# Pleural fluid myths and elusive effusions

James Goldring

# Pleural fluid appearances

What proportion of transudates are turbid?

- 9%

What proportion of MPE are bloody?

- 11%

(47% of bloody effusions are MPE)

Villena V et al. Clinical implications of appearance of pleural fluid at thoracentesis. *Chest* 2004;125:156

# Chylothorax

Chylothorax is milky?

- Serous: 26%, serosanguinous 26%, bloody 3%
- 14% have triglycerides <1.2mmol/L
- Depends what you eat
- If in doubt check for chylomicrons with lipoprotein electrophoresis

Maldonado F et al. Pleural fluid characteristics of chylothorax. *Mayo Clin Proc* 2009;84:129

# Optimal quantity (mls) for cytology

- There is no point in sending >50mls for cytology?

50ml vs the remainder 55% regardless

Abouzgheib W et al. A prospective study of the volume of pleural fluid required for accurate diagnosis of malignant pleural effusion. *Chest* 2009;135:999

Depends on what your lab does with it:

10mls 49% 60mls 63% 150mls 69% (if doing **cell block** as well as smear/cytospin)

Swiderek J et al. Prospective study to determine the volume of pleural fluid required to diagnose malignancy. *Chest* 2010;137:68

# Delays in sending sample

- Pleural fluid should be analysed asap?

## Cytology (incl IHC, genotyping) 14d refrigerated

Manosca F et al.Diagnostic effects of prolonged storage on fresh effusion samples. *Diagn.Cytopathol.* 2007;35:6

## Glucose 24hrs

Rahman NM et al. Clinically important factors influencing the diagnostic measurement of pleural fluid pH and glucose. *Am. J .Respir. Crit. Care Med.* 2008;178:483

## Cell differential 1d

Conner BD et al. Variations in pleural fluid WBC count and differential counts with different sample containers and different methods. *Chest* 2003;123:1181

## pH 4hrs

Rahman NM (2008)

# Light's criteria

- Light's criteria is the best method for separating transudates from exudates?

Light's criteria 98% sensitive, 74% specific

Requires serum sampling (up to 5d later)

Jenkinson F et al. Biochemical analysis of pleural and ascitic fluid: effect of sample timing on interpretation of results. *Ann. Clin. Biochem*. 2007;44:471

Single tests improve specificity (pleural protein >30g/L 92% sensitive, 83% specific)

Heffner JE et al. Diagnostic value of tests that discriminate between exudative and transudative pleural effusions. *Chest* 1997; 111:970

# Misclassification of transudates

- 30% of CCF related effusions & 18% of hepatic hydrothoraces (HH) are misclassified by light's criteria mostly because both chronicity and diuretic increase LDH & protein

Romero-Candeira S et al. Influence of diuretics on the concentration of proteins and other components of pleural transudates in patients with heart failure. *Am. J. Med.* 2001; 110: 681–6.

- If you suspect CCF use albumin gradient (s.alb-p.alb>12g/L) will correctly identify 83% of "false" exudates
- for HH use the albumin ratio (p.alb/s.alb<0.6) will correctly identify 78% of the "false" exudates
- Or the protein gradient (s.pr-p.pr) > 31g/L will correctly identify 55% of CCF and 61% of HH

Bielsa et al. Solving the light's criteria misclassification rate of cardiac and hepatic transudates. *Respirology* 2012;17:721

Romero-Candeira S et al. The separation of transudates and exudates with particular reference to the protein gradient. Curr. Opin. Pulm.Med. 2004;10:294

# Misclassification of CCF transudates and NT-proBNP

- Is serum NT-proBNP better than albumin gradients and protein gradients?
- Yes but only pleural NT-proBNP>1300pg/ml validated so far.

Porcel et al. Biomarkers of heart failure in pleural fluid. Respirology 2009;14:471

- Serum NT-proBNP >1500pg/ml usual cut off in trials
- Evidence for BNP is scarce

BTS 2010 pleural guidelines

# Protein/LDH discordance

- You only need 1 of Light's criteria to make an exudate- much of the time the 2 or 3 tests are concordant but…
- If the protein is high and LDH low think of
- 1 .bloody tap

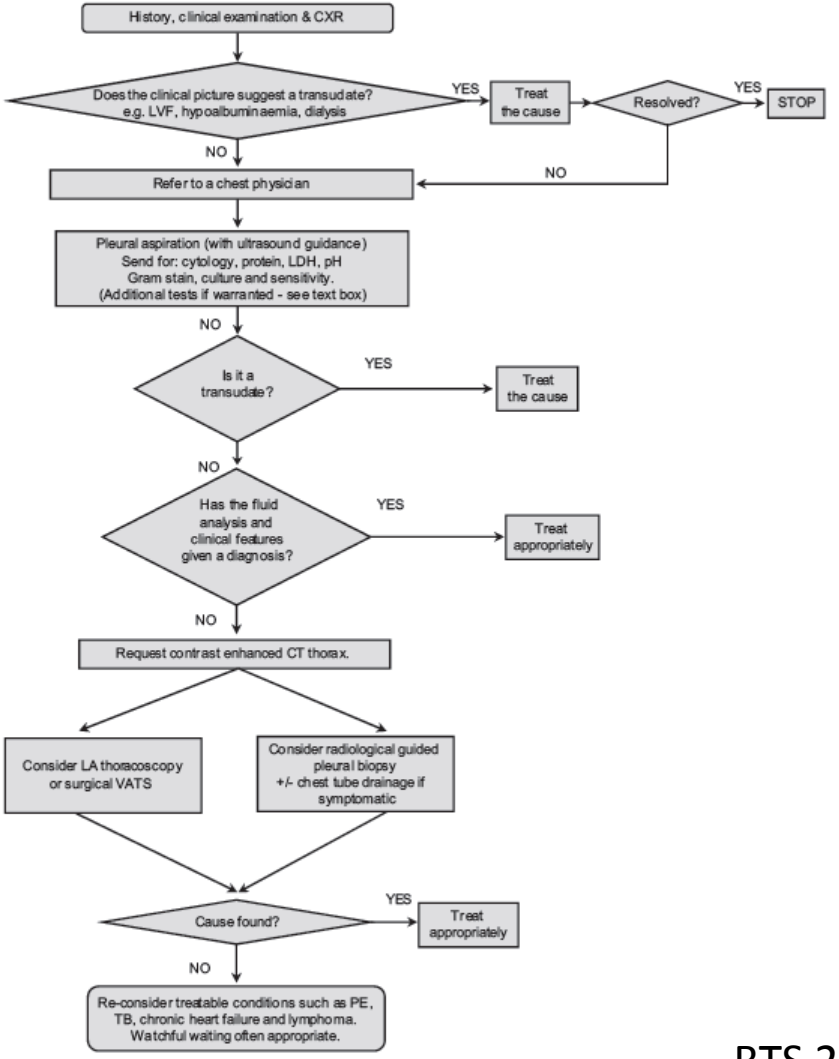
Porcel JM et al. Influence of pleural fluid red blood cell count on the misidentification of transudates. Med. Clin. (Barc.) 2008; 131: 770–2.

- 2. Chylothorax
- 3. Yellow nail syndrome

- If LDH high and protein low think of
- 1. malignancy
- 2. parapneumonic effusions
- 3. PCP

- V high LDH (>1000IU): infection, rheumatoid, malignancy
- V high protein (> 70g/L): multiple myeloma, waldenstroms macroglobulinaemia

# Investigation of unilateral pleural effusion

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# Elusive effusions

- Despite work up approx 5-20% of effusions remain undiagnosed

- Aims

Exclude a treatable cause

Avoid unnecessary interventions

# Undiagnosed pleural effusion algorithm

Think of uncommon causes: revisit history, examination, drug history

Exudate or transudate- use light's criteria,

Reconsider thoracoscopy ?LA

PE? d-dimer then CTPA

Abdo pathology? Subphrenic , chronic pancreatitis, ovarian

If clinical suspicion of CCF or HH use albumin or protein gradients

Tests: serum HIV, pleural lipids & amylase

High NT-proBNP? Treat for heart failure

Reconsider hepatic hydrothorax even if no ascites

Dialysis? Or Nephrotic syndrome

Test: serum TFTs

If no treatable cause found- watch & wait vs. interval scanning.

# Uncommon effusions

| Transudates | Exudates |
|---|---|
| Trapped lung (after initial inflammatory process) | Yellow nail syndrome |
| Constrictive pericarditis | Benign asbestos pleural effusion (BAPE) |
| Urinothorax | Fungal |
| Peritoneal dialysis | Connective tissue disease |
| SVC obstruction | Drugs |
| Mitral stenosis | Meigs |
| | Lymphoma |
| | Chylothorax |
| | Post cardiac injury |
| | |

# Drug induced effusions

10-50 cases on pneumotox

- Nitrofurantoin
- Methotrexate (some eosinophilic)
- Amiodarone
- Bromocriptine
- Docetaxel
- Imatinib
- Clozapine
- Sodium valproate (eosinophilic)
- Isoniazid (ANA +)
- Anti-TNF

# Pulmonary embolism as a cause of pleural effusion

- More common than we think- 4th leading cause
- Dyspnoea out of proportion to size of effusion
- 30% associated with effusion
- Only 5% in thoracocentesis series
- Usually unilateral and mostly just blunting of costophrenic angle
- Doesn't usually persist beyond 3 weeks

Marel et al. Incidence of pleural effusion in a well defined region: epidemiological study in central Bohemia. Chest 1993;104:1486

# “no cause found”: Idiopathic pleuritis

Venekamp LN et al. Does”idiopathic pleuritis” exist? Natural history of non-specific pleuritis diagnosed after thoracoscopy. *Respiration* 2005;72:74

- 75 patients with a histological diagnosis of non-specific pleuritis.
- Age 63.4 (±13.3) yrs,  Mean follow up 32.9 (±27.4) months
- 8.3% malignant (21.4% of patients with asbestos exposure compared to 4.3% of those without), 91.7% benign
- True idiopathic in 25% (15/60)

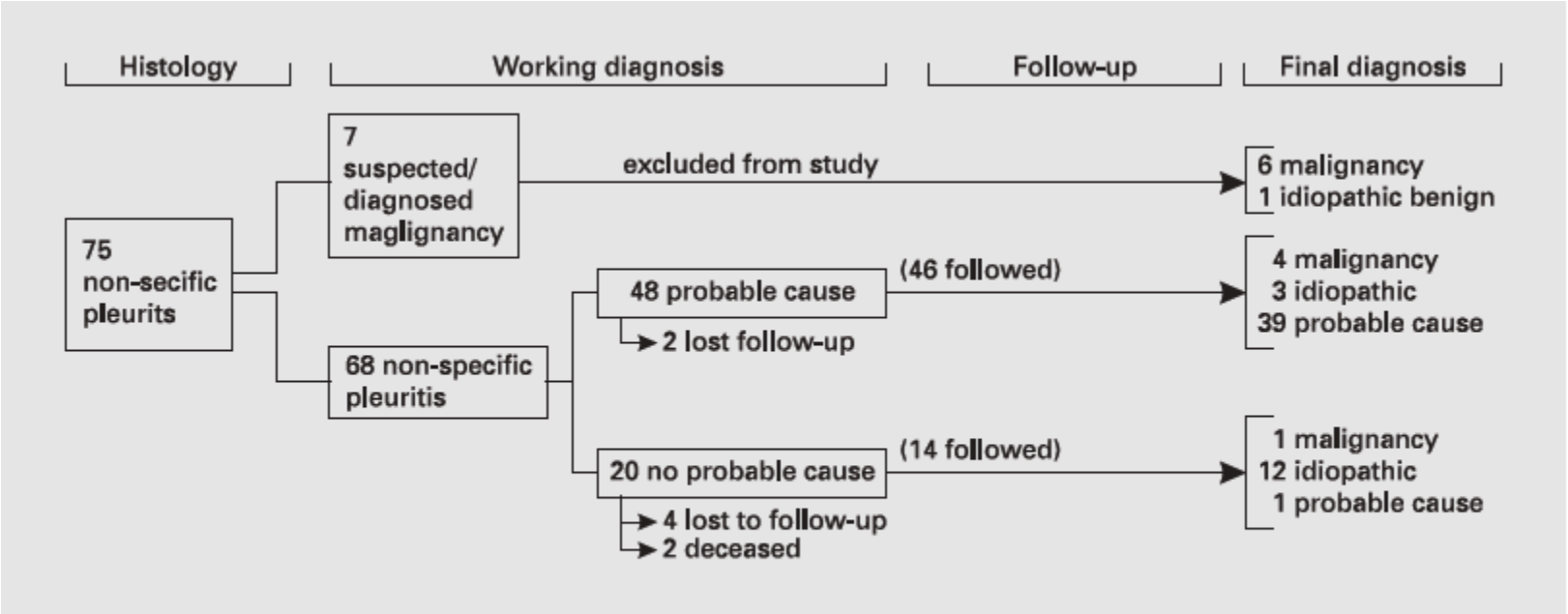


**Fig. 1.** Evolution of patients with the histological diagnosis of non-specific pleuritis after thoracoscopy.

# Truly idiopathic in 25%

**Table 2.** Probable diagnoses of patients with the histological diagnosis of non-specific pleuritis immediately after thoracoscopy (working diagnosis), and final clinical diagnosis after follow-up

| | Working diagnosis | Final clinical diagnosis |
|---|---|---|
| Probable cause | 48 | 40 |
| Asbestos pleuritis | 12 | 9 |
| Parapneumonic | 10 | 9 |
| Post-CABG | 6 | 6 |
| Radiotherapy | 4 | 3 |
| Empyema | 4 | 4 |
| Tuberculosis | 3 | 0 |
| Trauma | 2 | 2 |
| MCTD/SLE | 2 | 2 |
| CHF | 2 | 1 |
| Pulmonary embolism | 1 | 1 |
| Amyloidosis | 1 | 1 |
| Drugs (bromocryptine) | 1 | 1 |
| Whipple's disease | 0 | 1 |
| No probable cause (idiopathic): | 20 | 15 |
| Malignancy | | 5 |
| Lung carcinoma | | 3 |
| Mesothelioma | | 2 |
| Lost to follow-up or died | | 8 |
| Total | 68 | 68 |

CABG = Coronary artery bypass graft; MCTD/SLE = mixed connective tissue disease/systemic lupus erythematosus; CHF = chronic heart failure.

- 2 cases of BAPE ultimately mesothelioma
- 3 cases of TB- lymphocytic exudate, +TST, contact- no clinical benefit seen
- Radiotherapy ?

**Table 3.** Recurrence of effusions in 10 patients with non-specific pleural effusions

| Working diagnosis | Time to recurrence months | n |
|---|---|---|
| No probable cause | 38, 42, 72 | 3 |
| Amyloidosis | 3 | 1 |
| MCTD/SLE | 11 | 1 |
| Parapneumonic | 3 | 1 |
| Radiotherapy | 2[1], 7 | 2 |
| Post-CABG | 32, 45 | 2 |

[1] Patient with a second recurrence after 3 years, due to pulmonary embolism.

# Summary

- Correct interpretation of pleural fluid analysis and a systematic approach to undetermined effusions enables diagnosis in most cases

- Most undiagnosed effusions turn out to be benign and self-limiting

# IPC practical

- http://vimeopro.com/user26937648/rocketvideozone/video/91925239