Non-malignant Pleural Effusions

Outline
- Case presentation
- Epidemiology
- Pathophysiology
- Diagnostic approach
  - Pleural fluid analysis
  - Parapneumonic effusions/empyema
- Treatment

Case presentation
- 65 years old woman presents with 3 days of
  - Fever
  - Malaise
  - Cough
  - Purulent sputum
  - Worsening dyspnea
  - Left sided pleuritic chest pain
- Past Medical/Surgical History
  - COPD
  - Hypertension
  - Congestive Heart Failure
  - Cholecystectomy
- Social history
  - Current smoker
  - 50 pack-years

Case presentation (contd.)
- Physical examination
  - Febrile 101.5°F
  - Tachypneic
  - Tachycardiac
  - Hypoxemic (O2 sats 88% on RA)
  - Decreased breath sounds and tactile fremitus on left
- Lab data
  - WBC 22,000
  - Neutrophils 90%
  - Sodium 129
  - Chest x-ray (shown)

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Epidemiology

- Estimated 1.5 million cases of pleural effusions in the United States annually
- Associated with a wide variety of diseases
- Congestive heart failure, pneumonia and malignancy accounting for two thirds of the cases

Pathophysiology

- Parietal pleura supplied by microvessels from intercostal artery
  - Located close to mesothelial surface
- Visceral pleura supplied by microvessels from bronchial circulation
  - Located at a distance from the mesothelial surface
- Normal pleural fluid formation/resorption are functions of the parietal pleura

Pathophysiology (contd.)

- Ultrafiltrate of parietal pleural capillaries
  - Increased interstitial pressure
    - Movement of fluid into pleural space through mesothelial cell junction
    - Movement of fluid through stomata of parietal pleura
    - Movement through lymphatic lacunae, ducts and channels into lymph nodes
Pathophysiology (contd.)

- Normal pleural fluid
  - 0.1 to 0.2 ml/kg
  - Clear
  - Low protein (1.0 to 1.5 g/dl)
  - < 1500 nucleated cells / µL
    - 61% to 77% monocytes-macrophages
    - 9 to 30% mesothelial cells
    - 7% to 11% lymphocytes
    - 2% neutrophils
    - 0% eosinophils
  - pH > 7.60

Mechanism of abnormal pleural fluid formation
- Increased hydrostatic pressure (CHF)
- Decreased oncotic pressure (hypoalbuminemia)
- Decreased pleural pressure (trapped lung)
- Increased endothelial permeability (pneumonia)
- Decreased lymphatic drainage (malignancy)
- Movement from peritoneal space (hepatic hydrothorax)
- Movement from extra-vascular space (duropleural fistula, migrated/ misplaced CVC/ feeding tube)

Diagnostic Approach

1. Clinical History

- Could be asymptomatic
- Dyspnea and chest pain are the two most common presenting symptoms
- Dyspnea most likely from
  - decreased chest wall compliance
  - depression of ipsilateral diaphragm and increased output from neurogenic receptors
- Dyspnea out of proportion to exam findings can suggest PE

- Chest pain
  - Usually pleuritic
  - Intensity proportional to degree of pleural inflammation
  - May be decreased by splinting by manual pressure over the chest wall
  - May be localized or radiating
    - Central diaphragmatic inflammation causes radiating pain in the posterior neck, shoulder and trapezius area
Diagnostic Approach

1. Clinical History

Asymptomatic
- BAPE
- Rheumatoid pleural effusion
- Nephrotic syndrome
- Yellow nail syndrome
- Trapped lung
- Urinothorax
- Peritoneal dialysis associated effusion

Symptomatic
- Bacterial pneumonia
- Lupus pleuritis
- Postcardiac injury syndrome
- Pulmonary embolism
- Congestive heart failure

2. Physical Examination

- Signs depend on volume of pleural effusion
  - < 300 ml → not detectable on physical examination
  - 500 ml → dull percussion, decreased fremitus, decreased breath sounds
  - > 1000 ml → bulging of ICS, decreased chest expansion, bronchovesicular sounds and egophony at upper level of effusion

3. Chest Radiograph

- Sensitivity proportional to volume of pleural fluid
  - 5 ml → blunting of posterior costophrenic angle on lateral decubitus film
  - 50-75 ml → blunting of posterior costophrenic angle on lateral view
  - 175-200 ml → blunting of costophrenic angle on PA film
  - > 500 ml → opacification of lung base

Useful clues
- Orthopnea, PND, lower extremity → CHF
- H/O asbestos exposure → BAPE
- H/O alcoholism, poor dentition, loss of consciousness → aspiration/anaerobic empyema
- H/O of CABG → post-cardiac injury syndrome or trapped lung
- H/O retching → esophageal rupture
- H/O SLE (or procainamide use) → lupus pleuritis
- Obstructive uropathy → urinothorax
- Spinal surgery or trauma → duropleural fistula
### Diagnostic Approach

#### 3. Chest Radiograph

- Non-malignant causes of massive effusion with mediastinal shift
  - Tuberculosis
  - Empyema
  - Hepatic hydrothorax
  - Chylothorax
  - Hemothorax
  - Congestive heart failure

#### 4. Ultrasound

1. Diagnosis and sampling of loculated pleural effusions
2. Guided sampling of small pleural effusions

#### 5. Computed Tomography

- Most sensitive radiographic study
- Useful for differentiating free flowing effusions, loculated effusions, parenchymal lesions and extrapleural disease

#### 6. Pleural Fluid Analysis (PFA)

- Observation acceptable in
  - Small effusions (< 1 cm thickness on lateral decubitus films)
  - Patients presenting with typical symptoms of CHF and bilateral pleural effusions of similar size and absence of chest pain or fever
- PFA should be performed in all new effusions
- Therapeutic thoracentesis (1 to 1.5 L) in symptomatic effusions
## Diagnostic Approach
### 6. Pleural Fluid Analysis (PFA)

- Prospective study of 129 patients (Chest 1987; 91:817-822)
  - PFA provided definitive diagnosis in 18% of patients
  - Presumptive diagnosis in 55% of patients
  - Non-diagnostic in 27% of patients
  - Non-diagnostic PFA helpful in excluding infections
  - Approximately 30 ml of fluid needed for a complete PFA

### Diagnoses that can be established by PFA

- Empyema → pus
- TB pleuritis → + AFB smear and/ or culture
- Fungal disease → + KOH stain or culture
- Lupus pleuritis → high PF ANA or LE cells
- Chylothorax → chylomicrons
- Hemothorax → PF/ blood ratio > 0.5
- Biliopleural fistula → PF bilirubin/ serum > 1.0

## Diagnostic Approach
### 6. Pleural Fluid Analysis (PFA)

- Observation of pleural effusion
  - Pale yellow (straw colored) → transudate, some exudates
  - Red (bloody) → BAPE, PCIS, pulmonary infarction, trauma
  - White (milky) → chylothorax, cholesterol effusion (satin like sheen)
  - Brown → chronic bloody, ruptured amebic liver abscess (anchovy paste)
  - Black → *Aspergillus niger*
  - Yellow-green → rheumatoid pleurisy (with debris)
  - Color of enteral feeds or IV infusate → Feeding tube or CVC has entered pleural space
  - Pus → empyema
  - Putrid → anaerobic empyema
  - Urine → urinothorax
  - Water like → duropleural fistula

- Diagnoses that can be established by PFA (contd.)
  - Peritoneal dialysis associated effusion → protein < 0.5 g/dL, PF/serum glucose > 1.0
  - Esophageal rupture → high salivary amylase, low pH, food particles in PF
  - Rheumatoid pleurisy → low glucose (<30 g/dL), low pH, debris
  - Extravascular migration of CVC of feeding tube
  - Urinothorax → PF/serum Cr > 1.0
  - Duropleural fistula → β2 transferrin in pleural fluid
## Diagnostic Approach

### 6. Pleural Fluid Analysis (PFA)

#### Transudate vs. Exudate

- **Exudate** if anyone of the following criteria met:
  - PF protein > 2.9 g/dL
  - PF/S protein > 0.5
  - PF LDH > 0.67 upper limits serum LDH
  - PF/S LDH > 0.6
  - PF cholesterol > 45 mg/dL
  - PF/S cholesterol > 0.3
  - Serum albumin-PF albumin < 1.2 g/dL

#### Transudates

- CHF (most common cause)
- Hepatic hydrothorax
- Atelectasis
- Nephrotic syndrome
- Hypoalbuminemia
- Trapped lung
- Peritoneal dialysis associated pleural effusion
- Urinothorax (only transudate with a pH < 7.30)
- Duropleural fistula (β2-transferrin present in PF)

#### Exudates

- Infections (bacterial, viral, fungal, parasitic, mycobacterial)
- Pulmonary embolism (can be transudative)
- Post CABG
- Post cardiac injury syndrome (PCIS)
- GI disease associated (pancreatitis, esophageal rupture)
- Connective tissue diseases (SLE, RA, WG, CSS, SS)
- BAPE

#### Exudates (continued)

- Sarcomiosis
- Uremia
- Meig’s syndrome
- Endocrinopathies (hypothyroidism, ovarian hyperstimulation syndrome)
- Yellow nail syndrome
- Drug reaction (amiodarone, nitrofurantoin, dantrolene, methotrexate)
- Lung entrapment
- Radiation therapy
- Chylothorax
- Hemothorax

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*Am J Respir Crit Care Med. 1995; 151: 1700-1708*
### Diagnostic Approach

#### 6. Pleural Fluid Analysis (PFA)

- **Pleural fluid glucose and pH**
  - Direct relationship
  - Increased metabolism by neutrophils and bacteria → increased CO2, lactic acid (empyema, esophageal rupture)
  - Poor efflux of CO2 and lactate due to pleural membrane thickening (rheumatoid pleural effusion)
- **Low PF glucose and pH**
  - Complicated parapneumonic effusion/empyema
  - Esophageal rupture
  - Tuberculous empyema
  - Chronic rheumatoid pleurisy
  - Lupus pleuritis

### Diagnostic Approach

#### 6. Pleural Fluid Analysis (PFA)

- **Cell count and differential count**
  - Lymphocyte predominance (> 80% of nucleated cells)
    - TB pleurisy
    - Chylothorax
    - Yellow nail syndrome
    - Chronic rheumatoid effusion
    - Sarcoidosis
    - Acute lung rejection
    - Uremic pleural effusion
    - Post-CABG surgery

### Diagnostic Approach

#### 6. Pleural Fluid Analysis (PFA)

- **Cell count and differential count**
  - Neutrophil predominant (> 50% of nucleated cells)
    - Parapneumonic (with infiltrate)
    - PE (without infiltrate)
    - Acute viral infection
    - Pancreatitis
    - Acute TB pleuritis (rarely)

### Diagnostic Approach

#### 6. Pleural Fluid Analysis (PFA)

- **Cell count and differential count**
  - Eosinophilic predominant (> 10% of nucleated cells)
    - Pneumothorax
    - Hemothorax
    - BAPE
    - Pulmonary infarction
    - Parasitic disease
    - Fungal disease
    - Drug induced lung disease
    - *Unlikely to be TB pleuritis*
Diagnostic Approach
6. Pleural Fluid Analysis (PFA)

- PF amylase
  - Acute pancreatitis (pancreatic)
  - Pancreatic pseudocyst - several thousand fold (pancreatic)
  - Esophageal rupture (salivary)
  - Pneumonia (salivary)
  - Ruptured ectopic pregnancy (salivary)

Diagnostic Approach
6. Pleural Fluid Analysis (PFA)

- PF rheumatoid factor and ANA
  - Not routinely performed
  - PF ANA > 1:320 or greater than serum ANA → lupus pleuritis
  - PF rheumatoid factor > 1:320 or greater than serum RF → rheumatoid pleurisy
    - Can be high in bacterial pneumonia
  - PF adenosine deaminase (ADA)
    - 40-60 units/ L → TB pleurisy
    - PF/serum ADA > 1 → TB, RA, empyema

Diagnostic Approach
6. Pleural Fluid Analysis (PFA)

<table>
<thead>
<tr>
<th>Chylothorax</th>
<th>Pseudochylothorax</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute/ subacute</td>
<td>Chronic, insidious</td>
</tr>
<tr>
<td>Trauma, surgery, LAM</td>
<td>RA, TB, empyema</td>
</tr>
<tr>
<td>Dyspnea common</td>
<td>Dyspnea uncommon</td>
</tr>
<tr>
<td>Milky/ turbid or bloody</td>
<td>Milky, satin like sheen</td>
</tr>
<tr>
<td>Lymphocyte predominant exudate</td>
<td>Neutrophil predominant exudate</td>
</tr>
<tr>
<td>PF Tg &gt;110 mg/dL, PF Tg &lt; 50 mg/dL excludes</td>
<td>PF Cholesterol &gt; 200mg/dL</td>
</tr>
<tr>
<td>Chylothorax</td>
<td>PF Tg maybe &gt; 110mg/dL</td>
</tr>
<tr>
<td>PF cholesterol &lt; 200mg/dL</td>
<td>Cholesterol crystals in PF</td>
</tr>
<tr>
<td>Chylomicrons in PF</td>
<td></td>
</tr>
</tbody>
</table>

Diagnostic Approach
6. Pleural Fluid Analysis (PFA)

- Microbiological tests (cultures, stains)
  - Positive Gram stain or culture diagnostic of empyema
  - TB pleuritis
    - Pleural biopsy histology 63% to 85% sensitive
    - Pleural biopsy culture 55% to 80%
    - Pleural fluid culture 13% to 70%
    - Pleural biopsy smear 5% to 18%
    - Pleural fluid AFB smear < 5%
Parapneumonic Effusions/
Empyema

- 40% to 57% of cases of pneumonia associated with parapneumonic effusion
- Complicated parapneumonic effusions in 10% to 15% of patients
- Empyema (pus in the pleural space) in 5% of patients
- Exudative phase (0–72h) → fibrinopurulent phase (3-10 days) → organizational phase (10–21 days)

Parapneumonic Effusions/
Empyema (contd.)

- Diagnosis
  - Exudative to gross pus
  - Cell count may be low due to cell lysis
  - pH < 7.30
  - Low glucose
  - High LDH
  - + Gram stain and/or culture
  - CT chest with contrast showing “split pleura sign” with pleural enhancement
  - Pleural fluid loculations (seen better with chest ultrasound)
  - Indicates poor prognosis

Parapneumonic Effusions/
Empyema (contd.)

- Microbiology
  - Anerobic bacteria
  - S. pneumoniae
  - Staphylococcus aureus
  - H. influenza
  - Klebsiella pneumoniae
  - Gram negative bacilli
  - Fungi (incidence increasing)
  - Atypical organisms, virus, parasites
### Treatment of Non-malignant Effusions (contd.)

- **Rheumatoid pleurisy**: resolve spontaneously after several months
- **PCIS**: NSAIDs, steroids
- **Chylothorax**: hyperalimentation, medium chain TG, bed rest, thoracic duct ligation
- **Parapneumonic effusions/empyema**: antibiotics, pleural drainage, intrapleural fibrinolytics (?), decortication (VATS vs. thoracotomy)

### Treatment of Non-malignant Effusions (contd.)

- Treat the underlying cause
- Persistent or recurrent effusions can require repeat thoracentesis, indwelling pleural catheter, tube thoracostomy or pleurodesis
- **Hepatic hydrothorax**: medical management, TIPS
- **VATS** to repair diaphragmatic defect
- Chemical pleurodesis rarely successful
- Chest tube contraindicated
- **Lupus pleuritis**: steroids
- **Trapped lung**: Reassurance if asymptomatic; decortication if symptomatic and underlying lung normal

### Treatment of Non-malignant Effusions (contd.)

- Intrapleural fibrinolytic therapy for empyema
- No evidence for routine use
- Trend towards reducing need for surgery in some groups
- Recommended by ACCP and BTS on a case to case basis
Management of Malignant Pleural Effusion

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Case

- 37 year old female with metastatic breast cancer and left pleural effusion
- 1 week history of dyspnea
<table>
<thead>
<tr>
<th><strong>Epidemiology of MPE</strong></th>
</tr>
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<tbody>
<tr>
<td>• Most common exudative effusion 40%-70%</td>
</tr>
<tr>
<td>• Lung 32%, Breast 18%, Lymphoma 11%</td>
</tr>
<tr>
<td>• More common in females &lt;60 (50% vs 35%)</td>
</tr>
<tr>
<td>• 15% of patients with Lung Cancer have MPE at diagnosis</td>
</tr>
</tbody>
</table>

Gomez et al. CHEST 2007, 618S
Marel M. Eur Respir Mon, 2002;22:146-156

<table>
<thead>
<tr>
<th><strong>Etiology</strong></th>
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<tbody>
<tr>
<td>• Direct invasion</td>
</tr>
<tr>
<td>• Increased capillary permeability</td>
</tr>
<tr>
<td>• Tumor emboli to visceral pleura secondary seeding of parietal pleura</td>
</tr>
<tr>
<td>• Hematogenous spread to parietal pleura</td>
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</tbody>
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<table>
<thead>
<tr>
<th><strong>Epidemiology</strong></th>
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</thead>
<tbody>
<tr>
<td>• Primary tumor not identified 5-10% MPE</td>
</tr>
<tr>
<td>• 20-30% of malignant lymphoma</td>
</tr>
<tr>
<td>• 50% of patient with breast Ca</td>
</tr>
<tr>
<td>• Ovarian, GI, mesothelioma ~15%</td>
</tr>
<tr>
<td>• Usually &lt;6 months survival except in breast Ca</td>
</tr>
</tbody>
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Marel M. Eur Respir Mon, 2002;22:146-156

<table>
<thead>
<tr>
<th><strong>Paramalignant effusion</strong></th>
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</thead>
<tbody>
<tr>
<td>• Effusion without pleural involvement</td>
</tr>
<tr>
<td>• Low oncotic pressure</td>
</tr>
<tr>
<td>• Blockage of mediastinal lymphatics</td>
</tr>
<tr>
<td>• Lymphoma, Squamous Cell Ca</td>
</tr>
<tr>
<td>• Postobstructive pneumonia, atelactasis</td>
</tr>
<tr>
<td>• Trapped lung</td>
</tr>
<tr>
<td>• Post radiation</td>
</tr>
<tr>
<td>• Chemo related</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Progressive Dyspnea</td>
</tr>
<tr>
<td>• Decreased chest wall compliance</td>
</tr>
<tr>
<td>• Mediastinal shift</td>
</tr>
<tr>
<td>• Increased shunt fraction from atelactatic lung</td>
</tr>
<tr>
<td>• Dull chest pain</td>
</tr>
<tr>
<td>• Malignant mesothelioma</td>
</tr>
<tr>
<td>• Cough</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>History</td>
</tr>
<tr>
<td>Symptoms</td>
</tr>
<tr>
<td>Imaging</td>
</tr>
<tr>
<td>• CXR, CT chest, Ultrasound</td>
</tr>
<tr>
<td>Thoracentesis</td>
</tr>
<tr>
<td>Pleuroscopy/Pleural biopsy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pleural Fluid results</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Protein 4.5/7.1</td>
</tr>
<tr>
<td>• LDH 645/219</td>
</tr>
<tr>
<td>• WBC 1653</td>
</tr>
<tr>
<td>• Lymphocytes 15%</td>
</tr>
<tr>
<td>• Malignant cells 85%</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Case</th>
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<tbody>
<tr>
<td>• Therapeutic thoracentesis (1.8L removed)</td>
</tr>
<tr>
<td>• Bedside ultrasound by clinician</td>
</tr>
<tr>
<td>• Symptom relieved</td>
</tr>
<tr>
<td>• No PTX</td>
</tr>
<tr>
<td>• Biochemical studies ordered</td>
</tr>
</tbody>
</table>
Other Fluid Studies

- Amylase
- Lymphoma, Ovarian Ca, Pancreatic Ca
- CEA, B72.3, Leu-M1
- Calretinin and cytokeratin 5/6 identifies mesothelioma but not benign mesothelial cells
- Flow cytometry
  - if lymphocytic effusion with possibility of lymphoma
- Tumor markers
  - CEA (>10-12ng/mL)
  - Vascular Endothelial Growth Factor (VEGF)

Entrapped Lung?

- Pleural Manometry
- Lung Elastance (Pel)
  - Change in pleural pressure in relation to volume of fluid removed <19cm H2O/L
- Entrapped lung
  - Visceral pleural restriction from malignancy or active disease
  - poor success with pleurodesis
  - Pneumothorax ex-vacuo

Goal for thoracentesis

- Diagnostic & therapeutic (large volume)
- Any relief of symptom?
- Will it recur?
- If so, how soon?
- Did the lung expand?
Patient Update

- Left lung expanded after thoracentesis
- Dyspnea improved
- However, effusion returned after 12 days

Management options

- Repeat thoracentesis
- Indwelling Pleural Catheter Placement
- Pleurodesis
  - Chest tube
  - Medical thoracoscopic
  - VATS
- Pleuroperitoneal shunts
- Surgery

What is the best option?

Personalized Care

Primary Tumor type

- NSCLC effusion respond poorly to chemo
- Small cell Ca effusion respond to chemo
### Pleural Fluid Tests

- Poor survival with
  - Low pH
  - Low glucose
  - High LDH
  - CEA

### Lung re-expansion

- Extensive intrapleural deposition, multiple loculations, trapped lung, endobronchial airway obstruction will cause of failure of pleurodesis
- Pneumothorax after large volume thoracentesis suggest trapped lung

### Performance Status

- Karnofsky score <30, <1 month survival

### Patient Preference

- Duration of hospital stay
- Invasiveness of procedures
- Success of a definitive therapy
- Associated risks
### Repeat thoracentesis

- Only if reaccumulation >30 days
- Limited life expectancy
- Poor performance status
- May trigger cytokine, fibrin and cause loculations
- Large volume thoracentesis with pleural manometry safe

### Chemical Pleurodesis

- Dyspneic and life expectancy more than 4-6 weeks
- Frequent recurrence with symptoms
- Success rate 71%~97%

Heffner J. Semin Respir Crit Care Med 2010; 31:723-733

### Chemical Agents

- Doxycycline
  - Severe CP, thru Chest tube
  - Used with lidocaine
- Talc:
  - Slurry thru CT
  - Lower success rate
  - Poudrage during thoracoscopy 90% success rate *
  - No ARDS with larger calibrated particles
- Other Agents
  - Quinacrine
  - Bleomycin
  - Silver nitrate
  - IFN alpha-2b
### Thoracoscopic vs Chest tube Pleurodesis

- No large RCT available
- Cochrane review of 112 patients
  - Slightly better with thoracoscopy
- Better success with thoracoscopy in breast and primary lung Ca
- Center dependent
- May be better with talc poudrage vs talc slurry

Shaw P et al. Cochrane database Systemic review 2004; CD002916
Dressler et al Chest 2005; 127:909-915

### Medical Thoracoscopy vs. VATS

- Similar
- Adhesions if present can be lysed
- Poudrage sprayed effectively under vision
- Sedation
- VATS more invasive
- Cost
- Requires 3-7 days of hospital stay

### Indwelling Pleural Catheter

- Outpatient placement
- Patients may remain active with good QOL
- Can be placed in trapped lung or in failed pleurodesis cases
- Complications
  - Obstruction, tumor seeding, infection
**Indwelling Pleural Catheter**

- Spontaneous pleurodesis in 40%
- Removed in 60% with resolution of effusion
- Sclerosants can be instilled through catheter

Musani et al. Respiration 2004;71:559-566

**Patient Update**

Examination of pleural space
Pleural space after talc poudrage

**Surgery**

- Pleuroperitoneal Shunting with 95% efficacy if other options fail
- Parietal pleurectomy
- Decortication
- Higher mortality

**Thoracoscopic Pleurodesis**
Conclusion

- MPE indicates advanced disease
- Palliative management is variable depending on tumor type, patient preference, life expectancy, fluid characteristics, performance status and available resources
- Tunneled catheter is safe and cost effective