

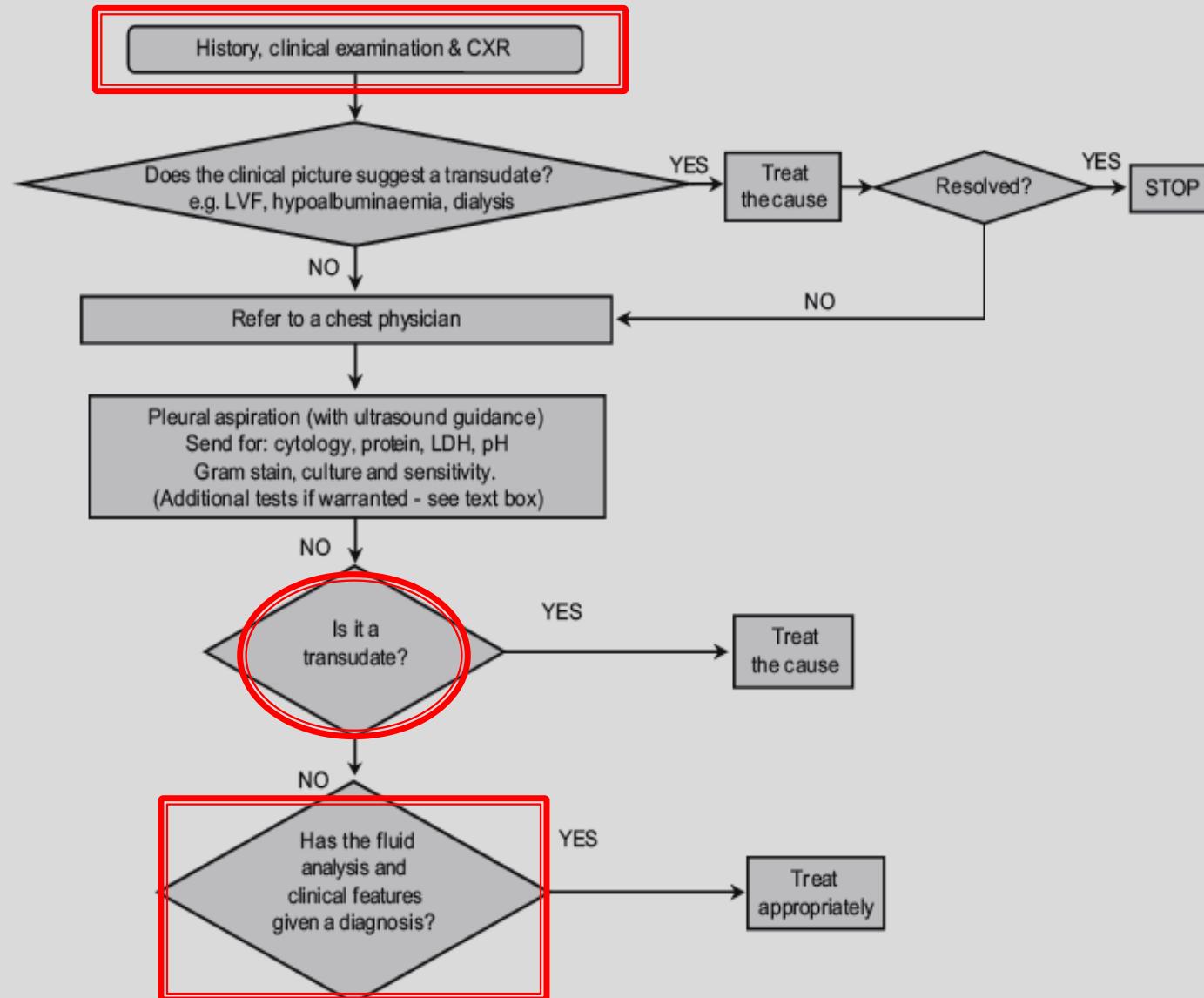
Διαγνωστική προσέγγιση ασθενούς με υπεζωκοτική συλλογή

Διονύσης Σπυράτος

Λέκτορας Πνευμονολογίας ΑΠΘ

Πνευμονολογική Κλινική ΑΠΘ, ΓΝΘ “Γ. ΠΑΠΑΝΙΚΟΛΑΟΥ”

Diagnostic algorithm for the investigation of a unilateral pleural effusion



Medical history and clinical examination

- ▶ Large volume, smoker, weight loss, history of malignancy, no pain/fever: **malignant pleural effusion**
- ▶ Acute onset, clinical symptoms of infection, loculated effusion, pulmonary infiltrate: **parapneumonic effusion**
- ▶ Young adult, low-grade fever, risk factors, high prevalence of TB in the community: **tuberculous pleural effusion**
- ▶ Connective tissue disease, drug history, risk factors for pulmonary embolism

Διαγνωστική παρακέντηση

- ▶ Η αρχική θωρακοκέντηση θέτει τη διάγνωση (σίγουρη ή πιθανή) στο 70-75% των ασθενών (25%: κακοήθεια ή + καλλιέργεια)
- ▶ Εξετάσεις ρουτίνας του υπεζωκοτικού υγρού: κύτταρα, pH, γλυκόζη, λεύκωμα (αλβουμίνη, σφαιρίνες), LDH, χρώσεις και καλλιέργειες (κοινά μικρόβια και ΜΦ)
- ▶ Συχνά χρησιμοποιούμενες εξετάσεις: αμυλάση, τριγλυκερίδια, χοληστερόλη

Diagnoses established "definitively" by pleural fluid analysis

Disease	Diagnostic pleural fluid tests
Empyema	Observation (pus, putrid odor), positive culture
Malignancy	Positive cytology
Tuberculous pleurisy	Positive AFB stain, culture
Esophageal rupture	High salivary isoenzyme form of amylase, low pH (often as low as 6), ingested vegetable or meat fragments
Fungal-related effusions	Positive fungal stain, culture
Chylothorax	Triglycerides >110 mg/dL, chylomicrons by lipoprotein electrophoresis
Cholesterol effusion	Cholesterol >200 mg/dL with a cholesterol to triglyceride ratio >1, cholesterol crystals under polarizing light
Hemothorax	Ratio of pleural fluid to blood hematocrit >0.5
Urinothorax	Pleural fluid creatinine to serum ratio always >1 but diagnostic if >1.7
Peritoneal dialysis	Protein <0.5 mg/dL and pleural fluid to serum glucose ratio >1 in peritoneal dialysis patient
Extravascular migration or misplacement of a central venous catheter	Pleural fluid to serum glucose ratio >1, pleural fluid gross appearance mirrors infusate (eg, milky white if lipids infused)
Rheumatoid pleurisy	Cytologic evidence of elongated macrophages and distinctive multinucleated giant cells (tadpole cells) in a background of amorphous debris
Glycinothorax	Measurable glycine after bladder irrigation with glycine-containing solutions
Cerebrospinal fluid leakage into pleural space	Detection of beta-2 transferrin
Parasite-related effusions	Detection of parasites

Causes of pleural transudates

► Very common causes

1. Left ventricular failure
2. Liver cirrhosis

► Less common causes

1. Hypoalbuminaemia
2. Peritoneal dialysis
3. Hypothyroidism
4. Nephrotic syndrome
5. Mitral stenosis

► Rare causes

1. Constrictive pericarditis
2. Urinothorax
3. Meigs' syndrome

**What about
pulmonary
embolism?**

Pleural effusion in pulmonary embolism

Two studies analysed 60 and 26 pleural fluids from patients with pulmonary embolism and found that **all** fell into the **exudative category** when Light's criteria were applied

PLEURAL FLUID APPEARANCE

- ▶ **Transudates:** straw-coloured (67%), water-appearance (13%), bloody (11%) and turbid (9%)
- ▶ **Frankly bloody:** malignancy (47%)
- ▶ Other causes: trauma, pneumonia, post-cardiac injury syndrome and pulmonary embolism
- ▶ **Chylothorax:** milky (45%), serous (26%), serosanguineous (26%) and bloody (3%)

Γαλακτώδες υπεζωκοτικό υγρό

- ▶ **Εμπύημα:** κλινική εικόνα, οσμή, διαχωρισμός μετά φυγοκέντηση
- ▶ **Χυλοθώρακας:** τριγλ. >110 mg/dL, χοληστερ. <200 mg/dL, χυλομικρά, αιματολογικά νοσήματα/τραύμα/χειρουργείο
- ▶ **Ψευδοχυλοθώρακας:** τριγλ. <110 mg/dL, χοληστερ. >250 mg/dL, κρύσταλλοι χοληστερόλης, χρόνια πορεία, TB εμπύημα/RA/παραγονιμίαση

Light's criteria for differential diagnosis

1. Pleural fluid (PF) protein / serum protein >0.5
 2. PF LDH / serum LDH >0.6
 3. PF LDH >2/3 of the upper limit of normal for serum LDH
-
- ▶ If **at least one** of the above three criteria is present, the fluid is an **exudate**
 - ▶ Diagnostic accuracy: 93-96%

Άλλα χρησιμοποιούμενα κριτήρια

1. Pleural fluid protein >2.9 g/dL
 2. Pleural fluid cholesterol >45 mg/dL
 3. Pleural fluid LDH greater than 0.45 times the upper limit of the laboratory's normal serum LDH
-
- ▶ Στόχος των περισσοτέρων κριτηρίων είναι να αποφύγουμε τον χαρακτηρισμό εξιδρωμάτων (πιθανότητα κακοήθειας) ως διϊδρώματα

Light's criteria for differential diagnosis

- ▶ **≈20%** of patients with pleural effusion caused by heart failure may fulfill the criteria for an exudative effusion **after receiving diuretics**

Porcel JM et al. Ann Clin Biochem 2001;38:671-5

- ▶ If serum protein – PF protein **>3.1 g/dL**, the patient should be classified as having a transudative effusion

Romero-Candeira S et al. Am J Med 2001;110:681-6

- ▶ If serum albumin – PF protein **>1.2 g/dL** also can indicate a true transudative effusion

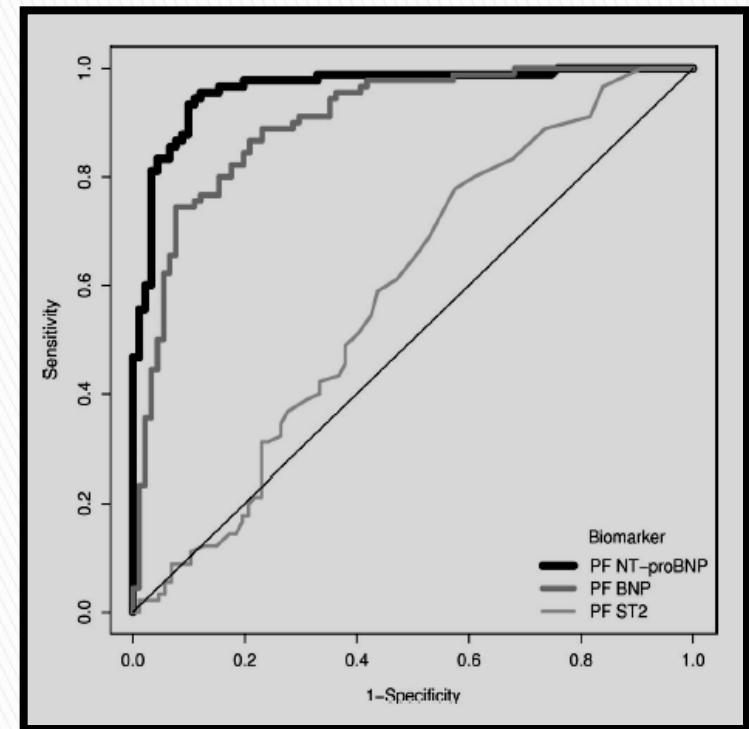
Romero-Candeira S et al. Curr Opin Pulm Med 2004;10:294-8

Διαχωρισμός διϊδρωμάτων-εξιδρωμάτων επί υποψίας KA

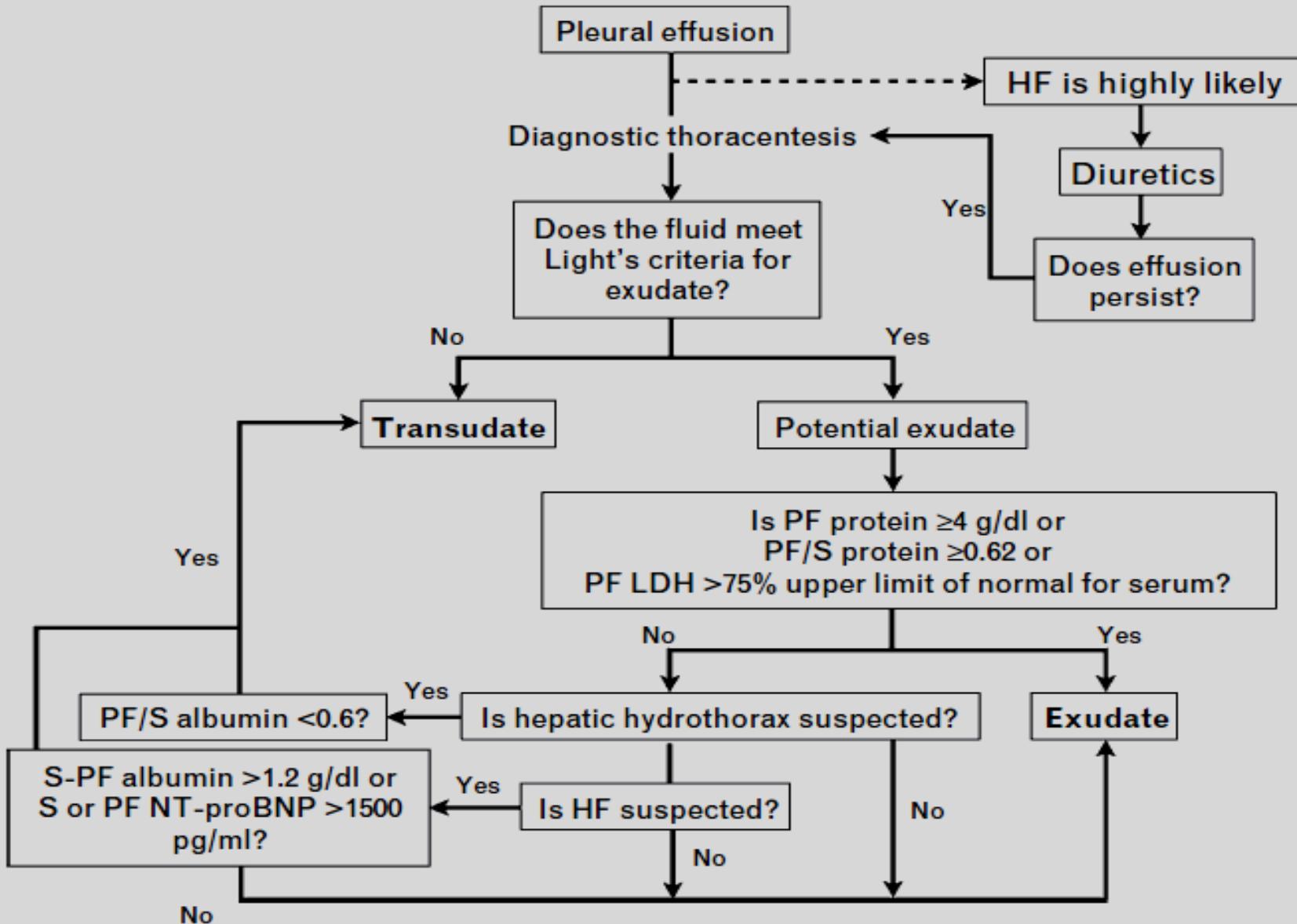
Study	No. of transudates/ HF/HH	Misclassified transudates by Light's criteria, No. (%)	Misclassified transudates with protein gradient >3.1 g/dl, No. (%)	Misclassified transudates with albumin gradient >1.2 g/dl, No. (%)
Roth et al. [13]	18/15/1	5 (28)	ND	5 (100)
Akkurt et al. [14]	27/24/0	5 (19)	ND	5 (100) ^b
Burgess et al. [15]	123/84/ND	19/112 (17)	ND	13 (68)
Gonlugur et al. [16]	71/62/0	28 (39)	20/26 (78) ^c	25/26 (96)
Han et al. [17]	98/82/16	32 (33)	18/28 (64) ^d	ND
Bayram et al. [18]	54/51/2	19 (37) ^d	13 (68) ^d	14 (74) ^d
Bielsa et al. [7**]	466/364/102	125/466 (27)	70/123 (57)	37/49 (76)
Total	857/682/121	233/846 (27.5)	121/196 (62)	99/123 (80.5)

Biomarkers of Heart Failure in Pleural Fluid

- ▶ The “best” cutoff values were: **1,300 pg/mL** for NT-pro-BNP and **115 pg/mL** for BNP
- ▶ **20 patients** were misclassified as exudates by the Light’s criteria
- ▶ 18 patients (**90%**) and 14 patients (**70%**), respectively, would have been correctly categorized by **NT-pro-BNP** and BNP
- ▶ Only 10 patients (**50%**) would have been appropriately classified by the S/PL protein gradient.



AUC: 0.96 for NT-pro-BNP AUC: 0.9 for BNP



Χαμηλή (<60mg/dL) γλυκόζη στο υπεζωκοτικό υγρό

- ▶ Rheumatoid pleurisy (σχεδόν πάντα)
- ▶ Complicated parapneumonic effusion or empyema
(σχεδόν πάντα)
- ▶ Malignant effusion (περιστασιακά)
- ▶ Tuberculous pleurisy (περιστασιακά)
- ▶ Lupus pleuritis (περιστασιακά)
- ▶ Esophageal rupture

Χαμηλό (<7,2) pH στο υπεζωκοτικό υγρό

- ▶ Τα αίτια είναι αυτά των περιπτώσεων χαμηλής γλυκόζης στο υγρό
- ▶ Παραπνευμονική συλλογή: ένδειξη τοποθέτησης **Θωρακοσωλήνα**
- ▶ Κακοήθης συλλογή: αυξημένη πιθανότητα για (+) κυτταρολογική, **μειωμένη επιβίωση**, αποτυχία πλευρόδεσης

Άλλες εξετάσεις ρουτίνας

- ▶ **Λεύκωμα υγρού >7-8 gr/dL:** μακροσφαιριναιμία Waldenström, πολλαπλούν μυέλωμα
- ▶ **LDH υγρού >1000 IU/L:** εμπύημα, ρευματοειδής πλευρίτιδα, παραγονιμίαση, σπάνια σε κακοήθη συλλογή
- ▶ **Υψηλή αμυλάση υγρού:** οξεία παγκρεατίτιδα, ψευδοκύστεις, ρήξη οισοφάγου (σιαλική μορφή), κακοήθεια (10% των ασθενών με αδενοκαρκίνωμα, σιαλική μορφή)

PF differential cell count

- ▶ **Neutrophils >50%:** most common cause is parapneumonic effusion
- ▶ Other diagnoses: pulmonary embolism, subphrenic abscess, pancreatitis and less commonly malignancy (20%) or TB (<10%)
- ▶ >2/3 of **lymphocytic** pleural effusions are the result of malignancy or TB

Eosinophilic pleural effusion (EPE) eosinophils >10% of the total nucleated cells

- ▶ A retrospective analysis of 2,205 pleural fluid samples

- ▶ 135 patients with EPE (7.2%)

- ▶ Aetiology of EPE was:
 1. malignancy (34.8%)
 2. infectious (19.2%)
 3. unknown (14.1%)
 4. post-traumatic (8.9%)
 5. miscellaneous (23.0%)

Eosinophils in PE	N	Patients with malignant EPE	Patients with EPE of unknown origin
≤40%	100	40 (40%)	9 (9%)
>40%	35	7 (20%)	10 (28.5%)

- ▶ Η ηωσινοφιλία στο υπεζωκοτικό υγρό οφείλεται συνήθως στην παρουσία **αέρα ή/και αίματος** στην υπεζωκοτική κοιλότητα
- ▶ Η παρουσία ηωσινοφιλίας **δεν αποκλείει** τη διάγνωση **κακοήθειας**
- ▶ Η παρουσία ηωσινοφιλίας στο αρχικό δείγμα **αποκλείει** τη διάγνωση της **Φυματιώδους πλευρίτιδας**

Gram stain and microbiological culture

- ▶ Retrospective study among 476 patients with pleural effusion and microbiological investigations **as a routine**
- ▶ **Only** 15 true-positive fluid cultures (**3.2%**)

Barnes TW et al.Chest 2005; 127: 916–21

- ▶ Cultures are expected to be positive in about 25% of patients with nonpurulent complicated parapneumonic effusions and 70% of patients with empyemas

Porcel JM. Curr Opin Pulm Med. 2010 ;16(4):357–61

Gram stain and microbiological culture

- ▶ Pleural fluid cultures should be ordered **only when an infection is suspected** on clinical symptoms/signs (e.g. associated pneumonia, fever, sepsis or loculated effusion)
- ▶ In this case it is best to inoculate PF **directly** into blood culture **bottles** (for aerobes and anaerobes) at bedside

Adenosine deaminase (ADA)

A meta-analysis of 63 studies, **2796 patients** with **tuberculous** pleuritis reported:

- ▶ sensitivity of ADA: **92%**, specificity: **90%**, AUC:**0.96**
- ▶ positive likelihood ratio: 9.03, negative likelihood ratio: 0.10

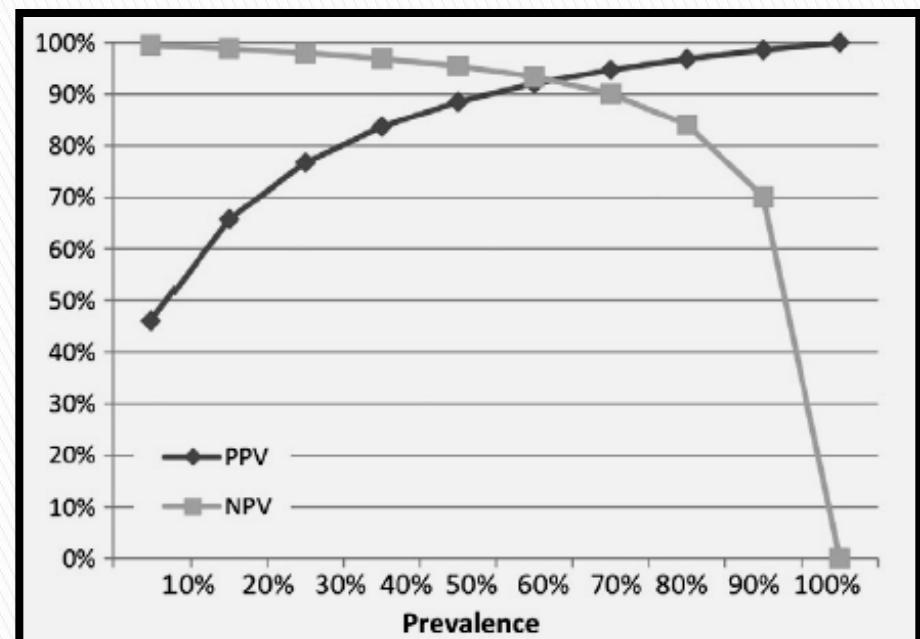
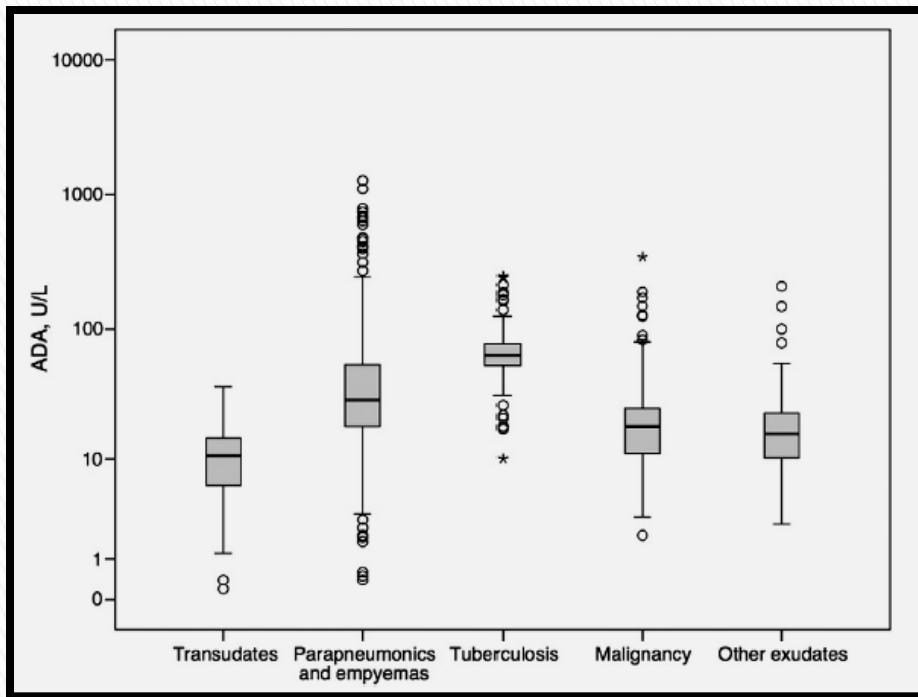
In a retrospective study of 2104 consecutive patients, **ADA >35U/L AND lymphocytic exudate** yielded:

- ▶ 93% sensitivity, 90% specificity
- ▶ positive likelihood ratio (LR): 10.05, negative LR: 0.07 for the diagnosis of TB.

Other diseases with elevated ADA

- ▶ $\approx 1/3$ of **parapneumonic** effusions and $2/3$ of **empyemas** have ADA > 40 U/L
- ▶ Less commonly high pleural fluid ADA has been reported in malignancies (5%, particularly **lymphomas**), infectious diseases (e.g. brucellosis, Q fever) and connective tissue diseases such as **rheumatoid arthritis**

Diagnostic performance of ADA in pleural fluid: A single-center experience (2100 patients)



Diagnostic tests for tuberculous pleuritis

- ▶ Pleural fluid culture (BACTEC system): (+) 24%
- ▶ Closed pleural biopsy: (+) for granulomas in **80%**
- ▶ AFB stain of the biopsy: (+) in 25.8%
- ▶ Culture of the biopsy tissue: (+) in **56%**

Is (+) ADA enough for the diagnosis of TB pleuritis?

Culture Positive for M tuberculosis	Pleural TB Patients						Pulmonary TB Patients					
	Foreign Born		US Born		Total		Foreign Born		US Born		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Initial susceptibility for INH and rifampin												
Total	1,491	100	2,705	100	4,215	100	43,189	100	68,038	100	111,787	100
INH resistance	130	8.7	125	4.6	255	6.0	5,136	11.9	3,557	5.2	8,733	7.8
MDR	18	1.2	25	0.9	43	1.0	799	1.8	821	1.2	1,627	1.5
Initial susceptibility for INH, rifampin, streptomycin, ethambutol, and pyrazinamide												
Total	1,504	100	2,728	100	4,251	100	43,392	100	68,402	100	112,362	100
Any first-line drug resistance	214	14.2	207	7.6	422	9.9	7,401	17.1	5,883	8.6	13,350	11.9

Καρκινικοί δείκτες στο υγρό

- ▶ Θετικότητα σε συνδυασμό **4** καρκινικών δεικτών (CEA, CA 125, CA 15-3, και CYFRA 21) παρουσίαζε ευαισθησία 54%
- ▶ Η διαγνωστική ακρίβεια της κυτταρολογικής εξέτασης αυξήθηκε κατά 18% με την προσθήκη του παραπάνω κριτηρίου
- ▶ Σε καμιά περίπτωση **δε συνιστώνται ως ρουτίνα**

Porcel JM et al. Chest. 2004;126(6):1757.
Liang QL et al. Thorax. 2008;63(1):35.

Volume of pleural fluid

- ▶ Cytologic tests were positive for malignancy in 23 of the 44 patients (55%).

The submission of **>50 mL** of pleural fluid for cytologic analysis **does not increase diagnostic yield**

Abouzgheib W et al. Chest 2009; 135:999 -1001

Table 3—Direct Smear/Cytospin Only Results (n = 107)

Volume, mL	Sensitivity	Specificity	PPV	NPV
10	48.7% (38/78)	96.6% (28/29)	97.4% (38/39)	41.2% (28/68)
60	62.8% (49/78)	89.7% (26/29)	94.2% (49/52)	47.3% (26/55)
150	69.2% (54/78)	86.2% (25/29)	93.1% (54/58)	51.0% (25/49)

Number of specimens

- ▶ 215 patients with a total of 570 specimens
- ▶ A cytological diagnosis of malignancy was made for 55 patients (26%)
- ▶ (+) diagnosis: initial specimen in 36 patients (**65%**), on the second in 15 patients (**27%**), the third in 3 (5%), and the fifth in 1 (2%)
- ▶ If both direct and **concentrated smears** had been used: initial specimens were (+) in **89%** of the cases.

Thin-prep technique



Diagnostic accuracy of cytology

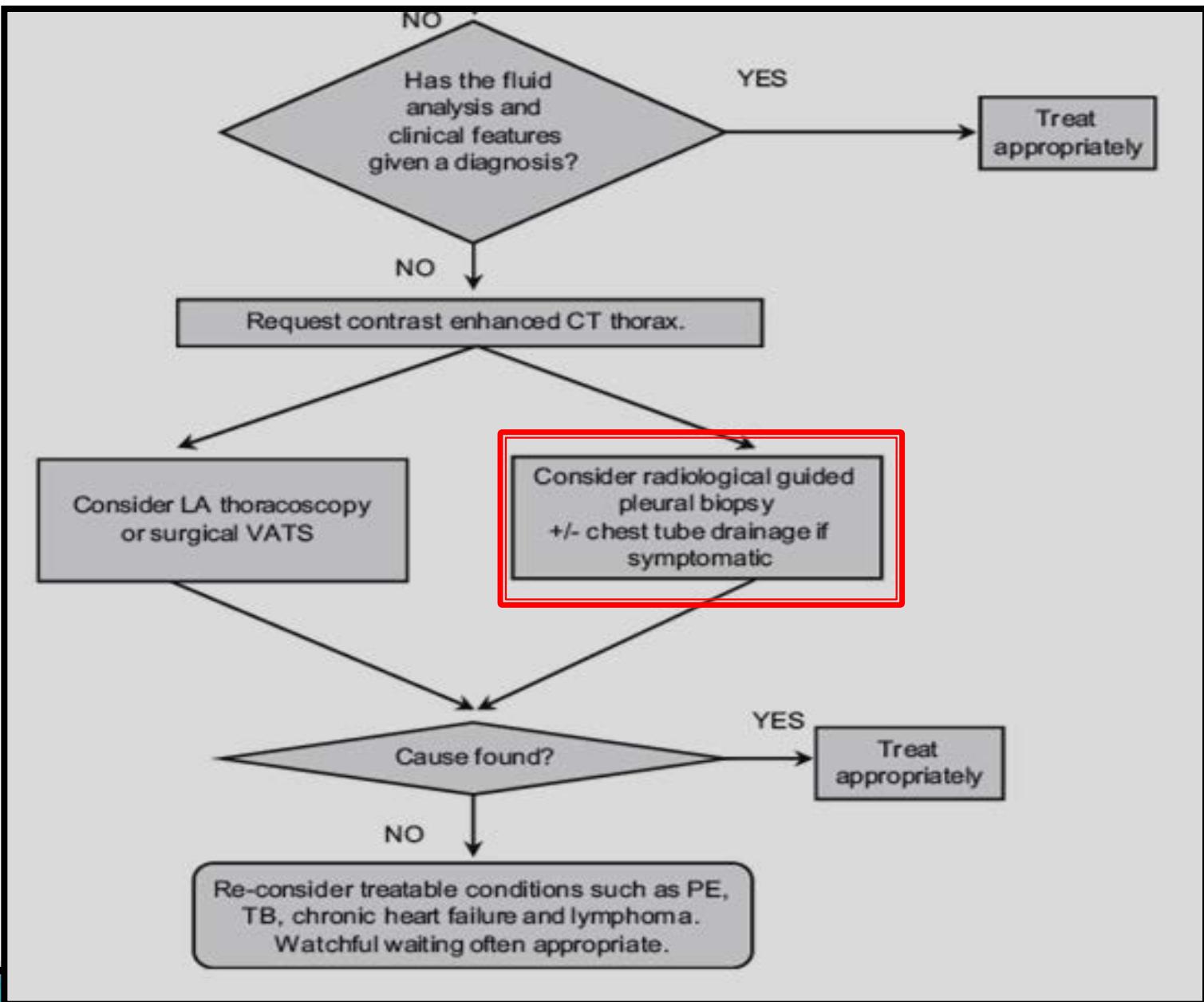
	Number of cases	Sensitivity	Specificity
Bueno CE et al. Arch Intern Med 1990;150:1190-4	414 (189 malignant)	52.3%	100%
Prakash UB et al. Mayo Clin Proc 1985;60:158-64	414 (281 malignant)	57.6%	100%
Loddenkemper R et al. Am Rev Respir Dis 1983;127 (Suppl. 4): 114	208 malignant effusions	62%	100%

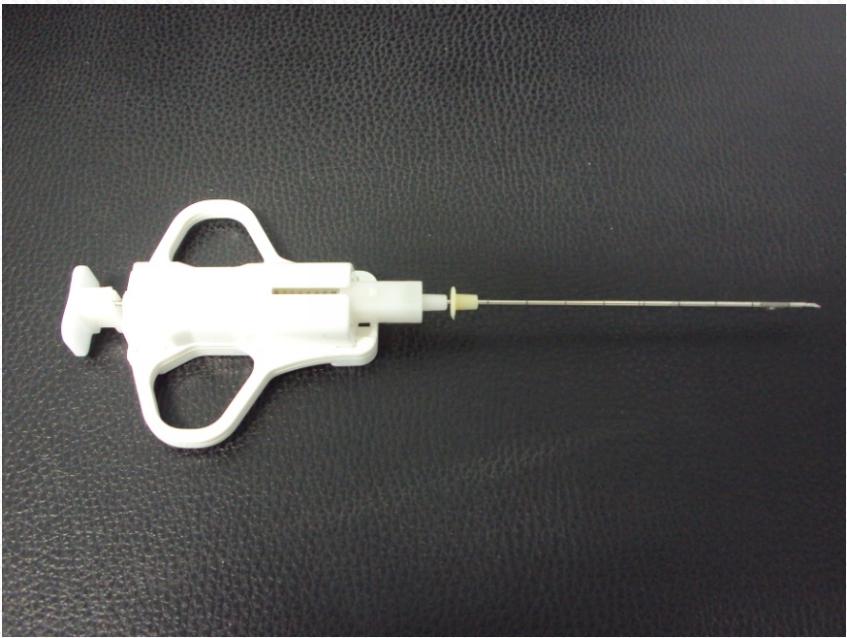
Type of malignancy

Origin of tumor	B+	C+
Total (556)	95	60
Lung (135)	91	57
Breast (101)	98	78
Mesothelioma (81)	94	41
Ovary (27)	100	83
Lymphoma (51)	86	18
Colon (18)	92	62
Kidney (24)	100	54
Others (56)	100	67
Unknown (63)	95	71

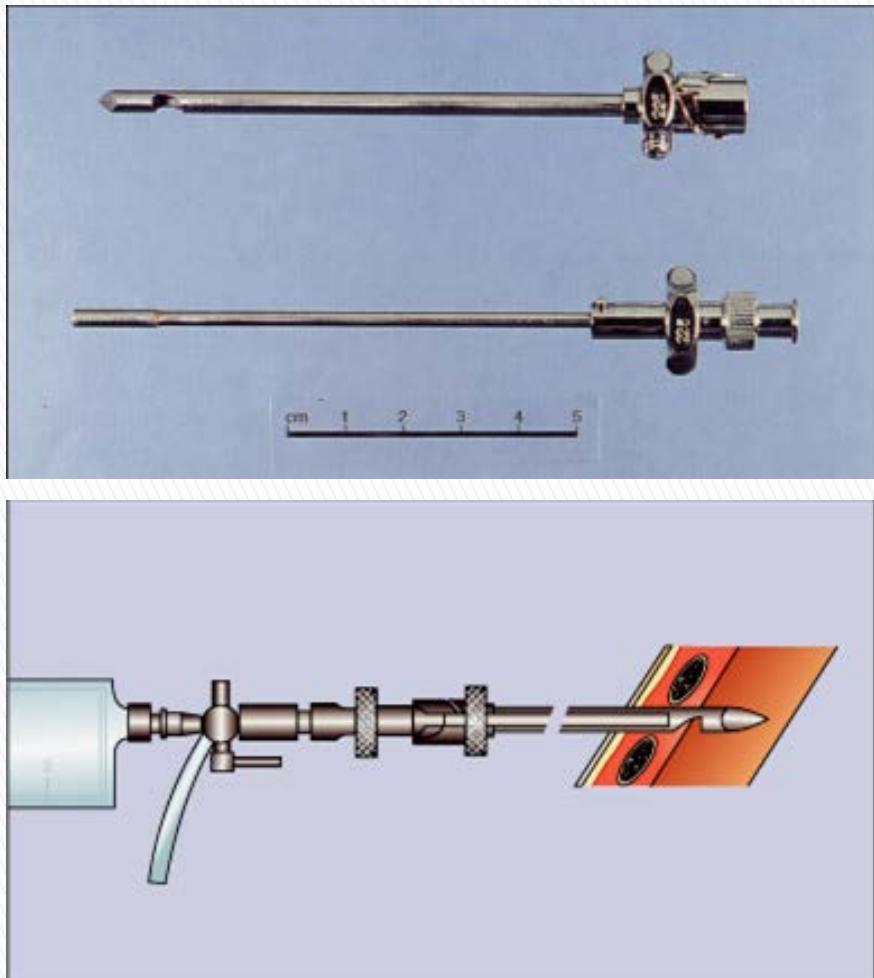
Type of malignancy

- ▶ Sensitivity: adenocarcinoma > squamous cell carcinoma, lymphoma, mesothelioma, sarcoma
- ▶ **It is not recommended** to make a diagnosis of mesothelioma based on cytology alone because of the high risk of diagnostic error (grade 1B)
- ▶ It is recommended that a cytological suspicion of mesothelioma is followed by **tissue confirmation** (grade 1B)



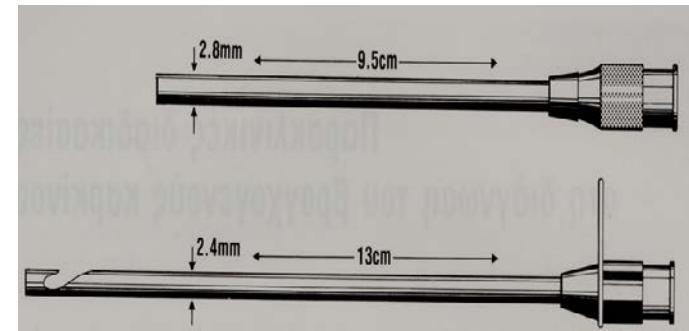
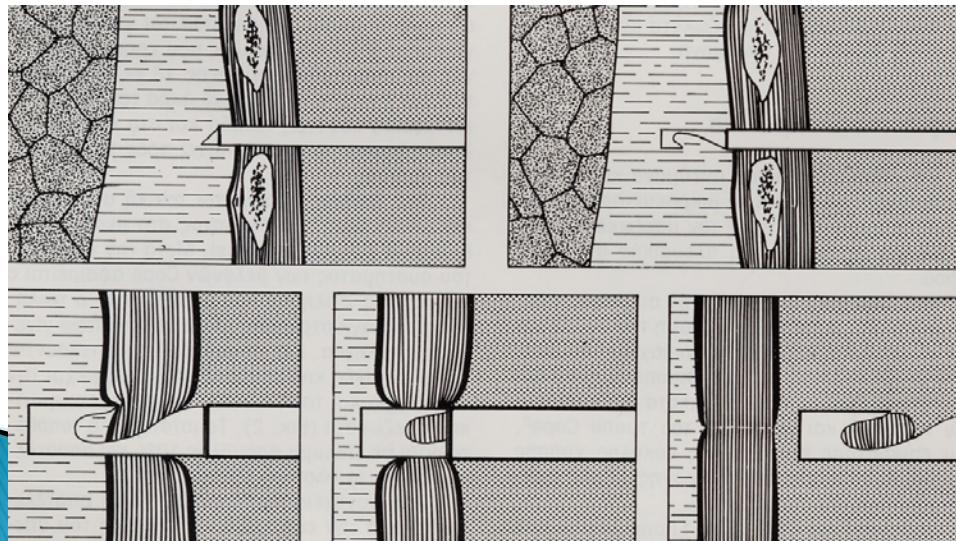
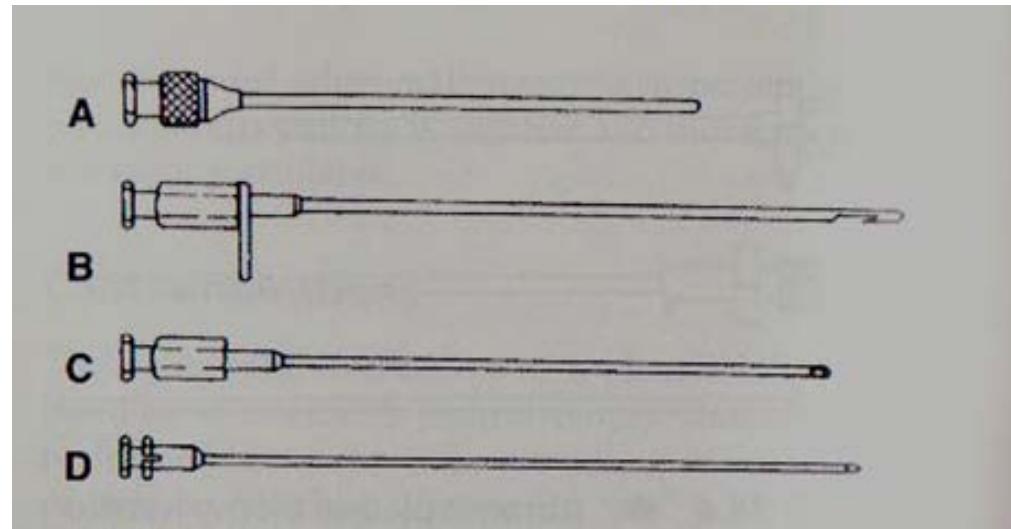


Tru-cut needle biopsy

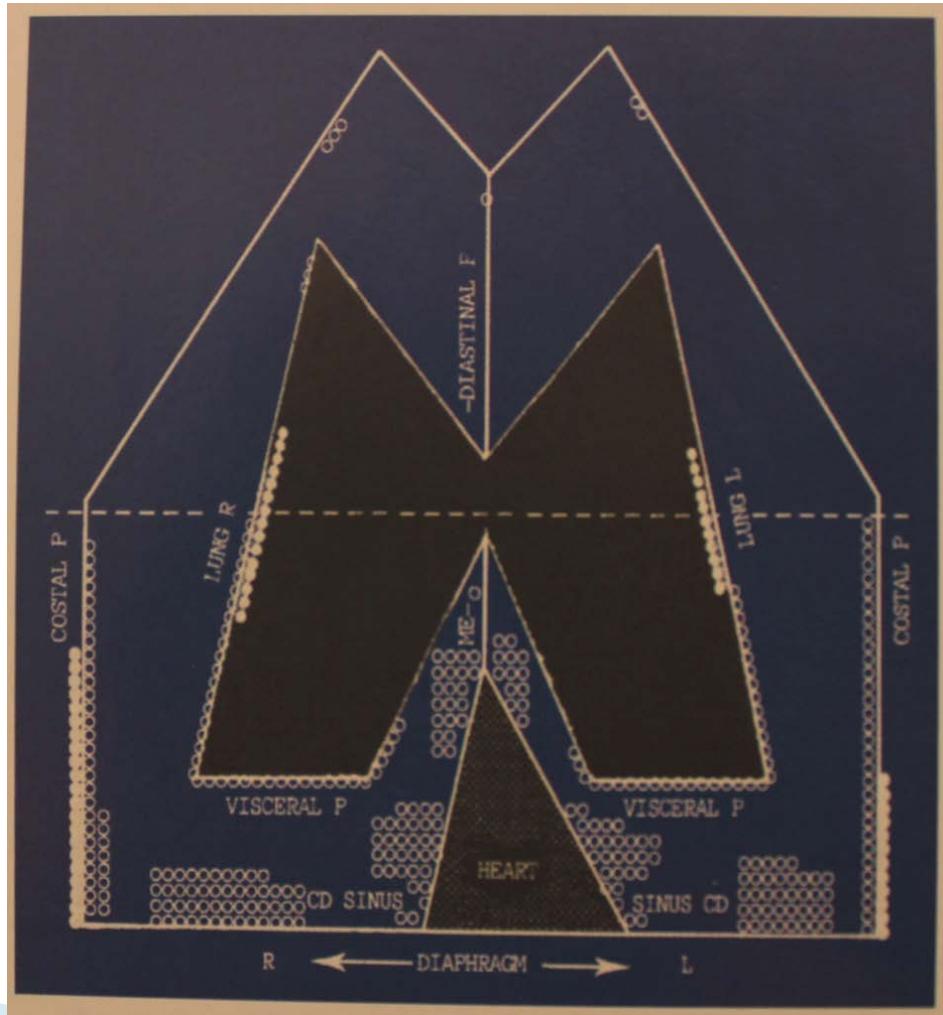


Abrams' needle

Cope needle

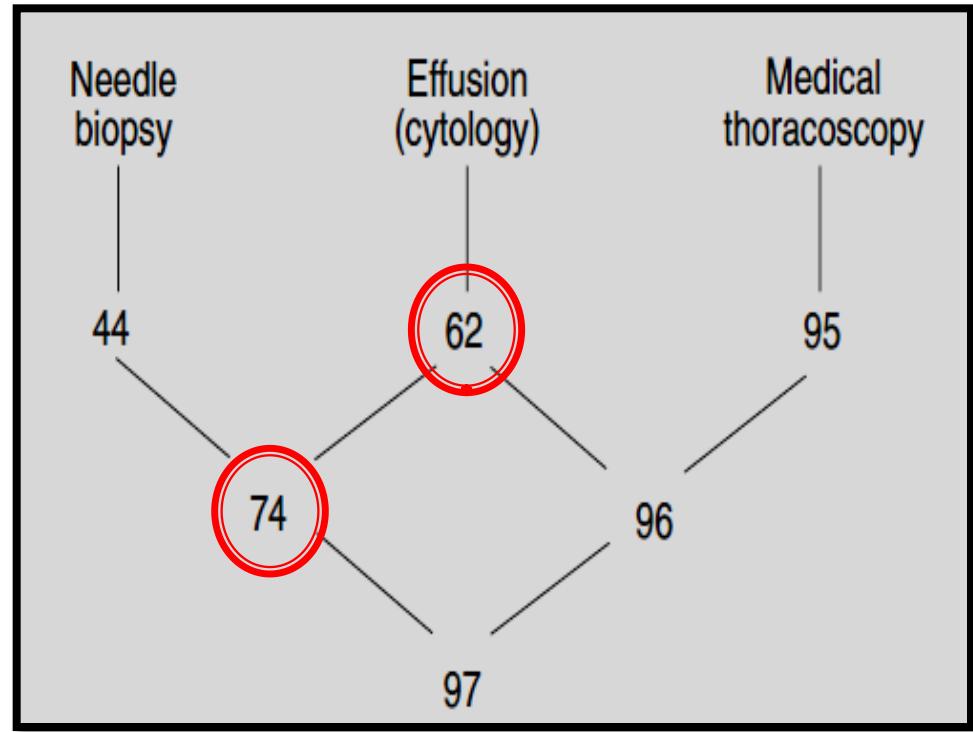


Malignant lesions and pleural topography



Blind pleural biopsy vs cytology

- 281/414 patients with malignant pleural effusions
- In only **7.1%** of them did biopsy was diagnostic when the results of cytologic study were negative for malignant disease



Closed Pleural Biopsy: Not Dead Yet!

Variables	All Initial Blind Biopsies (n = 75)	Blind Biopsies Obtaining Adequate Pleural Tissue (n = 59)
Sensitivity	38 (43)	43 (51)
Specificity	100 (100)	100 (100)
Positive predictive value	100 (100)	100 (100)
Negative predictive value	40 (51)	33 (51)

*Data are presented as % (% of malignancy).

No fatalities, 8 cases of pneumothorax
(2 cases required specific intervention)

Number of specimens with Cope needle

	General cases	Carcinoma	Tuberculosis
n	84	35	16
D ₁	35 (42%)	19 (54%)	13 (81%)
D ₂	27 (32%)	17 (49%)	7 (43%)
D ₃	36 (43%)	21 (60%)	11 (68%)
D ₄	34 (40%)	21 (60%)	9 (56%)
D ₁₊₂	41 (49%)	24 (69%)	13 (81%)
D ₁₊₂₊₃	47 (56%)	27 (77%)	14 (87.5%)
D ₁₊₂₊₃₊₄	49 (58%)	31 (89%)	14 (87.5%)

Image-guided biopsies of the pleura: one step before thoracoscopy

	Sensitivity	Specificity
Abrams' pleural biopsy (n=25) ¹	47% (malignancy)	100%
CT-guided cutting needle biopsy (n=25) ¹	87% (malignancy)	100%
CT-guided Abrams' pleural biopsy (n=62) ²	86.8% (malignancy)	
Thoracoscopy (n=62) ²	95.2% (malignancy)	
US-guided Tru-Cut biopsy (n=25) ³	70% (malignancy)	
Abrams' needle biopsy (n=24) ³	44% (malignancy)	

1. Maskell NA et al. Lancet 2003; 361: 1326-31
2. Metintas M et al. Chest 2010;137;1362-8
3. Chang DB et al. Chest 1991;100;1328-33

ΕΙΔΙΚΕΣ ΠΕΡΙΠΤΩΣΕΙΣ

ΥΠΕΖΩΚΟΤΙΚΩΝ ΣΥΛΛΟΓΩΝ

Ρευματοειδής πλευρίτιδα

- ▶ Παρατηρείται στο 3-5% των ασθενών με RA
- ▶ Είναι συχνότερη στους άντρες
- ▶ Κατά ακολουθεί μετά από χρόνια από τη διάγνωση, στο 80% συνυπάρχουν υποδόρια οζίδια
- ▶ Οι ασθενείς είναι ασυμπτωματικοί ή αναφέρουν πλευριτικό άλγος
- ▶ Είναι αμφίπλευρη σε περίπου 25% των περιπτώσεων, στο 1/3 συνυπάρχει παρεγχυματική βλάβη

Ρευματοειδής πλευρίτιδα

- ▶ Χαμηλή γλυκόζη (<40 mg/dL σε >80% των περιπτώσεων)
- ▶ Χαμηλό pH (<7.20)
- ▶ Υψηλή LDH (>700 IU/L)
- ▶ Χαμηλά επίπεδα συμπληρώματος
- ▶ Υψηλό τίτλο RF (>1:320, τουλάχιστον όσο στον ορό)

- ▶ Στην **πλευρίτιδα του SLE** οι τιμές γλυκόζης, pH και LDH κατά κανόνα δεν είναι τόσο ακραίες
- ▶ Κυτταρολογική/ιστολογική εικόνα: (a) slender, elongated or round giant multinucleated macrophages and (b) necrotic background material

Πλευρίτιδα στα παισια SLE

- ▶ Αναφέρεται στο **15-45%** των περιπτώσεων με σοβαρού βαθμού νόσο
- ▶ Είναι συχνότερη στις **γυναίκες**
- ▶ Εκδηλώνεται συνήθως με πλευριτικό άλγος το οποίο **κυριαρχεί** στην κλινική εικόνα ενώ συχνά προηγούνται αρθραλγίες ή αρθρίτιδα
- ▶ Αμφίπλευρη εντόπιση στο 50% των περιπτώσεων
- ▶ **'Άλλα αίτια** υπεζωκοτικής συλλογής σε ασθενείς με SLE: πνευμονική εμβολή, παραπνευμονική συλλογή, κακοήθεια, νεφρωσικό σύνδρομο, περικαρδιακή συλλογή, συμφορητική καρδιακή ανεπάρκεια

Pearl: it is not worth performing a pleural fluid antinuclear antibody test because serum antinuclear antibody provides the same key information

- ▶ There is no additional value in measuring PF ANA beyond the serum test to diagnose lupus pleuritis. **Negative or low titles** argue strongly against lupus as the aetiology of the effusion and other causes should be sought
- ▶ ANA υγρού $\geq 1:160$: ευαισθησία (92-100%), ειδικότητα (83%), θετικοποιείται επίσης σε εξιδρωματική παραπνευμονική και κακοήθη συλλλογή

Φάρμακα που είναι δυνατόν να προκαλέσουν υπεζωκοτική συλλογή

- ▶ Nitrofurantoin
- ▶ Dantrolene
- ▶ Ergot alkaloids
- ▶ Amiodarone
- ▶ Interleukin 2 (IL-2)
- ▶ Procarbazine
- ▶ Methotrexate
- ▶ Clozapine
- ▶ Drugs that produce the lupus-like syndrome

Γενικό πλάνο διαχείρισης ασθενών με υπεζωκοτική συλλογή

1

- Λεπτομερές ιστορικό, λήψη φαρμάκων
- Κλινική εξέταση, απεικόνιση

2

- Διαγνωστική παρακέντηση
- Τουλάχιστον 3 κυτταρολογικές σε λεμφοκυτταρικό εξίδρωμα χωρίς προφανές αίτιο

3

- Ακτινολογικά κατευθυνόμενη βιοψία, κλειστή βιοψία επί υποψίας TB
- Medical thoracascopy, VATS

Conclusions

- ▶ Medical history, clinical examination and diagnostic thoracentesis is the first step for every pleural effusion
- ▶ At least **2 specimens** (50-60 ml each) should be sent for cytology
- ▶ **Immunocytochemistry** is essential to identify the primary tumor
- ▶ Blind pleural biopsy could be considered in the **appropriate clinical setting** (e.g. possibility of TB pleuritis, no availability for thoracoscopy)
- ▶ **Image-guided** pleural biopsy is an alternative diagnostic step before thoracoscopy for visible pleural lesions

**Η υπεζωκοτική
συλλογή
υποδηλώνει
συνήθως
υποκείμενο
νόσημα**

