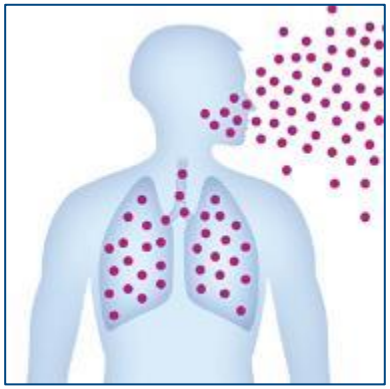
Pneumo Update Europe 2016

24-25 June, Prague

Pleural Diseases



Julius Janssen, Netherlands

Subtopics:

Spontaneous pneumothorax

Diagnosis of pleural effusion

Treatment of pleural effusion

Spontaneous Pneumothorax

State of the Art

- About treatment of spontaneous pneumothorax , much is said and little is evidence based.
- Primary spontaneous pneumothorax (PSP) is defined as Pneumothorax in normal lungs.
- Secondary spontaneous pneumothorax (SSP) is pneumothorax with underlying lung disease.

State of the Art

- Lack of well-designed prospective studies.
- Guidelines are limited, and are not strictly followed.
- Optimal Treatment is not well defined:
  - role of surgical treatment: 1st or recurr. PTX?
  - Ambulatory treatment?
  - Spontaneous resolution?
- Epidemiology data are scarce

Epidemiology of spontaneous pneumothorax (PTX)

- Review of patients hospitalised for non-traumatic PTX France 2008-11

- 42.500 patients; 59.600 hospital stays

- Annual rate PTX 22,7/100.000
- 28% recurrence rate

Bobbio A et al. Thorax 2015;70:653-658

Epidemiology of spontaneous pneumothorax (PTX):gender related differences

- Women/ men ratio; 1:3.3
- Mean age: women 41y, men 37y
- In the group < 30 y, no gender differences
  - Type of PTX (primary, secondary)
  - Hospitalisation unit
  - Treatment modality
  - ICU stay
  - Hospital stay

Bobbio A et al. Thorax 2015;70:653-658

Epidemiology of spontaneous pneumothorax (PTX):gender related differences

- Secondary PTX:
  - men 16%,
  - women 13%
- Surgical procedure:
  - men 24%,
  - women 23%
- Hospital stay: men 10.1, women 9.5 days

Bobbio A et al. Thorax 2015;70:653-658

Epidemiology of spontaneous pneumothorax (PTX)

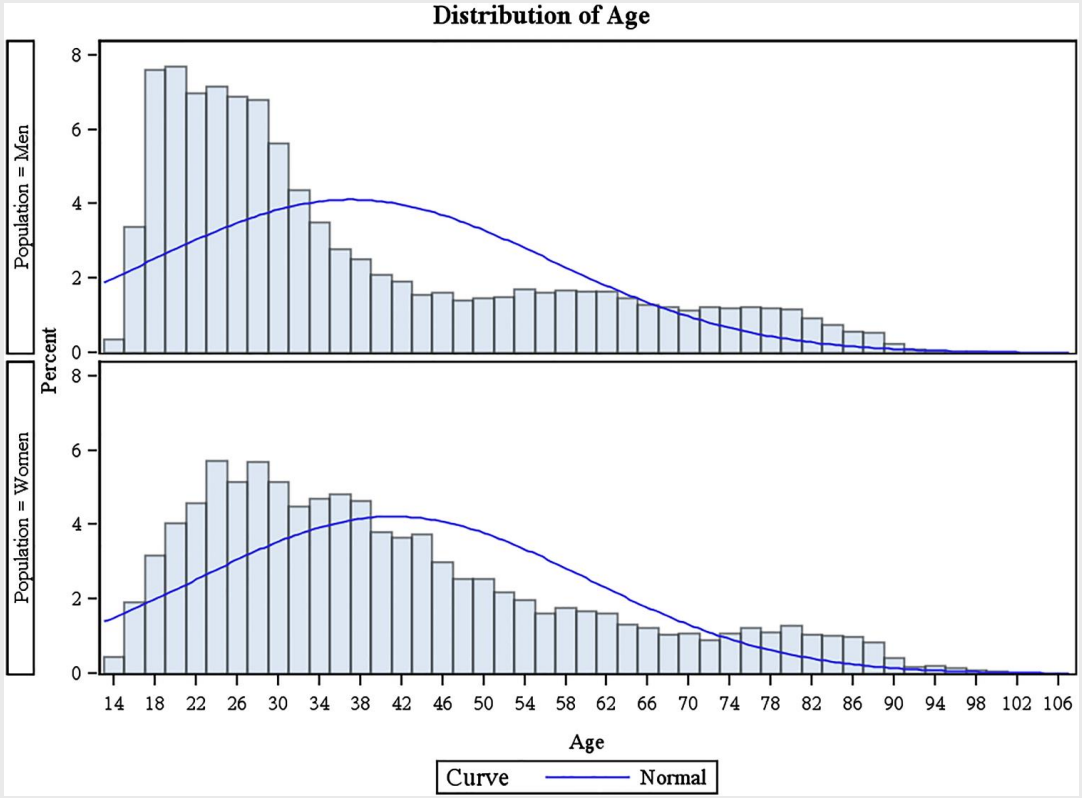


Figure 1 Distribution of hospitalisations for spontaneous pneumothorax with respect to sex and age class. Each bar represents a 2-year age class.

Bobbio A et al. Thorax 2015;70:653-658

Epidemiology of spontaneous pneumothorax (PTX)

Table 4 Comparison of hospitalisation characteristics between idiopathic and secondary pneumothorax

Characteristics	Overall N=59 637	Idiopathic N=50 596	Secondary N=9041	p Value
Age (years), mean (SD)	38 (19)	35 (18)	53 (20)	<0.0001
Sex, male, n (%)	45 711 (77%)	38 508 (76%)	7203 (80%)	<0.0001
Place of hospitalisation				<0.0001
Surgical ward	16 236 (27%)	12 938 (26%)	3298 (36%)	
Medical ward	43 401 (73%)	37 658 (74%)	5743 (64%)	
Intensive or intermediate care unit	16 057 (27%)	12 456 (25%)	3601 (40%)	<0.0001
Surgical treatment	14 352 (24%)	11 398 (23%)	2954 (33%)	<0.0001
Hospitalisation duration, days, median (Q1, Q3)	7.0 (9.0)	6.1 (7.2)	12.2 (14.5)	<0.0001
Rehospitalisations, n (%)	29 126 (49%)	24 432 (48%)	4694 (52%)	<0.0001

Bobbio A et al. Thorax 2015;70:653-658

Epidemiology of spontaneous pneumothorax (PTX)

- Striking lack of SSP: 14%
  - (previous estimations : 50%)

- Peak incidence between 20-30 yrs
- No second age peak incidence 55yrs.
  - Contrary to previous data

Bobbio A et al. Thorax 2015;70:653-658

Initial management of primary spontaneous pneumothorax (PSP)with VATS

- In 10 years, 185 patients with 1st episode of PSP treated with wedge resection and pleurectomy
- Subpleural emphysema like changes found in every resection specimen
- Mean follow up 33 months; recurrence rate 2.2%
- Procedure related morbidity 7.6%
- Patient satisfaction score: 86%

Hermann et al. Eur J Cardiothorac Surg 2016;49:854-59

Are we ready to go to surgery for first episode of spontaneous PTX?

- Significant morbidity (21% paresthesia, 17% pain > 12 weeks)
- Mortality 1.6% (> 55y)
- French epidemiology study: 28% recurrence rate.
- Surgery is overtreatment in 72%.
- Thoracoscopy / Talc pleurodesis is cheaper, less complications, same result

Treasure et al. Eur J Cardiothorac Surg 2016;49:860-61

Spontaneous PTX: are we treating the X-ray or the patient?

- There is no consensus about the need for drainage of a large pneumothorax.
- In case of a completely collapsed lung, without symptoms, many would still perform drainage for quick re-expansion.
- conservative management is possibly the preferred option in patients with minimal symptoms, even with complete PTX.

A. Kelly. HongKong J Emerg. Med 2015;22:135-36

Spontaneous pneumothorax: time to rethink management?

- Reclassification of primary (PSP) and secondary (SSP) spontaneous pneumothorax?
  - classification of PSP and SSP 1932; importance to exclude tuberculosis (‚SSP‘)
  - Today COPD most important SSP
  - In PSP, majority has emphysema like changes, not ‚normal lungs‘.

Bintcliffe et al. Lancet Resp Med 2015;3:578-588

Spontaneous pneumothorax: time to rethink management?

- Primary PTX is probably a misconception
- Primary and secondary PTX are the extremes of a spectrum of emphysema like changes, causing pneumothorax
- A relation of the degree of lung abnormality and recurrence rate should be assessed, for better tailoring of surgical treatment / thoracoscopy

Bintcliffe et al. Lancet Resp Med 2015;3:578-588

Spontaneous pneumothorax: time to rethink management?

- We need studies to tailor treatment according to risk stratification of recurrence/prolonged airleak.

- Which patient with Spontaneous PTX:
  - Can be managed conservatively
  - Can be managed as outpatient (with heimlich valve)
  - Should get surgical treatment or talc pleurodesis at the first episode to prevent recurrence
  - Will profit from digital air-leak measurement

Bintcliffe et al. Lancet Resp Med 2015;3:578-588

Take-Home Message

- Patient selection still unclear for
  - Conservative -
  - Outpatient -
  - Surgical/talc pleurodesis management

- Randomised controlled trials are on the way

Diagnosis of pleural effusion

Diagnosis of pleural effusion: State of the Art

- Thoracocenthesis and analysis of pleural effusion (biochemistry, cytology) is the first step if it is an exudate
- Malignant pleural effusion is sometimes misclassified as a transudate
- Blind pleural biopsy is obsolete, because of low diagnostic yield
- In case of exudate of unknown origin, diagnostic thoracoscopy will provide the diagnosis in >90% of cases

Diagnosis of pleural effusion: State of the Art

- Thoracoscopy is an in-hospital procedure
- In the developed world, tuberculous pleural effusion is rare, and can be difficult to diagnose
- Tumor markers in pleural effusion are not very helpful in the diagnosis
- A specific diagnosis of benign disease is rare after thoracocenthesis

Diagnosis of pleural effusions

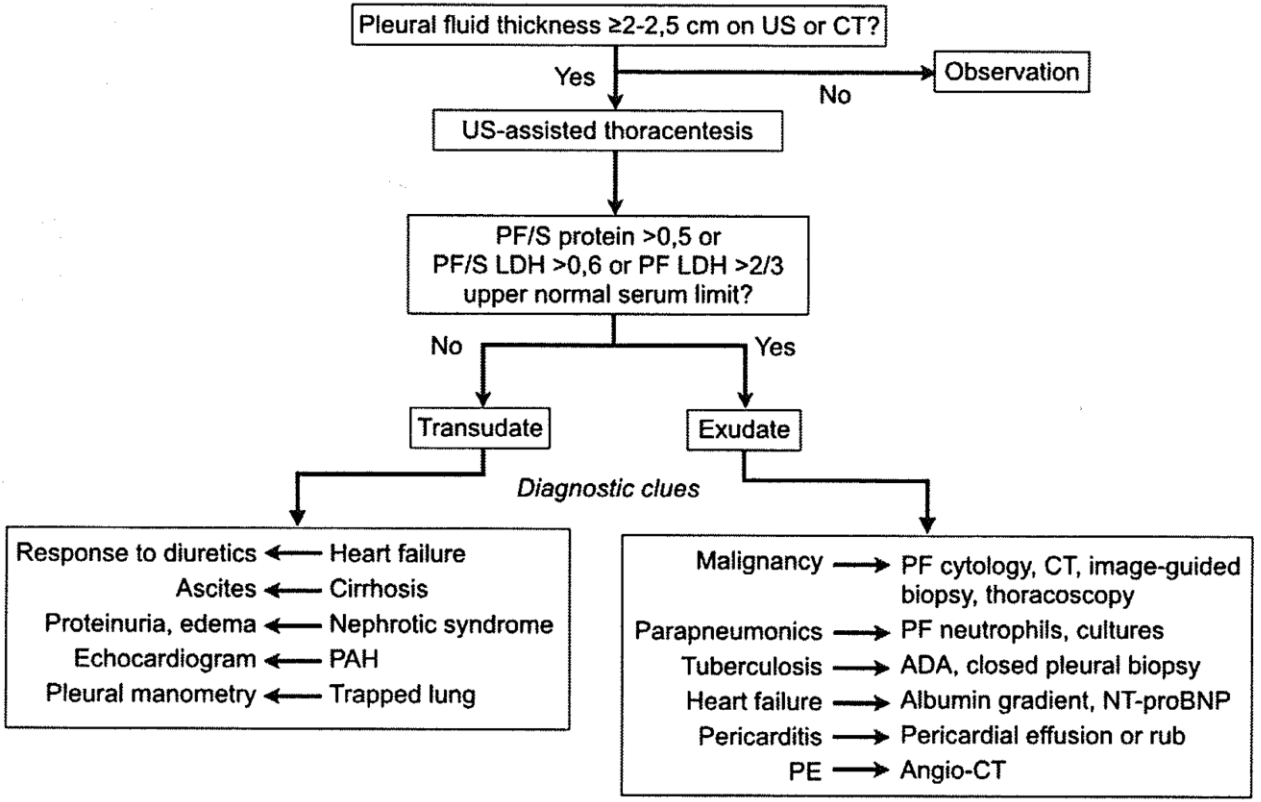


Figure 1. Approach to the diagnosis of pleural effusions.[1,6]
ADA, adenosine deaminase; CT, computed tomography; LDH, lactate dehydrogenase; NT-proBNP, amino terminal fraction of pro-brain natriuretic peptide; PAH, pulmonary arterial hypertension; PE, pulmonary embolism; PF, pleural fluid; PF/S, pleural fluid to serum; US, ultrasonography.

Porcel et al. Expert Review 2015;9: 801-15

Unilateral pleural effusions (PE) with more than one apparent etiology

- Prospective observational study
- Follow up 12 months in 126 patients
- 88 patients (70%) single cause for PE
- 38 patients (30%) multiple causes
- Serum NT pro-BNP > 1500 pg/ml predictive multiple etiology
- 13 patients with MPE had BNP >1500

Bintcliffe et al. Annals ATS epub april 2016

ADA in diagnosis of pleural effusion in low incidence population

- In high TB incidence populations, pleural fluid Adenosine deaminase (ADA) is helpful in the diagnosis of pleural TB, with good spec/sens.

- In low TB populations, the evidence is unknown

- 338 patients with exudate, in low TB region (SW England), 7 (2%) confirmed pleural TB

Arnold et al. PLoS ONE 10(2): e0113047

ADA in diagnosis of pleural effusion in low incidence population

- All TB effusions were lymphocyte predominant, median ADA: 72 IU/L
- Population median ADA: 12 IU/L
- Optimal ADA cut off: 35 IU/L
- NPV 99.7%, sensitivity 85.6%

Arnold et al. PLoS ONE 10(2): e0113047

ADA in diagnosis of pleural effusion in low incidence population

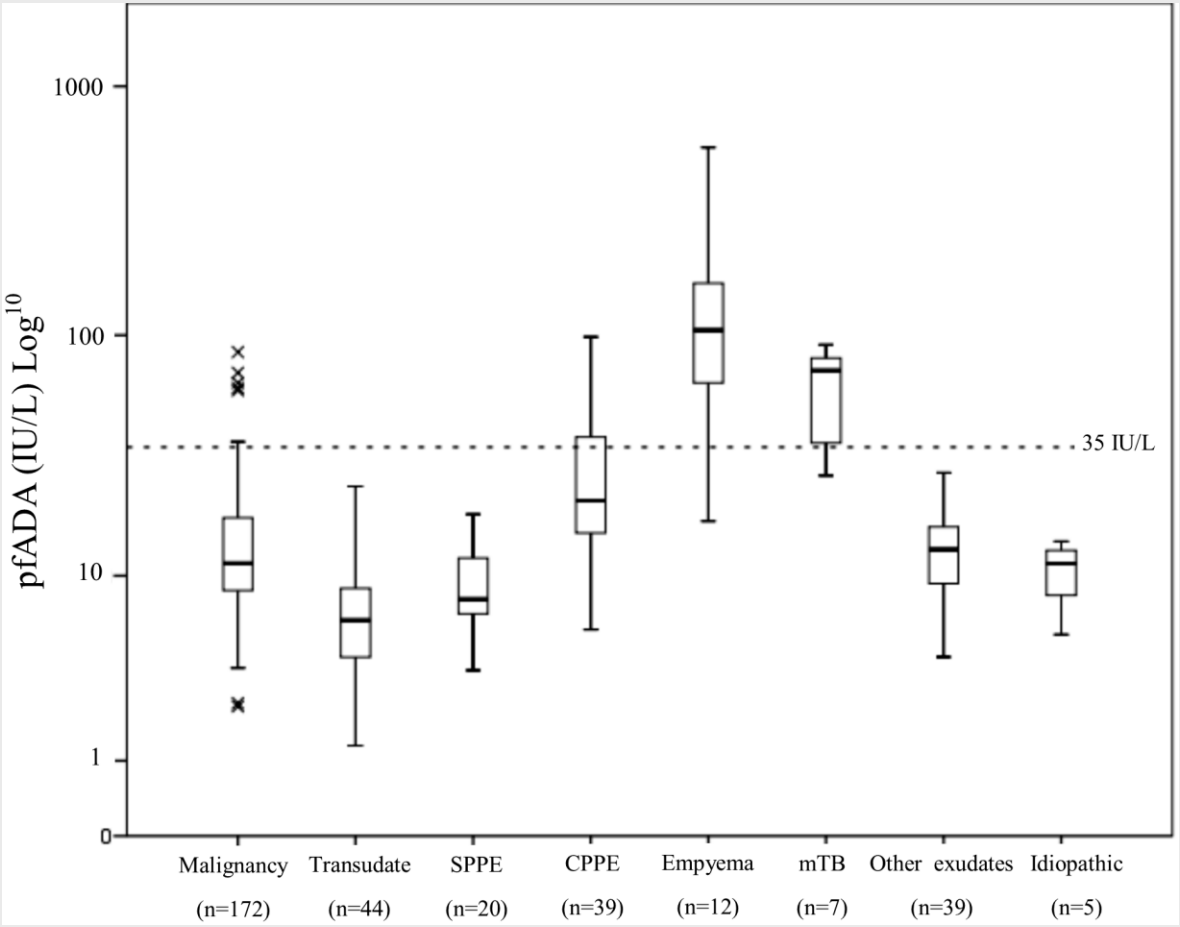


Fig 1. Boxplot of pfADA levels by diagnostic category for all effusions (n = 338). Abbreviations; SPPE—Simple parapneumonic effusion, CPPE—Complicated parapneumonic effusion, mTB—mycobacterium tuberculosis.

Arnold et al. PLoS ONE 10(2): e0113047

ADA in diagnosis of pleural effusion in low incidence population

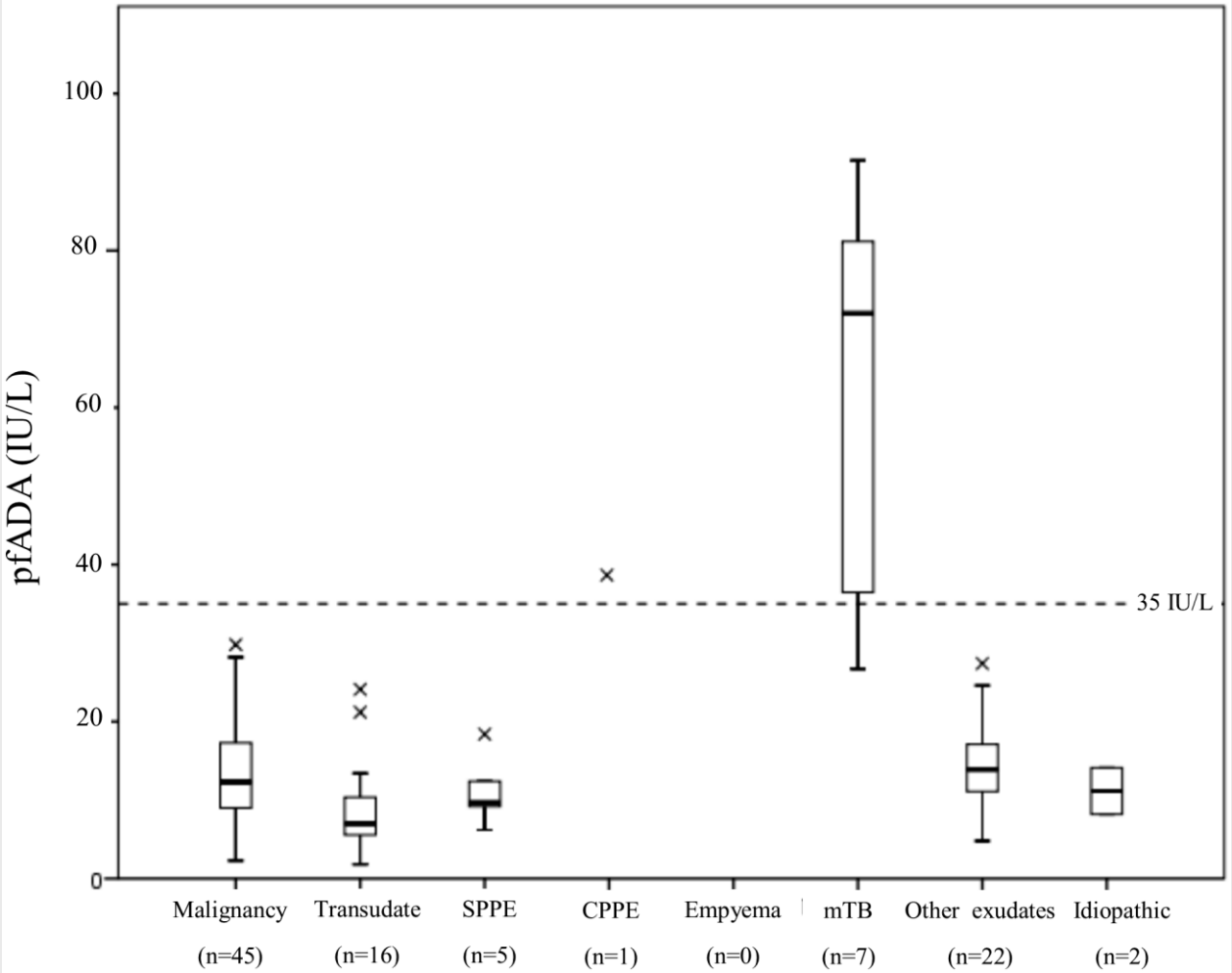


Fig 2. Boxplot of pfADA levels by diagnostic category for lymphocyte predominant effusions (n = 98). Abbreviations; SPPE—Simple parapneumonic effusion, CPPE—Complicated parapneumonic effusion, mTB—mycobacterium tuberculosis.

Arnold et al. PLoS ONE 10(2): e0113047

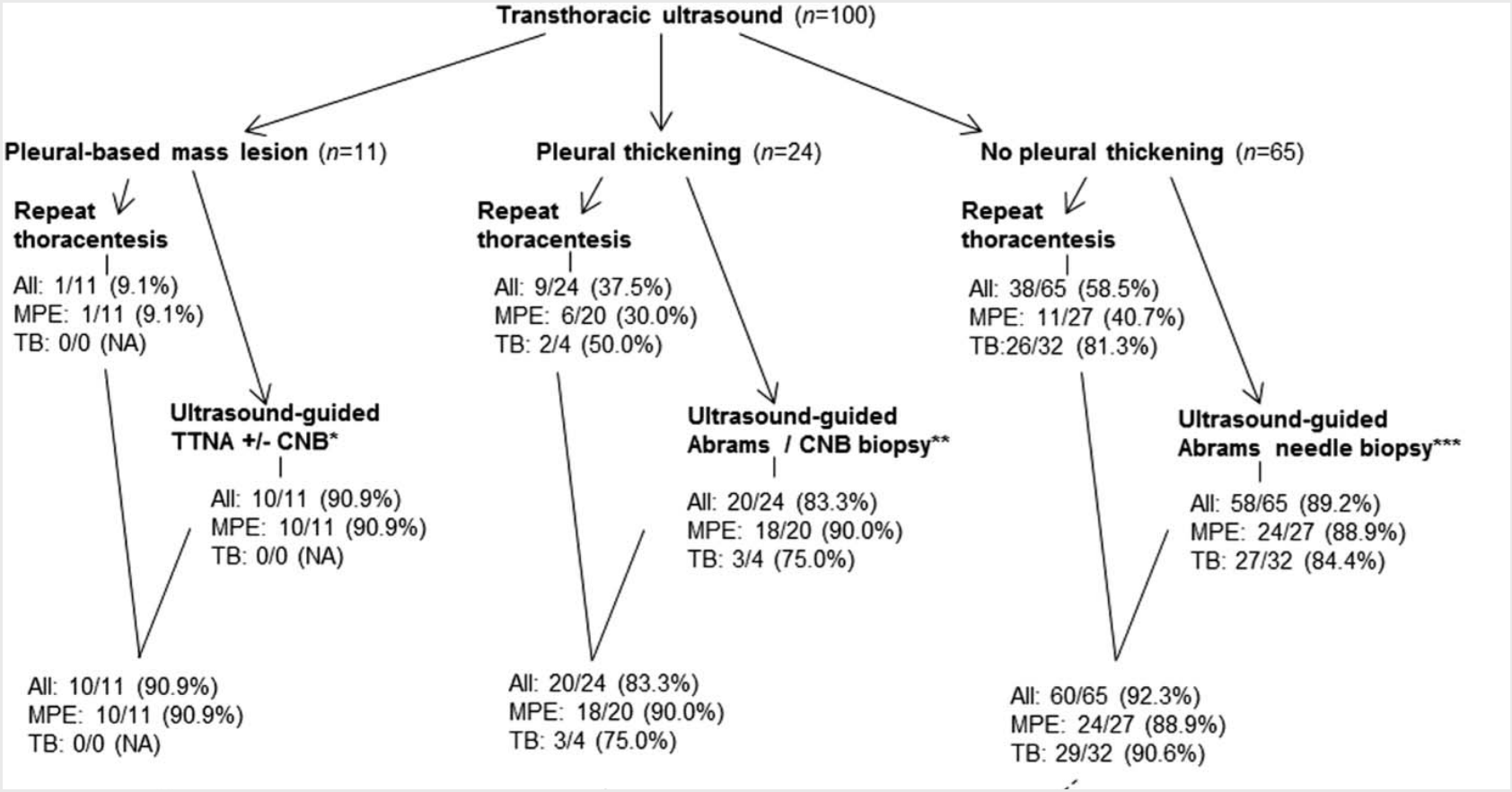
Utility of ultrasound-guided thoracocenthesis and pleural biopsy in undiagnosed pleural exudates

Prospective study of 100 patients, exudative pleuritis, (high TB prevalence area) undiagnosed after 1st thoracocenthesis

2nd thoracocenthesis: (US guided)	Plus US guided biopsy:
• Diagnost. yield 48%	• Diagnost. yield 90%
• Malignancy 31%	• Malignancy 90%
• TB 78%	• TB 89%

Koegelenberg. Thorax 2015;70:995-997

Utility of ultrasound-guided thoracocenthesis and pleural biopsy in undiagnosed pleural exudates



Koegelenberg. Thorax 2015;70:995-997

Utility of ultrasound-guided thoracocenthesis and pleural biopsy in undiagnosed pleural exudates

Prospective study of 100 patients, exudative pleuritis,
undiagnosed after 1st thoracocenthesis

- No diagnosis in 10%, 4 non-specific pleuritis
- Thoracoscopy:
  - Diagnosis obtained in 86% (5 MPE, 4 TB)

Koegelenberg. Thorax 2015;70:995-997

Diagnostic value of tumor antigens in malignant pleural effusion

- Reliable tumor markers in Malignant pleural effusion would be very helpful
- Review of 49 studies.
- Tumor markers: CEA, CA, CA19-9, CA 125, CYFRA, NSE.
- All markers exhibit high specificity (>90%)
- All markers had low sensitivity (37-62%)
- Insufficient accuracy for clinical use

Nguyen et al. Translational research 2015; 166:432-39.

Take-Home Message

- After 45 years, Light‘s criteria are still the best to discriminate exudate from transudate.
- ADA is helpful in the diagnosis of TB in low incidence population.
- 1/3 patients may have more than one cause of unilateral pleural effusion, mostly heart failure
- Thoracic ultrasound increases the diagnostic yield of thoracocenthesis and closed pleural biopsy.
- The sensitivity of pleural tumor markers is too low for reliable use in clinical practice.

Treatment of pleural effusion

Treatment of pleural effusion State of the Art

- NSAIDS should not be used before and after talc pleurodesis, they suppress the inflammation proces.
- In pleural drainage, small bore tubes are prefered; these are less painful and equally effective as large bore drains.
- The use of indwelling pleural catheters in chemotherapy patients should be avoided.
- Patients with indwelling pleural catheters may develop symptomatic pleural loculations

Effect of NSAIDS / large vs small chest tubes on talc pleurodesis efficacy in malignant pleural effusion

- 206 patients thoracoscopy, 103 opioids, 103 NSAIDS
- 114 Non-thoracoscopy patients split in 4 groups:
  - 24F chest tube and opioids (28)
  - 24F chest tube and NSAIDS (29)
  - 12F chest tube and opioids (29)
  - 12F chest tube and NSAIDS (28)
- Endpoints: 1. VAS Pain score
  2. pleurodesis efficacy 3 mths.

Rahman et al. JAMA 2015;314:2641-53

Effect of NSAIDS / large vs small chest tubes on talc pleurodesis efficacy in malignant pleural effusion

- Pain scores in the opiate group vs. The NSAIDS group were not significantly different.

- NSAIDS group needed more rescue analgesia

- Pain scores were lower in 12F tube group

Rahman et al. JAMA 2015;314:2641-53

Effect of NSAIDS / large vs small chest tubes on talc pleurodesis efficacy in malignant pleural effusion

- Pleurodesis failure occurred in 23% in NSAIDS group and 20% in opiate group (ns)

- 12F chest tubes were associated with higher pleurodesis failure vs 24F tubes: 30% vs 24%

  (failure of noninferiority criteria)

- Complications during chest tube insertion occurred more in 12F tubes (24% vs 14%)

Rahman et al. JAMA 2015;314:2641-53

Use of Indwelling pleural catheters (IPC) for recurrent pleural effusions in patients with hematologic malignancies

- Retrospective study of 91 patients
- 62% lymfoma, 21% leukemia
- Active chemotherapy treatment
- IPC for recurrent pleural effusion
- In situ dwell time mean 90 days

Gilbert et al. Chest 2015;148:752-58

Use of Indwelling pleural catheters (IPC) for recurrent pleural effusions in patients with hematologic malignancies

- Complications:
  - 7 (7.7%) pleural infections
  - 2 patients died of septic shock
- Complication rate similar to previous studies, despite active chemotherapy
- IPC is a reasonable clinical option for PE in immunosuppression due to chemotherapy

Gilbert et al. Chest 2015;148:752-58

Intrapleural fibrinolysis for symptomatic IPC related loculations

- Indwelling pleural catheters (IPC) are effective in management of malignant pleural effusion
- 14% develop symptomatic loculations

- 66 patients with loculations had fibrinolytic instillations of TPA (52), urokinase (12), streptokinase (2)
- 70% received only one dose

Thomas R et al. Chest 2015;148:746-51.

Intrapleural fibrinolysis for symptomatic IPC related loculations

- Pleural fluid drainage increased in 93%
- Dyspnea improved in 83%
- Area of opacity on chest x-ray decreased from 52% to 31% of the hemithorax
- 2 cases (3%) of non-fatal pleural bleeding

- Conclusion: Intrapleural fibrinolysis can be effective in IPC, optimal patient selection and dosing regimen are not clear yet

Thomas R et al. Chest 2015;148:746-51.

Survival in patients with IPC for MPE who developed pleural infection

- Of 672 IPC‘s inserted, 25 infected (3.7%)

- Median survival infection was longer than control group (386 vs 132 days)
- Median survival of mesothelioma and infection was twice as long (753 vs 339 days)
- Pleural infection in patients with IPC for MPE is associated with longer survival.

Bibby et al. Chest 2015;148:235-41

Take-Home Message

- NSAIDS do not reduce pleurodesis effectivity
- Small bore chest tubes were associated with higher pleurodesis failure rate.
- IPC in haematologic malignancy is safe
- Intrapleural fibrinolysis in IPC is feasable and effective.
- Pleural infection during IPC treatment of MPE seems to prolong survival in mesothelioma.

List of References

1. Bobbio et al. Thorax 2015;70:653-658
2. Hermann et al. Eur J Cardiothorac Surg 2016;49:854-59
3. Treasure et al. Eur J Cardiothorac Surg 2016;49:860-61
4. Kelly. HongKong J Emerg. Med 2015;22:135-36
5. Bintcliffe et al. Lancet Resp Med 2015;3:578-588
6. Porcel et al. Expert Review 2015;9: 801-15
7. Bintcliffe et al. Annals ATS epub april 2016
8. Arnold et al. PLoS ONE 10(2): e0113047
9. Koegelenberg. Thorax 2015;70:995-997
10. Nguyen et al. Translational research 2015; 166:432-39.
11. Rahman et al. JAMA 2015;314:2641-53
12. Gilbert et al. Chest 2015;148:752-58
13. Thomas et al. Chest 2015;148:746-51.
14. Bibby et al. Chest 2015;148:235-41

List of Abbreviations

- PSP primary spontaneous pneumothorax
- SSP secondary spontaneous pneumothorax
- PTX pneumothorax
- VATS video-assisted thoracic surgery
- PE pleural effusion
- ADA adenosine d-aminase
- US ultrasound
- IPC indwelling pleural catheter
- TPA tissue –plasminogen activator
- MPE malignant pleural effusion