# Non-malignant Pleural Effusions

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# **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

# **Outline**

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

# **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)



# **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

# **Epidemiology**

- Estimated 1.5 million cases of pleural effusions in the United States annually
  - Light R. Pleural Diseases. 4th ed. Philadelphia, PA: Williams and Wilkins: 2001
- Associated with a wide variety of diseases
- Congestive heart failure, pneumonia and malignancy accounting for two thirds of the cases

# 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</p>
    - 61% to 77% monocytes-macrophages
    - 9 to 30% mesothelial cells
    - 7% to 11% lymphocytes
    - 2% neutrophils
    - 0% eosinophils
  - pH ≥ 7.60

# **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

# Pathophysiology (contd.)

- Mechanism of abnormal pleural fluid formation
  - Increased hydrostatic pressure (CHF)
  - Decreased oncotic pressure (hypoalbuminemia)
  - Decreased pleural pressure (trapped lung)
  - Increased endolethial 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

- 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

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

# **Diagnostic Approach**

- Signs depend on volume of pleural effusion
  - < 300 ml → not detectable on physical
    </p> 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

# **Diagnostic Approach**

1. Clinical History

- Useful clues
  - Orthopnea, PND, lower extremity→ CHF
  - H/O asbestos exposure→ BAPE
  - H/O alcoholism, poor dentition, loss of consciousness→ aspiration/ anerobic 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

- Sensitivity proportional to volume of pleural fluid
  - 5ml→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



3. Chest Radiograph

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

# **Diagnostic Approach**

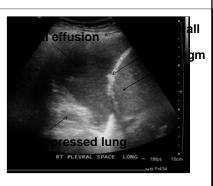
5. Computed Tomography

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



# Diagnostic Approach 4. Ultrasound

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



# **Diagnostic Approach**

- Observation acceptable in
  - Small effusions (< 1 cm thickness on</li> 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
- Approximately 30 ml of fluid needed for a complete PFA

# **Diagnostic Approach**

6. Pleural Fluid Analysis (PFA)

- 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)

- 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

- Observation of pleural effusion
  - Pale yellow (straw colored)→ transudate, some
  - Red (bloody)→ BAPE, PCIS, pulmonary infarction,
  - White (milky)→ chylothorax, cholesterol effusion (satin
  - 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→ anerobic empyema
  - Urine→ urinothorax
  - Water like→ duropleural fistula

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</p>

Am J Respir Crit Care Med. 1995; 151: 1700-1708

# **Diagnostic Approach**

6. Pleural Fluid Analysis (PFA)

- 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

### **Diagnostic Approach**

6. Pleural Fluid Analysis (PFA)

- 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)</li>
  - Duropleural fistula (β2-transferrin present in PF)

# **Diagnostic Approach**

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

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
  - 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
  - Total cell count nonspecific
  - Differential count more helpful
    - Neutrophil predominant (> 50% of nucleated cells)
      - Parapneumonic (with infiltrate)
      - PE (without infiltrate)
      - Acute viral infection
      - Pancreatitis
      - Acute TB pleuritis (rarely)

# **Diagnostic Approach**

- 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

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)

### Chylothorax

- Acute/ subacute
- Trauma, surgery,
- Dyspnea common
- Milky/ turbid or bloody
- Lymphocyte predominant exudate
- PF Tg >110 mg/dL, PF Tg < 50 mg/dL excludes chylothorax
- PF cholesterol < 200mg/dL
- Chylomicrons in

### **Pseudochylothorax**

- Chronic, insiduous
- RA, TB, empyema
- Dyspnea uńcommon
- Milky, satin like sheen
- Neutrophil predominant exudate
- PF Cholesterol > 200mg/dL
- PF Tg maybe > 110mg/dL
- Cholesterol crystals in PF

# 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%
    - 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

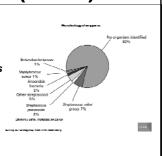
- 40% to 57% of cases of pneumonia associated with parapneumonic effusion
- Complicated parapneumonic effusions in 10% to 15% of patients
- Empyema (pus in the pleural space) in 5% of patients
- Exudative phase (0–72h)→ fibrinopurulent phase (3-10 days)→ organizational phase (10–21 days)

### 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





### Parapneumonic Effusions/ Empyema (contd.)

Pleural Space Anatomy		Pleural Fluid Bacteriology		Pleural Fluid Chemistry*	Category	Risk of Poor Outcome	Drainage
A <sub>0</sub> minimal, free-flowing effusion (< 10 mm on lateral decubitus)†	AND	$B_X$ culture and Gram stain results unknown	AND	$\mathrm{C}_{\mathrm{X}}$ p H unknown	1	Very low	No!
A <sub>1</sub> small to moderate free-flowing effusion (> 10 mm and < ½ hemithorax)	AND	B <sub>0</sub> negative culture and Gram stain§	AND	$C_0$ pH $\geq 7.20$	2	Low	Noll
A <sub>2</sub> large, free-flowing effusion (≥ ½ hemithorac)¶ loculated effusion,# or effusion with thickened parietal pleura**	OR	B <sub>1</sub> positive culture or Gram stain	OR	C <sub>1</sub> pH < 7.20	3	Moderate	Yes
		$B_2$ pus			4	High	Yes
*pH is the preferred pleural fluid chemistry test pleural fluid glucose* should be used (P <sub>0</sub> gluco thresholds for pH and glucose have not been Clinical experience indicates that effusions of the fluorentesis were performed in a patient.	ose ≥ 6 well-e this si with A <sub>0</sub>	90 mg/dL; P <sub>1</sub> glucose < 60 s stablished. ze do not require thoracent	ng/dL). esis for and $P_1$ c	The panel cautions evaluation, but will or B <sub>1</sub> status found.	that the c l resolve. <sup>2</sup> clinical exp	linical utility as serience sugges	nd decision

Chest 2000; 18: 1158-1171

# Treatment of Non-malignant Effusions (contd.)

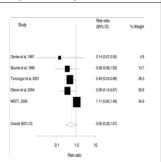
- Rheumatoid pleurisy→ resolve spontaneously after several months
- PCIS→NSAIDs, steroids
- Chylothorax→hyperalimentation, medium chain TG, bed rest, thoracic duct ligation
- Parapneumonic effusions/ empyema > antibiotics, pleural drainage, intrapleural fibrinolytics (?), decortication (VATS vs. thoracotomy)

# 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.)

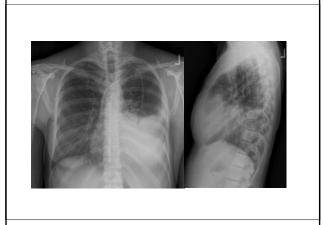
- Intrapleural fibrinolytic therapy for empyema
- No evidence for routine use
- Trend towards reducing need for surgery in some groups
- Recommended by ACCP and BTS on a case to case basis



CHEST 2006; 129:783-790

# 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



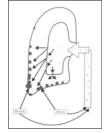
### **Epidemiology of MPE**

- Most common exudative effusion 40%~70%
- Lung 32%, Breast 18%, Lymphoma 11%
- More common in females <60 (50% vs 35%)</li>
- 15% of patients with Lung Cancer have MPE at diagnosis

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

### **Etiology**

- Direct invasion
- Increased capillary permeability
- Tumor emboli to visceral pleura secondary seeding of parietal pleura



 Hematogenous spread to parietal pleura

### **Epidemiology**

- Primary tumor not identified 5-10% MPE
- 20-30% of malignant lymphoma
- 50% of patient with breast Ca
- Ovarian, GI, mesothelioma ~15%
- Usually <6 months survival except in breast Ca

Marel M. Eur Respir Mon, 2002;22:146-156 Ruckdeschel JC Semin Oncol 1995; 22:58-63

# Paramalignant effusion

- Effusion without pleural involvement
- Low oncotic pressure
- Blockage of mediastinal lymphatics
  - Lymphoma, Squamous Cell Ca
- Postobstructive pneumonia, atelactasis
- Trapped lung
- Post radiation
- Chemo related

Statement by ATS on MPE, AJRCCM 2000; 162:1987-2001

# **Clinical features**

- Progressive Dyspnea
  - · Decreased chest wall compliance
  - Mediastinal shift
  - Increased shunt fraction from atelactatic lung
- Dull chest pain
  - Malignant mesothelioma
- Cough

# Case

- Therapeutic thoracentesis (1.8L removed)
- Bedside ultrasound by clinician
- Symptom relieved
- No PTX
- Biochemical studies ordered



# **Diagnosis**

History
Symptoms
Imaging
CXR, CT chest, Ultrasound
Thoracentesis
Pleuroscopy/Pleural biopsy

### **Pleural Fluid results**

- Protein 4.5/7.1
- LDH 645/219
- WBC 1653
  - -Lymphocytes 15%
- Malignant cells 85%

# **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</li>
- Entrapped lung
  - Visceral pleural restriction from malignancy or active disease
  - poor success with pleurodesis
  - Pneumothorax ex-vacuo

Doelken et al. Chest 2004; 126:1764-69

# **Goal for thoracentesis**

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

# **Entrapped Lung?**

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Normal lung

Entrapped lung

Trapped lung

Doelken et al. Chest 2004; 126:1764-69

# **Patient Update**



- •Left lung expanded after thoracentesis
- Dyspnea improved
- However, effusion returned after12days

### What is the best option?

**Personalized Care** 

# **Management options**

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

# **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

# Individual Management Options

# **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

# **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 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 callibrated 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

# **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



# Medical Thoracoscopy vs. VATS

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

## **Indwelling Pleural Catheter**

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# **Indwelling Pleural Catheter**

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

Putnam et al. Cancer 1999; 86:1992-1999 Musani et al. Respiration 2004;71:559-566 Warren et al. Eur J Cardiothoracic Surg 2008;33:89-94

# Patient Update | Solution | Solu

# **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