	74	0.53
	32	RAMESH	65	M	Tuberculosis	3.1	5.2	0.59	66	86	0.76	68	0.49
	33	PANJU	68	F	Tuberculosis	3.9	5.9	0.66	298	387	0.77	64	0.46
	34	PALANIVEL	60	M	Tuberculosis	3.6	5.3	0.67	250	320	0.78	82	0.59
	35	MEENAKSHI	61	F	Tuberculosis	4.1	6.1	0.65	114	235	0.48	80	0.57
	36	RANJITHAM	30	F	Tuberculosis	3.1	6.4	0.43	99	219	0.45	83	0.59
	37	ARUMUGAM	32	M	Pneumonia	3.5	6.5	0.53	306	421	0.72	84	0.60
	38	GANESAN	57	M	Pneumonia	3.2	6.6	0.42	112	216	0.4	86	0.61
	39	VIMALA	36	F	Pneumonia	3.4	6.1	0.56	341	487	0.71	84	0.60

	40	SUMATHI	52	F	Pneumonia	2.9	6.5	0.58	221	362	0.61	78	0.56
	41	KANNAN	52	M	Malignancy	3.2	5.9	0.54	74	116	0.63	68	0.49
	42	SANTHA RAM	60	M	Malignancy	3.1	5.8	0.53	102	154	0.66	64	0.46
	43	VASANTHA	39	M	Malignancy	2.7	5.9	0.42	82	198	0.41	85	0.61
	44	INDRA	68	F	Malignancy	3.4	6.3	0.53	68	85	0.79	65	0.46
	45	KASIRAJAN	75	M	Malignancy	3.3	6.1	0.54	41	79	0.51	64	0.46
	46	THAVAMANI	47	F	Malignancy	3.1	5.9	0.52	95	166	0.57	63	0.45
	47	MYTHILI	52	F	Malignancy	3.2	5.8	0.54	86	109	0.78	64	0.46
	48	VASUDEVAN	49	M	Malignancy	3.5	5.6	0.62	56	141	0.39	78	0.56
	49	NARAYANAN	62	M	Malignancy	3.2	5.8	0.43	112	163	0.42	78	0.56
	50	KALAISELVI	67	F	Malignancy	3.4	6.2	0.54	59	92	0.64	64	0.46
	51	MARI MUTHU	63	M	Hepatic hydrothorax	2.5	5.7	0.44	35	116	0.31	46	0.33
	52	SONAI MUTHU	59	M	CKD	2.5	5.9	0.45	19	85	0.22	48	0.34
	53	ARJUNAN	60	M	CKD	2.1	6.5	0.31	56	132	0.42	45	0.32
	54	ANGARYARKANNI	55	F	CKD	2.1	6.6	0.32	48	124	0.38	72	0.51
	55	ESHWAR LAL	65	M	CKD	2.3	6.7	0.34	38	106	0.35	48	0.34
	56	PANJU	68	F	Tuberculosis	3.9	5.9	0.66	298	387	0.77	68	0.49
	57	PALANIVEL	60	M	Tuberculosis	3.6	5.3	0.67	250	320	0.78	70	0.50
	58	MEENAKSHI	61	F	Tuberculosis	4.1	6.1	0.65	114	235	0.48	72	0.51
	59	RANJITHAM	30	F	Tuberculosis	3.1	6.4	0.41	99	219	0.44	76	0.54
	60	ARUMUGAM	32	M	Pneumonia	3.5	6.5	0.53	306	421	0.72	78	0.56
						3.03	6.11	0.49	105.40	191.57	0.50	58.25	0.42

Originality GradeMark PeerMark

Pleural fluid
BY 201411115 MD GENMED



5% SIMILAR

-- OUT OF C

Match Overview

1	www.scribd.com	Internet source	<1%
2	pt.scribd.com	Internet source	<1%
3	Broaddus, V. Courtney,...	Publication	<1%
4	www.ncbi.nlm.nih.gov	Internet source	<1%
5	issuu.com	Internet source	<1%
6	archive.org	Internet source	<1%
7	bmb.oxfordjournals.org	Internet source	<1%
8	pearl.sums.ac.ir	Internet source	<1%
9	www.slideshare.net	Internet source	<1%
10	Guo, Yubiao, and Rich...	Publication	<1%
11	essbronchology.com	Internet source	<1%
12	S CRAWFORD. "Bacte...	Publication	<1%
13	www.docstoc.com		<1%

INTRODUCTION

Pleural effusion is a very common clinical presentation of diseases. A correct diagnosis of the underlying disease is essential for the management of pleural effusion. A limited number of diseases cause Transudative Pleural Effusion, whereas exudative effusions require more extensive diagnostic investigations. Therefore, the first step is to classify them as transudates or exudates, even if this differentiation does not contribute to the etiological diagnosis.

Many criteria have been used to distinguish them, but none of them have been found to be satisfactory. Light's criteria is the most commonly used method. The criteria is one or more of the following to diagnose exudates.

1. Pleural fluid protein / Serum protein > 0.5
2. Pleural fluid LDH/ Serum LDH > 0.6
3. Pleural fluid LDH more than 2/3rd of the upper limit of serum

LDH

It was found that even Light's criteria misclassified a large number of effusions - 25% of transudates as exudates.

Hence, there is a need to probe into new parameters which will prove to be



Digital Receipt

This receipt acknowledges that Turnitin received your paper. Below you will find the receipt information regarding your submission.

The first page of your submissions is displayed below.

Submission author: 201411115 Md Genmed SHANMUG..
Assignment title: 2015-2015 plagiarism
Submission title: Pleural fluid Alkaline phosphatase ...
File name: plagiarism_final.docx
File size: 327.35K
Page count: 91
Word count: 12,090
Character count: 67,554
Submission date: 27-Sep-2016 03:29PM
Submission ID: 710008855

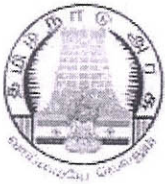
INTRODUCTION

Pleural effusion is a very common clinical presentation of diseases. A correct diagnosis of the underlying disease is essential for the management of pleural effusion. A limited number of diseases cause Transudative Pleural Effusion, whereas exudative effusions require more extensive diagnostic investigations. Therefore, the first step is to classify them as transudates or exudates, even if this differentiation does not contribute to the etiological diagnosis.

Many criteria have been used to distinguish them, but none of them have been found to be satisfactory. Light's criteria is the most commonly used method. The criteria is one or more of the following to diagnose exudates.

1. Pleural fluid protein / Serum protein > 0.5
2. Pleural fluid LDH / Serum LDH > 0.6
3. Pleural fluid LDH more than 2/3rd of the upper limit of serum LDH.

It was found that even Light's criteria misclassified a large number of effusions - 25% of transudates as exudates.



MADURAI MEDICAL COLLEGE
MADURAI, TAMILNADU, INDIA -625 020
(Affiliated to The Tamilnadu Dr.MGR Medical University,
Chennai, Tamil Nadu)



Prof Dr V Nagaraajan MD MNAMS
DM (Neuro) DSc.,(Neurosciences)
DSc (Hons)
Professor Emeritus in Neurosciences,
Tamil Nadu Govt Dr MGR Medical
University
Chairman, IEC

Dr.M.Shanthi, MD.,
Member Secretary,
Professor of Pharmacology,
Madurai Medical College, Madurai.

Members

1. Dr.K.Meenakshisundaram, MD
(Physiology)Vice Principal,
Madurai Medical College

2. Dr.Sheela Mallika rani, M.D.,
Anaesthesia , Medical
Superintendent Govt. Rajaji
Hospital, Maudrai

3. Dr.V.T.Premkumar,MD(General
Medicine) Professor & HOD of
Medicine, Madurai Medical & Govt.
Rajaji Hospital, College, Madurai.

4. Dr.D.Maruthupandian, MS.,
Professor & H.O.D. Surgery,
Madurai Medical College & Govt.
Rajaji Hospital, Madurai.

5. Dr.G.Meenakumari, MD.,
Professor of Pathology, Madurai
Medical College, Madurai

6. Mrs.Mercy Immaculate Rubalatha,
M.A., B.Ed., Social worker, Gandhi
Nagar, Madurai

7. Thiru.Pala.Ramasamy, B.A.,B.L.,
Advocate, Palam Station Road,
Sellur.


8. Thiru.P.K.M.Chelliah, B.A.,
Businessman,21, Jawahar Street,
Gandhi Nagar, Madurai.

ETHICS COMMITTEE
CERTIFICATE

Name of the Candidate : Dr.P.Shanmuganathan
Course : PG in MD., General Medicine
Period of Study : 2014-2017
College : MADURAI MEDICAL COLLEGE
Research Topic :
Usefulness of pleural fluid alkaline
phosphatase and its ratio to serum alkaline phosphatase levels
in classifying pleural effusions as exudates and transudates and
its correlation with Light's criteria
Ethical Committee as on : 27.07.2016

The Ethics Committee, Madurai Medical College has decided to inform
that your Research proposal is accepted.


Member Secretary


Chairman


Dean / Convener

Madurai Medical College
Madurai-20

