Pleural Effusions
Diagnostic Approach

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Conflict of interest

Nothing to declare
Symptoms

- Pleuritic chest pain or fever are suggestive of acute inflammatory process (i.e. parapneumonic effusion) or pulmonary emboli
- Dull thoracic pain and/or exertional dyspnea are suggestive of a subacute or chronic process, most often malignancy
- Tuberculous effusion most commonly appear with acute symptoms
- Dry cough relatively common pleural symptom
Imaging signs for malignancy

- CT: widespread, significant (>1 cm) or irregular pleural thickening, thickening of the mediastinal pleura, pleural nodularity suggestive of malignancy
- 31% with thoracoscopic-biospy proven malignancy had unsuspicious CT

Leung AN et al. AJR 1990; 154: 487-92
Hallifax ER et al. Thorax 2015; 70: 192-3
Tsim S et al. Lung Cancer 2017; 103: 38-43

- U/S: similar accuracy to CT in unveiling pleural disorders – does not reveal parenchymal/mediastinal abnormalities

Qureshi NR et al. Thorax 2009; 64: 139-43
CT scan

• CT scans for pleural effusion should be performed with contrast enhancement of the pleura and before complete drainage of pleural fluid. (C)

• CT scans should be performed in the investigation of all undiagnosed exudative pleural effusions and can be useful in distinguishing malignant from benign pleural thickening. (C)

• A CT scan should be requested for complicated pleural infection when initial tube drainage has been failed.

Hooper C et al. Thorax 2010; 65: ii4-ii17
**Ultrasound**

- The best way to demonstrate the presence of an effusion
- The best way to visualize septations
- Reveals pleural thickening and nodularity
- Should be used for aspiration and chest drainage insertion
PET/CT

- Sensitivity 81-95% - negative in slow-growing tumors
- Specificity 74-82% - positive in inflammatory diseases, fibrothorax, post-pleurodesis

Porcel JM et al. Chest 2015;147:502-12
Treglia G et al. Acad Radiol 2014;21:11-20

⇒ Not currently indicated for diagnostic purposes
Pleural Effusion

↓

Diagnostic aspiration
Diagnostic aspiration

- A diagnostic pleural fluid sample should be aspirated with a fine-bore (21G) needle and a 50 ml syringe.
- Bedside ultrasound guidance improves the success rate and reduces complications (including pneumothorax) and is therefore recommended for diagnostic aspirations.
- Pleural fluid should always be sent for protein, LDH, Gram stain, cytology and microbiological culture.

Hooper C et al. Thorax 2010; 65: ii4-ii17
When a diagnostic aspiration is not required?

A. Unilateral effusions

- Asymptomatic, small, effusion post-upper abdomen surgery
- When a diagnosis is known
- When the risk is higher than the expected benefit

B. Bilateral effusions

- Obvious heart failure or fluid overload with no other symptom than dyspnea – should be performed if there is pain, fever or persists after diuretic treatment

  Hooper C et al. Thorax 2010; 65: ii4-ii17

- If attempted, a bilateral thoracentesis is not needed

How the fluid looks like?

- Clear yellow
- Blood-stained (10% of transudates)
- Bloody

59 pts with bloody effusions

47% malignant, 12% trauma, 11% parapneumonic post-CABG, benign asbestos

→ only 11% of the malignant are bloody


► Hct > 50 % of that of blood = hemothorax
Milky or turbid fluid

Empyema, Chylothorax, Pseudochoylothorax

→ Centrifuge → Clear supernatant?

Yes = Empyema

No → Consider either

Chylothorax or Pseudochoylothorax

……… consider the clinical setting and determine lipid content in the effusion
Transudate or exudate

- **Transudate**: Extra-pleural, edematous disease. Fluid is accumulated as a result of pressure disequilibrium between the two sides of normal endothelial membranes.

  ➤ Do not worry about other pleural fluid features. Look at the list of causes of transudate.

- **Exudate**: Pleural disease (inflammatory/malignant). Fluid is accumulated as a result of increased endothelial permeability, secondary to locally produced mediators.

  ➤ Look at other fluid characteristics (type of inflammatory cells, cytology, microbiology etc).
Transudates

Heart failure (90%)  Translocation of vascular catheter
Liver Cirrhosis  Glycinothorax
Renal Failure  Hypoalbuminemia
Nephrotic syndrome
Peritoneal dilution
Urinothorax
Hypothyroidism
CSF leakage
Exudates

**Malignancies**
- Metastatic Ca
- Lymphoma
- Mal Mesothelioma

**Infections**
- Bacterial, Viral
- TB
- Fungus, Parasitic

**GI system disease**
- Esophageal perforation
- Pancreatitis
- Abdominal sepsis

**Collagen Vascular Disease – Vasculitis**
- Rheum. Arthritis
- SLE

**Post-surgery/intervention**
- Abdominal
- Thoracic, CABG, pace-maker insertion
- Sclerotherapy for esophageal varicces

**Post traumatic**
Transudate or Exudate: Light’s criteria

1. PF protein/serum protein > 0.5
2. PF LDH/serum LDH > 0.6
3. PF LDH > 2/3 of the upper normal limit

If one of the above is present then the fluid is an EXUDATE
Transudate or Exudate

- Light’s criteria: sensitivity ~ 100% but specificity < 80%
- Most of the misclassified transudates occur in HF patients taking diuretics

In those cases if…
- serum protein – PF protein > 3.1 or
- serum albumin – PF albumin > 1.2

…. It is likely a transudate

*Bielsa et al. Respirology 2012; 17:721-26*
Transudate or Exudate
marginal cases

When I see **marginal protein** or **LDH** values I also suspect a **combined etiology** and depending on the clinical/imaging information I may decide to start intensive diuretic therapy and/or order more tests

- 30% of 126 consecutive patients with one-side PEs had more than one etiologies

NT-proBNP

- Plasma levels accurately reflect fluid levels. **Diagnosis is made without pleural tap.**
- Increased in HF but not in other cardiac disease or pulmonary embolism
- Correct diagnosis in >85% of the HF effusions misclassified as “exudates” by Light’s criteria
- Better than albumin or protein gradient


- Meta-analysis (14 studies - 12 fluid/4 blood)

<table>
<thead>
<tr>
<th>Fluid</th>
<th>SEN 0.94</th>
<th>SPEC 0.91</th>
<th>PLR 10.9</th>
<th>NLR 0.07</th>
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<tbody>
<tr>
<td>Plasma</td>
<td>SEN 0.92</td>
<td>SPEC 0.88</td>
<td>PLR 7.8</td>
<td>NLR 0.1</td>
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</table>

Routine tests in exudates

• pH - glucose
• Nucleated cell count and differential
• Gram stain and culture for bacteria
• Culture for B-Koch
pH < 7.2 and glucose < 40 mg/dl

Common
Parapneumonic, Malignant, TB, Rheumatoid

Uncommon
Hemothorax, Paragonimiasis, Churg-Strauss, esophageal perforation, urinothorax, SLE
Clinical significance of low pH/Glucose

In parapneumonic, pH < 7.20 suggests the need of fluid drainage
Large mononuclear neutrophils lymphocytes
Nucleated Cells

**Neutrophils** $\Rightarrow$ acute disease

**Lympho/mononuclear** $\Rightarrow$ chronic disease
<table>
<thead>
<tr>
<th>Neutrophils</th>
<th>Lymphocytes/mono nuclear</th>
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<tbody>
<tr>
<td>Pneumonia</td>
<td>TB</td>
</tr>
<tr>
<td>Sub-diaphragmatic inflammation</td>
<td>Cancer</td>
</tr>
<tr>
<td></td>
<td>Post-CABG</td>
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</tbody>
</table>

- Pulmonary Embolism or collagen vascular disease may be NEU or LYMPH predominant
- But….15- 20% of malignant and 10% of TB are neutrophil predominant whereas ≈ 20% of parapneumonic are lymphocyte predominant

*Porcel JM. Respirology 2012; 16:44-52*
Eosinophilic Pleural Effusion

≥10% eosinophils

1/3 traumatic (blood/air)

> 20% idiopathic

rest, all other etiologies

Most common: malignancy

Kalomenidis I, Light RW. Curr Opin Pulm Med 2003; 9:254-60
## 817 patients with eosinophilic exudates

<table>
<thead>
<tr>
<th>μελέτη</th>
<th>trauma</th>
<th>Ca</th>
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<td>3</td>
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<td><strong>total</strong></td>
<td>256</td>
<td>153</td>
<td>90</td>
<td>35</td>
<td>21</td>
<td>72</td>
<td>190</td>
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</tbody>
</table>

31.3% 18.7% 11% 4.3% 2.5% 8.8% 23.2%
How to diagnose Cancer

- Pleural fluid cytology
- Pleural biopsy (closed, image-guided, thoracoscopic)
- Flow cytometry for lymphoma
Cytology

• Sensitivity 60-90%
... depending on the histological type and tumor burden
• Most sensitive for adenocarcinomas
• 2 samples are optimal
• Try to submit 50 ml per sample
• Fluid is adequate for molecular testing – not for PDL1 IHC
Cytology

Sensitivity
8 year, prospective, N=921 (515 malignant): 46% (95%CI 42-58)

- Pancreatic 100%
- Ovary 95%
- Breast 80-93%
- Lung 70% (mainly AD)
- Mesothelioma 6-56% (mainly epithelioid)
- Renal 53%
- Lymphoma 6-40%
- Head-Neck 38%
- Sarcoma 20-38%

Grocu HB et al. Respiration 2018
Arnold DT et al. ERJ 2018
How to diagnose TB

1. Detection of the mycobacteria in PF (sensitivity of culture 10-50%) or respiratory samples

2. PF ADA levels or IFN-γ levels

3. Pleural biopsy (histology + microbiology) – thoracoscopic specimens are ideal
ADA

- Cut-off 40-50 U/L.
- SENS: 88-100 % and SPEC: 81-98%
- SPEC > 95% if applied only in effusions with LYM/NEU >0.75
- *False (+) mainly in:* Parapneumonic and Haematological malignancies
- PPV varies between different populations, depending on the TB prevalence.
- In low prevalence countries may be < 50%
- NPV is consistently high (>95%)

How to use PF ADA in a low TB prevalence community

• A cut-off limit at 40 IU/L is reasonable
• Low ADA can be used as a rule out test together with the clinical/epidemiological findings
• High ADA should be used as a rule in test only in the presence of high clinical and/or epidemiological suspicion of TB pleurisy
• Other possible etiologies of high ADA lymphocyte-predominant pleural effusions should be considered

Surrogate markers of pleural TB are useful ‘rule out’ tests in low incidence countries. Adenosine deaminase is the most thoroughly validated to date.

Hooper C et al. Thorax 2010; 65: ii4-ii17
Chylothorax or Pseudochylothorax

Determine [Triglyceride] levels – may be misleading in fasting patients

- < 50 mg/dl = pseudochylothorax
- > 110 mg/dl = Chylothorax
- 50 - 110 mg/dl → determine Chylomicrons

Best cut-off for triglyceride (SENS and SPEC >95%)

- peritoneal: 187 mg/dl
- pleural: 240 mg/dl

If a chylothorax or pseudochoylothorax is suspected, pleural fluid should be tested for cholesterol crystals and chylomicrons and the pleural fluid triglyceride and cholesterol levels measured. (C)

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Pleural fluid lipid values in pseudochoylothorax and chylothorax</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feature</td>
<td>Pseudochoylothorax</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>&gt;5.18 mmol/l (200 mg/dl)</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>Usually low</td>
</tr>
<tr>
<td>Cholesterol crystals</td>
<td>Often present</td>
</tr>
<tr>
<td>Chylomicrons</td>
<td>Absent</td>
</tr>
</tbody>
</table>

_Hooper C et al. Thorax 2010; 65: ii4-ii17_
Drug-induced pleural effusion

Dasadinib
Amiodarone
Nitrofurantoin
Phenyntoin
Methotreaxate

www.pneumotox.com

Rare. Common diagnoses should be ruled out
Further studies when diagnosis is missing

1. **Thoracic CT** (? CTPA to get the maximum of information from all the anatomic structures)

2. **Abdominal CT** (?sub-diaphragmatic pathology)

3. **Pleural biopsy** useful for TB or malignancy

4. **Bronchoscopy**
Bronchoscopy

- Routine diagnostic bronchoscopy should not be performed for undiagnosed pleural effusion. (C)
- Bronchoscopy should be considered if there is haemoptysis or clinical or radiographic features suggestive of bronchial obstruction. (C)

Hooper C et al. Thorax 2010; 65: ii4-ii17
Pleural Biopsy

- **Blind needle**: for TB mean SENS 70% (28-88%) - for cancer καρκίνο SENS 7-47% in cyto (-) effusions
- **Thoracoscopy**: SENS for TB 100% and for cancer >90%.
- More sensitive than blind needle
  → 30-40% no specific diagnosis


- **CT-guided**: SENS > 85% for cancer, comparable to thoracoscopic, better than the blind

  *Maskell et al. Lancet 2003; 361: 1326*

- **U/S-guided**: SENS >90% for malignancy

  *Hallifax RJ et al. Chest 2014;148:1001-6*
  *Metintas M et al. Chest 2010;137:1362-68*
Pleural Biopsy

- When investigating an undiagnosed effusion where malignancy is suspected and areas of pleural nodularity are shown on contrast-enhanced CT, an image-guided cutting needle is the percutaneous pleural biopsy method of choice. (A)
- Abrams needle biopsies are only diagnostically useful in areas with a high incidence of TB, although thoracoscopic and image-guided cutting needles have been shown to have a higher diagnostic yield. (C)
- Thoracoscopy is the investigation of choice in exudative pleural effusions where a diagnostic pleural aspiration is inconclusive and malignancy is suspected. (C)

Hooper C et al. Thorax 2010; 65: ii4-ii17
Biopsy Method

Suspected TB $\rightarrow$ Thoracoscopy, blind needle biopsy can be used

Suspected κακοήθειας $\rightarrow$ Accessible pleural lesion

No accessible pleural lesion $\rightarrow$ CT or US-guided

thoracoscopy
Conclusions

• For defining the etiology of pleural effusions we need to combine clinical, imaging and pleural fluid features.

• Pleural fluid examination provides a specific diagnosis in the following cases:
  - (+) culture or stain for bacteria/mycobacteria
  - Positive cytology
  - Chylomicrons

• Pleural biopsy is useful in diagnosing malignancy or TB.
81 y.o patient, ex-smoker, with hypertension and COPD presents with dyspnea and fever for the last 3 days. NT-proBNP = 4.800

A. Thoracentesis is not required. Treat with diuretics
B. US-guided bilateral thoracentesis is required
C. US-guided thoracentesis at the left side is required
D. Clinically guided thoracentesis at the left side must be performed
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B. US-guided bilateral thoracentesis is required
C. US-guided thoracentesis at the left side is required
D. Clinically guided thoracentesis at the left side must be performed
Question 2

A 76 yo male, a smoker, presented with progressive dyspnea on exertion during the last 2 months and persistent pain at the left hemithorax for the last month. Diagnostic aspiration revealed an exudate with 65% lymphocytes. What next?
Question 2

A. Order a cytology and if negative proceed to thoracoscopy
B. Order a PET/CT scan
C. Order a cytology and if negative proceed to image-guided biopsy
D. A or C
Answer 2

A. Order a cytology and if negative proceed to thoracoscopy
B. Order a PET/CT scan
C. Order a cytology and if negative proceed to image-guided biopsy
D. A or C