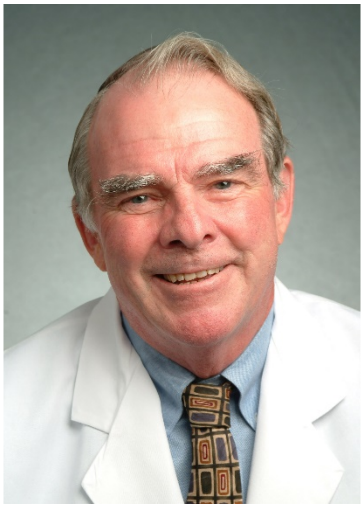
CALIFORNIA THORACIC SOCIETY
SOUTHERN CALIFORNIA
ANNUAL EDUCATIONAL CONFERENCE

ADVANCES IN DIAGNOSIS AND MANAGEMENT OF PLEURAL DISEASES

SATURDAY AFTERNOON
OCTOBER 5, 2019



Pleural disease: Review of Anatomy, Physiology and Pleural Fluid Analysis

Richard Light, MD
Vanderbilt University

Saturday, October 5, 2019 – 1:00 p.m. – 1:30 p.m.

Professor Richard Light was born in Steamboat Springs, Colorado, the son of a fox and mink farmer. He then attended medical school at Johns Hopkins University, USA from 1964 to 1968 and subsequently did his training in internal medicine and pulmonary diseases at that institution. He then spent nearly 20 years at the University of California Irvine, USA where his positions included Chief of the Pulmonary Diseases Section and Associate Chief of Staff for Research at the Veterans Administration Hospital in Long Beach. Dr. Light moved to Vanderbilt University, USA 22 years ago and is presently Professor of Medicine at Vanderbilt University in Nashville, Tennessee.

Dr. Light is best known for his research on pleural disease. He developed Light's criteria for the separation of transudates and exudates in 1972. Subsequently, he has published many papers concerning the pathogenesis, diagnosis, and management of pleural disease. Dr. Light is the editor of 16 books of which the two most famous are the single authored monograph *Pleural Diseases,* which is now in its sixth edition, and *The Textbook of Pleural Disease,* which he edits in conjunction with Dr. YC Gary Lee and is in its third edition. Dr. Light has been an author on more than 450 articles and has spoken in 57 countries.

Review of Anatomy, Physiology and Pleura Fluid Analysis

California Thoracic Society
Southern California
2019 Annual Educational Conference
October 4 – 5, 2019

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Disclosures

None

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Divisions of the Pleura

- Parietal pleura covers
  - Inside of thoracic cavity – costal pleura
  - Diaphragm – diaphragmatic pleura
  - Mediastinum – mediastinal pleura
- Visceral pleura covers
  - Lung
  - Interlobar fissures

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Nerves and the Pleura

- Sensory nerve endings are present in the costal and diaphragmatic parietal pleura
  - Supplied by the intercostal nerves
  - Stimulation of this pleura results in pain
- Visceral pleura contain no sensory nerve endings
  - Can be manipulated without causing pain
- Pleuritic pain indicates inflammation of the parietal pleura

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STARLING'S EQUATION AND PLEURAL FLUID EXCHANGE

$$Q_f = L_p * A\{(P_{cap} - P_{pl}) - \sigma_d(\pi_{cap} - \pi_{pl})\}$$

Q_f = liquid movement

L_p = filtration coefficient/unit area

A = surface area of the membrane

P = hydrostatic pressure

π = oncotic pressure

σ_d = solute reflection coefficient

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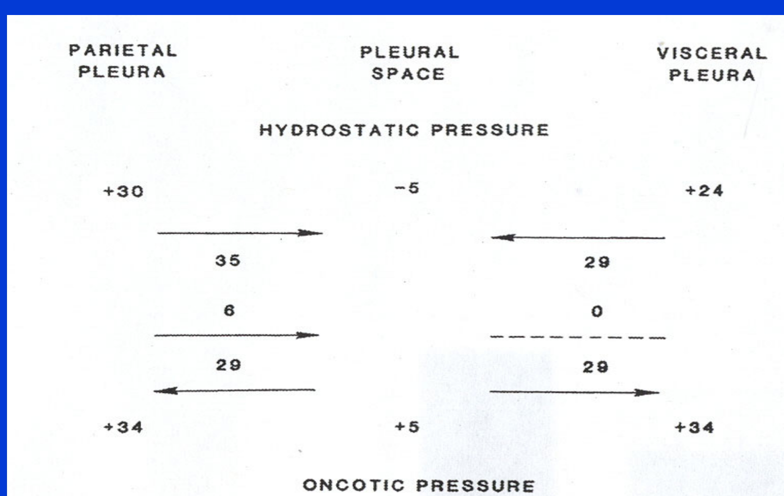
FLUID EXCHANGE IN ANIMALS WITH A THICK PLEURA SHEEP AND MAN



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WHERE DOES PLEURAL FLUID ORIGINATE?

- Normally the rate of pleural fluid formation is about 0.01 ml/kg/hr.
  - 20x less than the capacity of the lymphatics
- Source of fluid is parietal pleura
- In disease states, where does the fluid come from that overwhelms the capacity of the lymphatics and leads to a pleural effusion?
- The source of the fluid is the interstitial spaces of the lung in many cases
  - 20% of the fluid that enters the interstitial spaces in the lungs exits through the pleural space

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Pleural Fluid Absorption

- Pleural fluid absorption occurs via bulk flow
- The fluid exits the pleural space via the lymphatics in the parietal pleura
- Fluid enters the lymphatics through lacunae in the parietal pleura
- Capacity for fluid removal is approximately 0.25 ml/kg/hr
  - 360 ml/24 hours for 60 kg individual

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Pleural Effusion Occurs When Rate Of Pleural Fluid Formation Exceeds Capacity Of Lymphatics To Remove Fluid

- Increased formation
  - Increased interstitial fluid in lungs
  - Increased intravascular pressures in pleura
  - Increased pleural fluid protein level
  - Decreased pleural pressure
  - Increased fluid in peritoneal cavity
  - Ruptured thoracic duct (chylothorax)
  - Ruptured blood vessel (hemothorax)
- Decreased absorption
  - Lymphatic obstruction parietal pleura
  - Diseased lymph nodes
  - Increased systemic vascular pressure

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Transudative Pleural Effusion

Occurs when the systemic factors influencing the formation of pleural fluid are altered such that pleural fluid accumulates

Fluid may originate in the lung, pleura or peritoneal cavity

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Exudative Pleural Effusion

Occurs when the local factors influencing the accumulation of pleural fluid are altered such that a pleural effusion develops

Most common cause is increased capillary permeability in the lung leading to increased interstitial fluid

Other mechanisms for exudative pleural effusions include:

- Obstruction of the lymphatics in the pleura
- Increased capillary permeability of the pleura or of structures in the peritoneal cavity

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Why Separate Transudates from Exudates

- If patient has a transudative pleural effusion (usually heart failure or cirrhosis), then treat the cause of the effusion
- If patient has an exudative effusion, more investigation is indicated to determine what the local problem is that is causing the pleural effusion

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SEPARATING TRANSUDATES AND Exudates
Light's Criteria

An exudate meets one or more of the following criteria while a transudate meets none:

- Pleural fluid/serum protein > 0.5
- Pleural fluid/serum LDH > 0.6
- Pleural fluid LDH > two-thirds of upper normal limit for serum

  - Light RW et al. Ann Intern Med l972; 77:507-514.

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Do We Need Biochemical Tests?

For 249 patients, two physicians classified effusion as transudate or exudate just before thoracentesis

185 exudates and 64 transudates

Correct	Exudates	Transudates
Clinical	94%	56%
Light's criteria	99.5%	75%

ROMERO ET AL: CHEST 2002; 122:1524-1529

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Diuretics And Transudative Effusions

- Studied 21 patients with thoracentesis q 48 hrs after diuretics
  - 3 or more thoracenteses in 15 patients
- Changes in chemistries
  - Proteins increased from 2.3 to 3.3 gm/dl
  - LDH increased from 177 to 288 IU/l
  - Chol increased from 1304 to 1884
- After diuresis Light's criteria would misclassify majority as exudates
  - Romero-Candeira et al. Am J Med 2001; 110:681

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How Do We Identity True Transudates When Exudative Criteria Met?

Two Proposed Tests (Transudate)

Gradient = Serum Value – Pleural Fluid Value

- Protein Gradient > 3.1 Gm/Dl
- Albumin Gradient > 1.2 Gm/Dl

	Exudates	Transudates
Clinical	94%	56%
Light's Criteria	99.5%	75%
Protein Grad	84%	91%
Albumin Grad	88%	86%

Romero Et Al: Chest 2002; 122:1524-1529

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Recommendations - 2018

- Initially use Light's criteria to determine if transudate or exudate
- If patient clinically should have a transudative effusion, but Light's criteria are met by a small margin (PR < .65, LDH ratio < 0.9, LDH < upper normal limit for serum), look at gradient between serum and pleural fluid protein
- Gradient above 3.1 g/dl indicates transudate

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BNP and NT-pro BNP

- Biologically active pro-brain natriuretic peptide (BNP) and the larger aminoterminal part NT-pro-BNP are released in equimolar amounts in the circulation when the cardiac ventricles are subjected to increased pressure or volume loads.

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N Terminal Probrain Natriuretic Peptide (NT-proBNP)

- Comes from ventricles when there is a ventricular volume or pressure overload
- Pleural fluid NT-proBNP levels are useful in identifying effusions due to CHF
  - CHF (N = 44) 6931
  - CIRRHOSIS (N = 10) 551
  - MALIGNANCY (N = 25) 347
  - TUBERCULOSIS (N = 20) 101
  - PARAPNEUMONIC (N=13) 515
- NT-pro BNP >1500 diagnostic of CHF
- Serum values closely correlated with pleural fluid values

  - Porcel JM et al: Am J Med 2004; 116:417-20.

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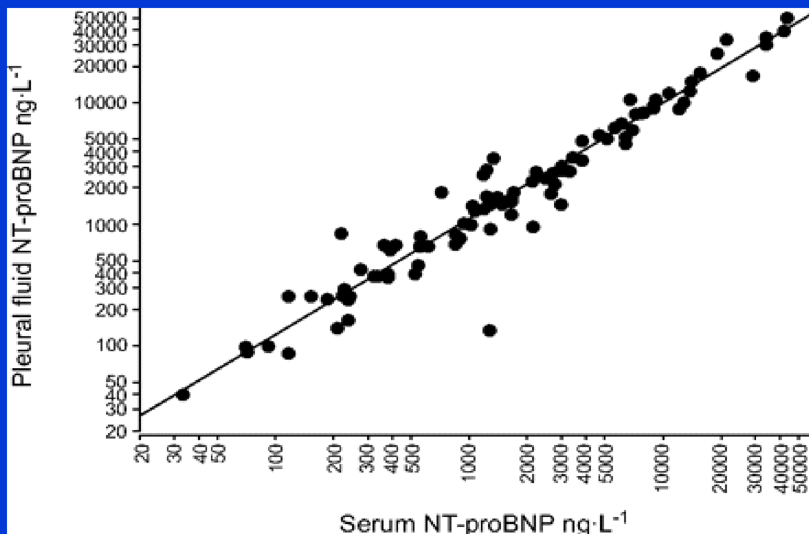

Kolditz M, et al. Eur Respir J. 2006; 28:7

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Comparison of NT-BNP with pleural fluid gradients for albumin and protein

- Twenty patients with CHF whose pleural fluid met exudative criteria by Light's criteria.
- Measured NT-BNP and pleural fluid gradients for albumin and protein
- 18/20 had NT-BNP above 1300
- 16/20 had NT-BNP above 1500
- 14/20 had BNP above 115
- 10/20 had protein gradients above 3.1
- 9/12 had protein gradients above 1.2
  - Porcel JM et al. Chest 2009; 136:671

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Questions About BNP and NT-proBNP

- Can you use the levels of BNP in the serum or pleural fluid to establish the diagnosis of CHF?
  - Levels of BNP are much lower and are not closely correlated with levels of NT-proBNP
  - Sanz MP et al. J Clin Lab Analysis 2006; 20:227
- Why are the levels in the serum and the pleural fluid so closely correlated?
- With treatment do the levels in the pleural fluid and the serum decrease at the same rate?
- What are the pleural fluid BNP levels when the patient has CHF plus another disease?

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Thoracentesis
Should Pleural Pressures be Monitored?

- Theory is that re-expansion pulmonary edema is more likely to occur when pleural pressures are below -20 cm H_2O.
  - This has not been proved
- Incidence of re-expansion pulmonary edema is very low >1%
- If thoracentesis is stopped with chest tightness or pernicious coughing, incidence of re-expansion pulmonary edema is even lower
- I do not recommend the routine monitoring of pleural pressures

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ANNUAL INCIDENCE OF PLEURAL EFFUSIONS IN THE USA

Congestive heart failure	500,000
Pneumonia	300,000
Malignant disease	200,000
Pulmonary embolism	150,000
Viral illness	100,000
Post CABG	60,000
Cirrhosis with ascites	50,000
Gastrointestinal disease	25,000
Collagen vascular disease	6,000
Tuberculosis	3,000

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Gross Examination Of Pleural Fluid

- Appearance
  - Yellow - if cloudy centrifuge
    - Cloudy supernatant - chylothorax or pseudochylothorax
    - Clear supernatant - cells or debris responsible for cloudiness
  - Pink - blood-tinged
  - Red- obtain Hct
    - Hemothorax if Hct > 20%
- Odor
  - Smells bad - anaerobic empyema
  - Urine - urinothorax

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Initial Laboratory Tests For An Undiagnosed Pleural Effusion

- Protein and LDH in pleural fluid and serum for separation of transudates and exudates
- For exudates or suspected exudates
  - Pleural fluid smears and culture
  - Cell count and differential
  - Pleural fluid glucose, pH
  - Pleural fluid cytology
  - Marker for TB pleuritis
    - ADA, gamma interferon or PCR

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Differential Cell Count

- Send with anticoagulant, heparin or EDTA
- Absolute cell count not very useful many diseases have WBC above 10,000
- Most transudates have WBC < 1000
- Differential - polys, small lymphocytes, other mononuclear cells and eosinophils
  - Polys - acute process
  - Mononuclear cells - chronic process
  - Small lymphocytes - malignancy, tuberculosis or post CABG pleural effusion
  - Eosinophils

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Pleural Fluid LDH

- Not useful in the differentiation of exudates because all exudates tend to have elevated LDH
- Very useful when following a patient with a pleural effusion because the level of pleural fluid LDH reflects degree of pleural inflammation
- If LDH increases with serial thoracenteses, process is worsening and one should be more agrressive
- If LDH decreases with serial thoracenteses, process is improving

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Differential Diagnosis Low Glucose (< 40 Mg/Dl)

- Complicated parapneumonic effusion
- Malignant pleural effusion
- Tuberculous pleural effusion
- Rheumatoid pleural effusion
- Paragonimiasis
- Hemothorax
- Churg Strauss syndrome

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Pleural Fluid pH

- Particularly useful in patients with suspected parapneumonic effusion
  - A pH less than 7.00 indicates that patient is likely to require tube thoracostomy
- Low pH (<7.20) also seen with malignancy (poor prognosis), rheumatoid pleuritis, TB, hemothorax, urinothorax, paragonimiasis and the Churg-Strauss syndrome
- Must be measured with blood gas machine
- A low glucose, low pH and high LDH are associated

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Pleural Fluid Markers For Tuberculosis

- Adenosine deaminase (ADA)
- Gamma interferon
- PCR for DNA of *M. Tuberculosis*
  - Don't use – low sensitivity and specificity

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Pleural Fluid ADA

- Patients with TB almost always have levels above 40 U/L
- High levels also seen with empyema and rheumatoid pleuritis
- Specificity increased if combined with PF lymph/poly ratio greater than 0.75
- Non-tuberculous lymphocytic effusions usually have levels < 40 U/L
- Two isozymes
  - ADA-1 produced by lymphocytes and monocytes
  - ADA-2 produced only by monocytes and elevated with tuberculosis
- ADA isozymes rarely used in diagnosis of TB pleuritis

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Pleural Fluid Gamma Interferon

- Produced by lymphocytes
- Lymphocytes specifically sensitized to PPD produce gamma interferon when incubated with PPD
- PF levels above 140 pg/ml are very suggestive of TB
  - Units vary from study to study
- Also elevated with and rheumatoid pleuritis
- More expensive than ADA

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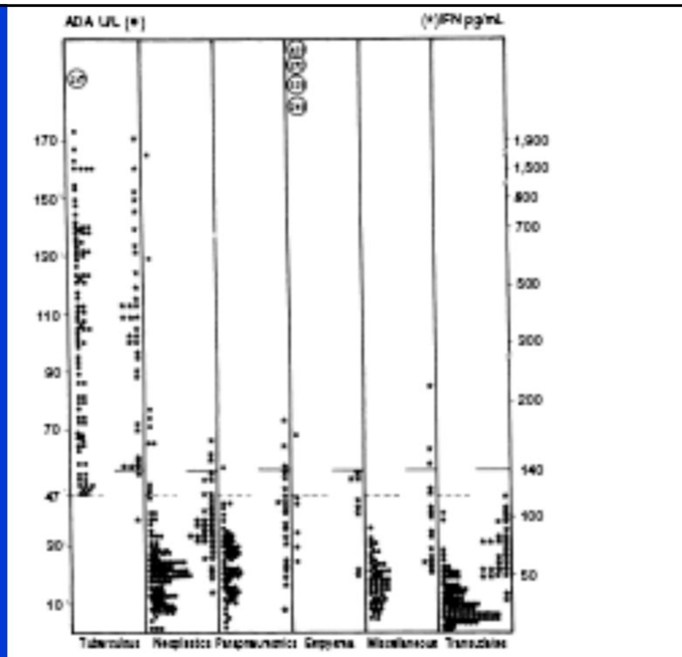

Valdes et al, Chest 1993; 103:458-465

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Pleural Fluid Cytology

- Very useful test
- 1st specimen positive in 60% and if three specimens submitted, may be positive in >80%
- Very effective with adenocarcinoma
- Less effective with lymphoma, squamous cell carcinoma, mesothelioma or hodgkin's disease
- With pleural fluid analysis can identify cancer driving mutations with adenocarinoma of the lung

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Pleural Diagnostic Interventions: Update on Thoracentesis, Manometry, and Pleuroscopy

Yaron Gesthalter, MD
University of California San Francisco

Saturday, October 5, 2019 – 1:30 p.m. –2:00 p.m.

Dr. Yaron B. Gesthalter is an Assistant Professor in the Division of Pulmonary, Sleep & Critical Care at the University of California San Francisco. He received his medical degree from the Sackler School of Medicine in Israel and completed an Internal Medicine residency at Yale followed by a Pulmonary & Critical Care fellowship at Boston University. He then went on to complete additional training in Interventional Pulmonary Medicine at Harvard. He is a member of The Thoracic Oncology Program where his practice focuses on the management of patients with complex airway and pleural disease.

Update on Thoracentesis, Manometry, and Pleuroscopy

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Director of Pleural Services
Interventional Pulmonary Medicine
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Disclosure Slide

- No relevant financial conflicts

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Talk outline

- Intro
- Thoracentesis
  - Characterizing the *biochemical* properties of the pleural space
- Manometry
  - Characterizing the *physiological* properties of the pleural space
- Pleuroscopy
  - As a diagnostic and therapeutic modality

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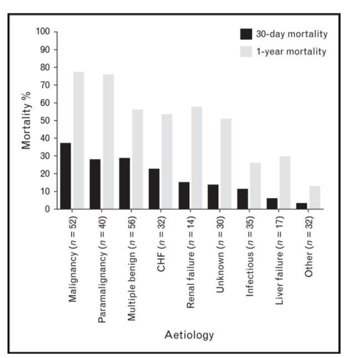
Burden of Disease and the Clinical Challenge

- 1.5 Million pleural effusions are diagnosed in the USA each year
- Prior estimates suggest 173,000 thoracentesis are performed each year in the USA
- Pleural effusion etiology carries significant therapeutic and prognostic information
- Despite the great need pleural effusions remain a diagnostic challenge



Kozak LJ et al Viral Health Stat 13. 1998
DeBiasi et al ERJ 2014

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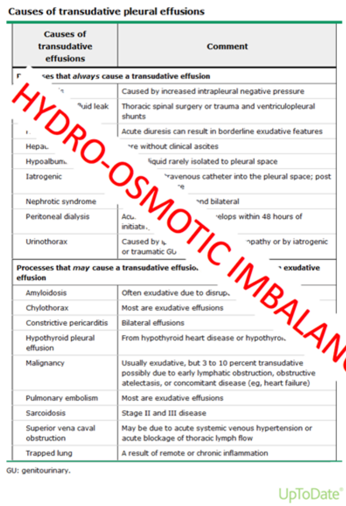
The “Diagnostic” Thoracentesis



Causes of transudative pleural effusions

Causes of transudative effusions	Comment
P[illegible]ses that *always* cause a transudative effusion	
[illegible]	Caused by increased intrapleural negative pressure
[illegible]uid leak	Thoracic spinal surgery or trauma and ventriculopleural shunts
[illegible]	Acute diuresis can result in borderline exudative features
Hepa[illegible]	[illegible]re without clinical ascites
Hypoalbum[illegible]	[illegible]liquid rarely isolated to pleural space
Iatrogenic	[illegible]ravenous catheter into the pleural space; post [illegible]
Nephrotic syndrome	[illegible]nd bilateral
Peritoneal dialysis	Acu[illegible]elops within 48 hours of initiati[illegible]
Urinothorax	Caused by [illegible]pathy or by iatrogenic or traumatic GU [illegible]
Processes that *may* cause a transudative effusio[illegible] exudative effusion	
Amyloidosis	Often exudative due to disrup[illegible]
Chylothorax	Most are exudative effusions
Constrictive pericarditis	Bilateral effusions
Hypothyroid pleural effusion	From hypothyroid heart disease or hypothyro[illegible]
Malignancy	Usually exudative, but 3 to 10 percent transudative possibly due to early lymphatic obstruction, obstructive atelectasis, or concomitant disease (eg, heart failure)
Pulmonary embolism	Most are exudative effusions
Sarcoidosis	Stage II and III disease
Superior vena caval obstruction	May be due to acute systemic venous hypertension or acute blockage of thoracic lymph flow
Trapped lung	A result of remote or chronic inflammation

GU: genitourinary.

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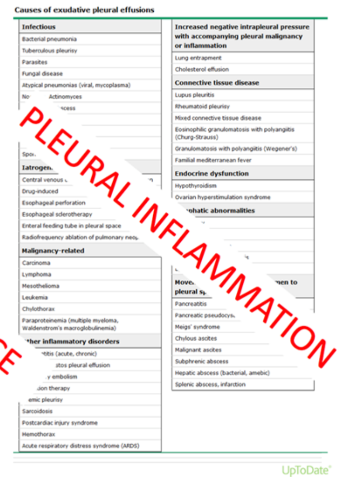

Causes of exudative pleural effusions

Infectious	**Increased negative intrapleural pressure with accompanying pleural malignancy or inflammation**
Bacterial pneumonia	Lung entrapment
Tuberculous pleurisy	Cholesterol effusion
Parasites	**Connective tissue disease**
Fungal disease	Lupus pleuritis
Atypical pneumonias (viral, mycoplasma)	Rheumatoid pleurisy
No[illegible] Actinomyces	Mixed connective tissue disease
[illegible]scess	Eosinophilic granulomatosis with polyangiitis (Churg-Strauss)
[illegible]	Granulomatosis with polyangiitis (Wegener's)
Spo[illegible]	Familial mediterranean fever
Iatrogen[illegible]	**Endocrine dysfunction**
Central venous [illegible]	Hypothyroidism
Drug-induced	Ovarian hyperstimulation syndrome
Esophageal perforation	**[illegible]phatic abnormalities**
Esophageal sclerotherapy	[illegible]
Enteral feeding tube in pleural space	[illegible]
Radiofrequency ablation of pulmonary neo[illegible]	[illegible]
Malignancy-related	[illegible]
Carcinoma	**Move[illegible]men to pleural s[illegible]**
Lymphoma	Pancreatitis
Mesothelioma	Pancreatic pseudocys[illegible]
Leukemia	Meigs' syndrome
Chylothorax	Chylous ascites
Paraproteinemia (multiple myeloma, Waldenstrom's macroglobulinemia)	Malignant ascites
[illegible]ther inflammatory disorders	Subphrenic abscess
[illegible]titis (acute, chronic)	Hepatic abscess (bacterial, amebic)
[illegible]stos pleural effusion	Splenic abscess, infarction
[illegible]y embolism	
[illegible]ion therapy	
[illegible]emic pleurisy	
Sarcoidosis	
Postcardiac injury syndrome	
Hemothorax	
Acute respiratory distress syndrome (ARDS)	

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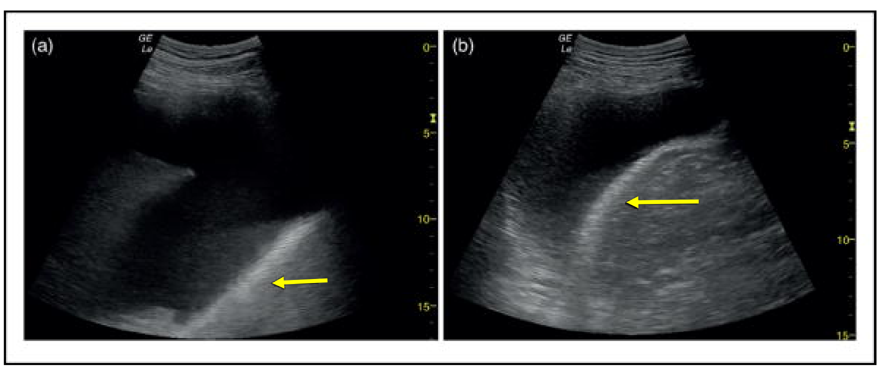
The “Therapeutic” Thoracentesis

Before

After 1 liter thoracentesis



Rajesh et al Curr Op Pul Med 2015

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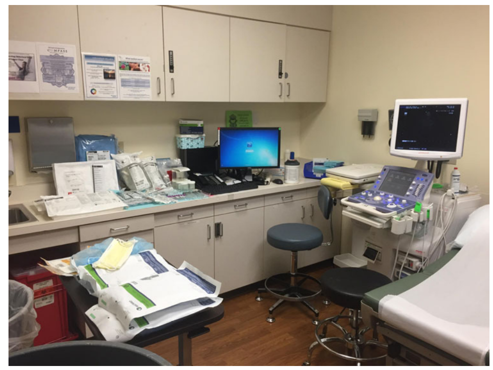
Pleural Clinics

- Establishing a diagnosis and optimal management can be challenging
- Delay in diagnosis and management can contribute to morbidity.
- Some data to suggest dedicated clinics are safer
- Dedicated units provide procedural training



Hooper et al Respirology 2010

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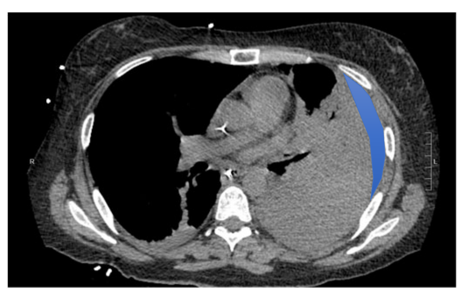
The Ideal Pleural Imaging Study

- Easy to perform
- Safe
- Cheap
- Objective measurements
- Good spatial resolution
- Ability to document for future reference



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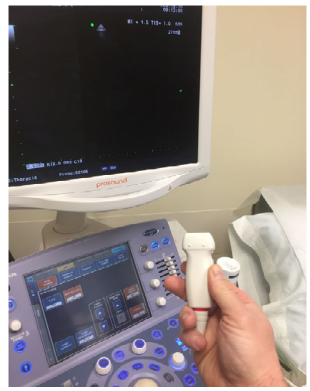
Ideal Pleural Imaging
Thoracic Ultrasound

- Cheap and readily available
- Safe
- Spatial resolution
- Improves procedural safety (PTX from 9% to 1%)
- Dynamic - guides procedures, increase procedural success
- Operator dependent - training



Cavanna et al World J Surg Oncol 2014
Gordon et al Arch Intern Med 2010

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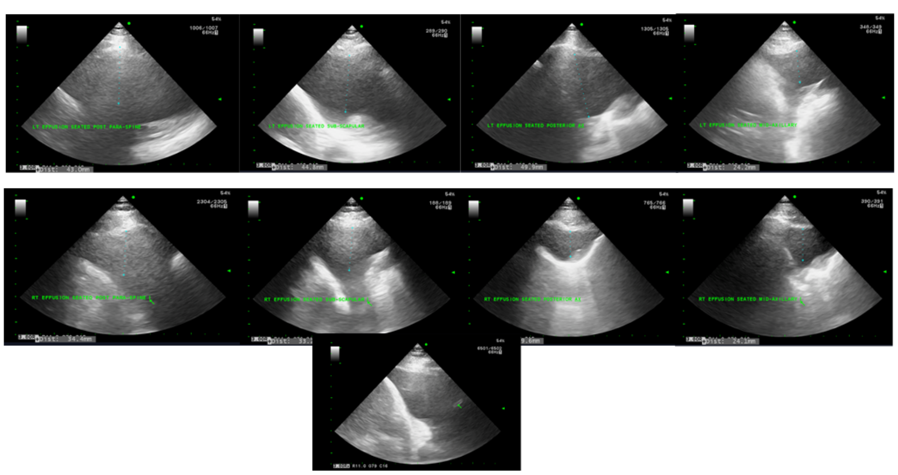
Thoracic Ultrasound Exam

Para-spine | Sub-scapular | Post-axillary | Mid-axillary

Left

Right



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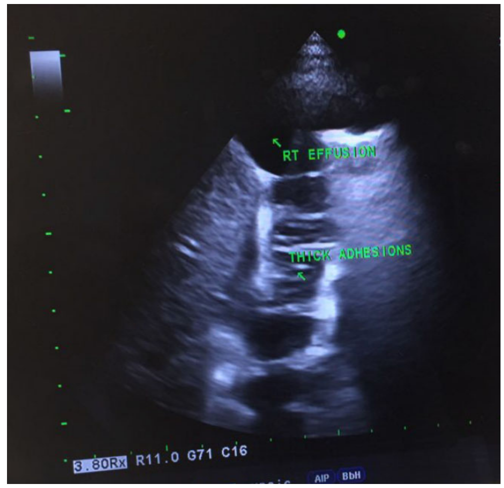

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Dynamic Ultrasonography

Pre

Post 1 liter thora

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Pleural Ultrasound

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Thoracentesis

- Easy
- No need for “hardware” or routine changes
- Effects short lived
- Cumulative procedural risk

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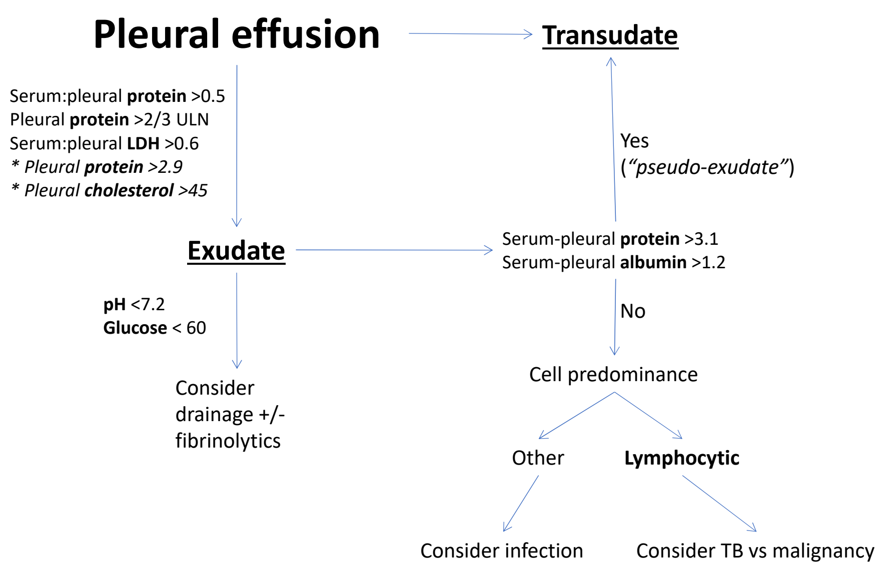
Diagnostics - Laboratory



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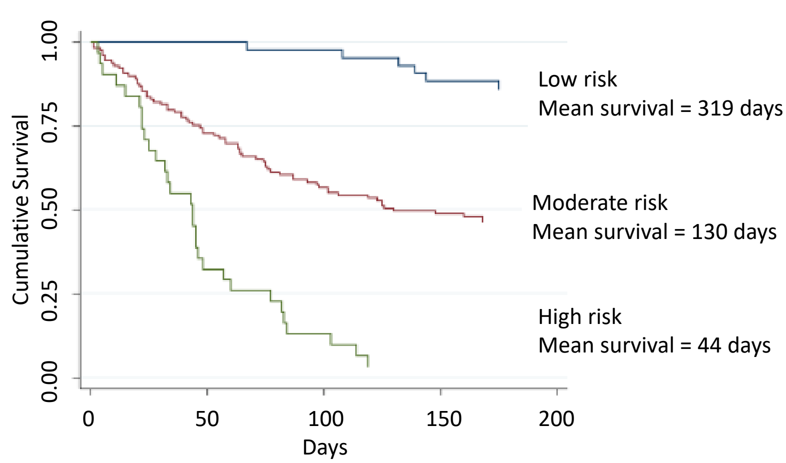
Malignant Pleural Effusion

Prognostication – LENT Score



Clive OA Thorax 2014

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Pleural Sepsis
Prognostication – RAPID Score

- Predictor of 3 month survival
- Generated using MIST I, cross validated on MIST II

Table 2—*Scoring System (RAPID) Derived From the Initial Prediction Model Using Baseline Characteristics*

Parameter	Measure	Score
Renal		
Urea, mM	<5	0
	5-8	1
	>8	2
Age, y	<50	0
	50-70	1
	>70	2
Purulence of pleural fluid		
Purulent	...	0
Nonpurulent	...	1
Infection source		
Community acquired	...	0
Hospital acquired	...	1
Dietary factors		
Albumin, g/L	≥27	0
	<27	1
Risk categories		
Score 0-2	...	Low risk
Score 3-4	...	Medium risk
Score 5-7	...	High risk

Each patient can obtain a score from 0 to 7. RAPID = renal, age, purulence, infection source, and dietary factors.

Rahman et al Chest 2014

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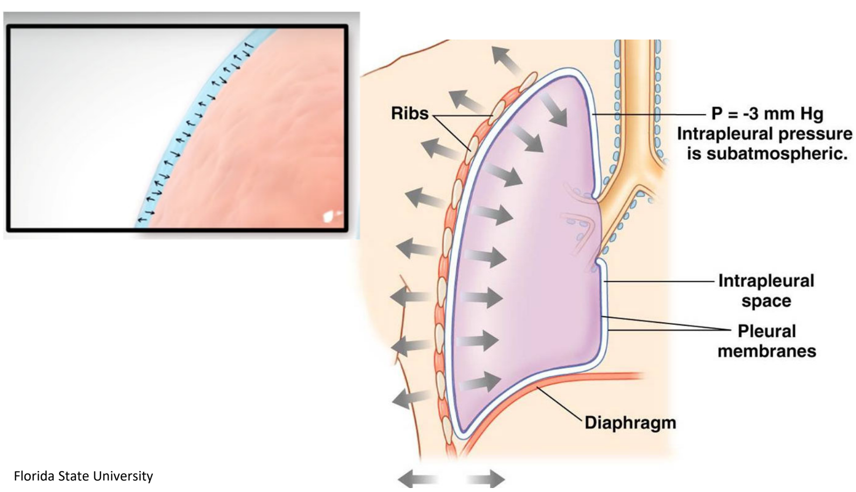
The Pleural Organ
Mechanical Coupling



Florida State University

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The Non-Expandable Trapped Lung

Albores et al NEJM 2015

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Getting the Pleura Dry

- *"PICO 3: In patients with symptomatic MPE, we **suggest large-volume thoracentesis** if it is uncertain whether the patient's symptoms are related to the effusion and/or **if the lung is expandable** (the latter if pleurodesis is contemplated), to assess lung expansion."*

Feller-Kopman AJRCCM 2018

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Pleural Effusion Morbidity Thoracentesis…

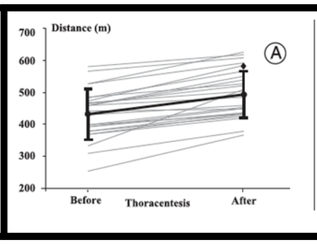
Improved Physiology

Table 1—*Pulmonary Function Results Before and After Thoracentesis*

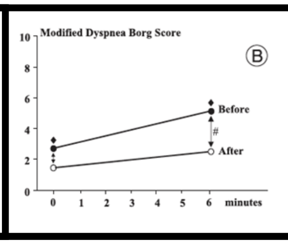
Parameters	Before Thoracentesis	After Theracentesis	Δ[a]	*P* Value
FVC				
L	1.9 ± 0.6	2.2 ± 0.7	0.3	.001
%	53.8 ± 12.8	64.5 ± 14.4	10.7	.001
FEV_1				
L	1.5 ± 0.5	1.8 ± 0.5	0.3	.001
%	52.7 ± 12.3	60.9 ± 12.5	8.3	.001
FEV_1/FVC	0.8 ± 0.1	0.7 ± 0.1	−0.1	.051

Data are presented as mean ± SD, unless otherwise indicated.
[a]After − before.

Improved Distance



Improved Symptoms



Cartaxo et al Chest 2011
Puri et al Ann Thorac Surg 2012

21

Complete Pleural Evacuation

Concerns for large volume thoracentesis
- Pneumothorax
- Re-expansion pulmonary edema (REPE)

Sub-optimal effusion evacuation:
- Incomplete symptom palliation
- May result in an increase in number of subsequent procedures
- Limits post-procedural imaging and the ability to evaluate for lung re-expansion for potential pleurodesis

22

Manometry

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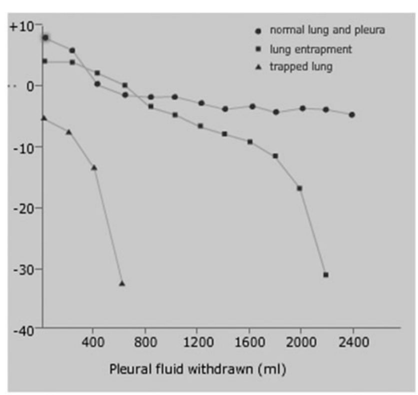
What is Manometry?

- Physiological read out
  - Pleural elastance = $\Delta P / \Delta V$
- Aim to measure the pleural pressure when the thorax is at Functional residual capacity (FRC) (normal pressure -3 to -5 cm H20)



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Performing Manometry

25

The Manometry Debate

Pro

- Adds clinical information that will impact management
- Easy to perform
- Few risks to the patient
- Doesn't add cost
- Provides info re:
    - Cause of effusion
    - Ability of lung to re-expand – predicts pleurodesis
    - Reduce risk of pressure related complications
- Optimizes fluid removal = symptom relief and improved radiographic yield

Con

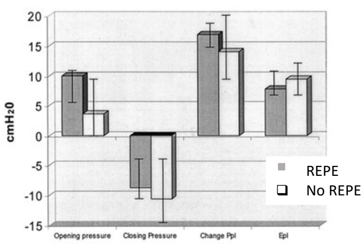
- Main argument against is for "routine" use
- "Arbitrary" cutoffs
- Sufficient surrogates – symptoms
- Advocate "maximal fluid removal"

Feller Kopman Chest 2012
Maldonado et al Chest 2012

26

Re-Expansion Pulmonary Edema

Single center – 185 thoras



1 clinical REPE
4 on imaging alone

12 year registry – 9320 thoras

E-Table 1: Patient Clinical and Demographic Characteristics for Re-expansion Pulmonary Edema (REPE) Cases. End Stage Liver Disease (ESLD).

Case Number*	Reason for Thoracentesis	Age (years)	Gender (0 male)	BMI	Volume (mL)
1	ESLD	35	0	26.68	700
2	Post Cardiac Surgery	54	1	22.69	1000
3	Metastatic Lung Cancer	49	1	19.14	1100
4	Metastatic Pancreatic Cancer	81	1	19.62	1500
5	Nephrotic syndrome	76	0	22.43	1600
6	ESLD/bacterial endocarditis	34	0	25.77	1800
7	s/p lung transplant	76	0	19.35	1800
8	ESLD	43	1	19.74	2200
9	ESLD	53	1	30.13	3200
10	Congestive Heart Failure	35	0	18.50	3300
Average (SD)		53.6 (18.15)	50% male	22.40 (3.94)	1820 (871.52)

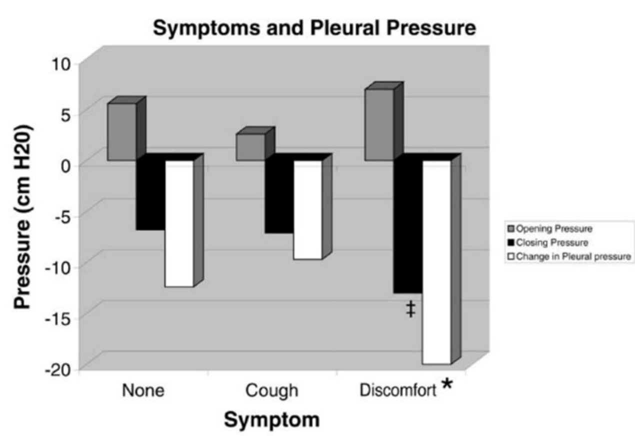
***No patients died as result of REPE.**

10 REPE (6>1.5L, 4<1.5L)

Ault MJ et al Thorax 2014
Feller Kopman D et al Ann Thorac Sur 2007

27

Symptoms as a Correlate to Closing and Δ Pleural Pressures



Feller Kopman Chest 2006

‡ p=0.04 from no symptom group
* p=0.001 from cough and no symptom

28

Routine Manometry?

- Pleural manometry during thoracentesis vs symptoms alone to protect against complications 1:1 RCT of ; 2 centers; n= 62 vs n = 62
- Primary outcome: pre and post overall **<u>chest discomfort</u>**
- No difference in discomfort of other secondary events (PTX, REPE)
- Control group with more PTX ex-vacuous (6 vs 0; P 0.01)

	Control (n=62)	Manometry (n=62)	Mean difference	p value
Volume drained (mL)	1087 (453)	1074 (486)	−13·9 (95% CI −180·9 to 153·2)	0·81
Thoracentesis duration (min)	14·9 (5·2)	16·4 (6·3)	1·5 (95% CI −0·6 to 3·5)	0·34
Drainage stopped				
Stopped spontaneously	32 (52%)	25 (40%)	χ^2=0	0·97
Chest discomfort	22 (35%)	21 (34%)	χ^2=0·66	0·42
Intractable cough	7 (11%)	2 (3%)	χ^2=1·89	0·17
Pleural pressure fell to less than −20 cm H_2O	NA	9 (15%)	NC	NC
Rapid fall in pleural pressure†	NA	4 (6%)	NC	NC
Aspiration of air	1 (2%)	0	NC	NC
Vagal episode	0	1 (2%)	NC	NC
Complication	6 (10%)	0	χ^2=6·31	0·01
Pneumothorax ex vacuo	6 (10%)	0	χ^2=6·31	0·01
Residual post-procedure effusion	25 (40%)	25 (40%)	χ^2=0·01	0·94
Post-procedure chest x-ray not done	7 (11%)	9 (15%)	χ^2=0·29	0·59

Data are n (%) or mean (SD). NA=not applicable. NC=not calculable. *Drop of >10 cm H2O between two measurements to a value ≤−10 cm H2O.

Table 3: **Procedure data**

Lentz R et al; Lancet Respir Med 2019

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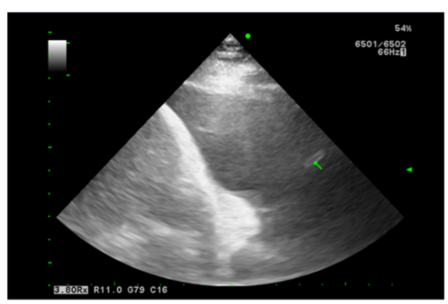
Case Study - Manometry

68 y.o. female s/p DLT for COPD
~4.5 months out
Recent TBBX = No evidence of rejection on.
Recurrent effusions noted on surveillance CT scans
Last drainage stopped after 450ml d/t pain
PFA = Transudative



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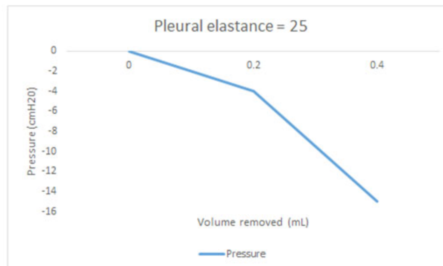
Case Study - Manometry

	Ref. Range	4/17/2019
Albumin	g/dL	1.8
Appearance	Unknown	Hazy
Color	Unknown	Orange
Viscosity	Unknown	Liquid
WBCs	x10E9/L	1.875
RBCs	x10E9/L	15.300
Conc Smear; # Cells	Unknown	100
Lymphs	%	92
Mono,Histio,Mesothel	%	7
Other Cells	%	1
Glucose	mg/dL	99
Lactate Dehydrogenase	U/L	153
Total Protein	g/dL	2.7
Triglycerides	mg/dL	<10
pH	Unknown	7.57



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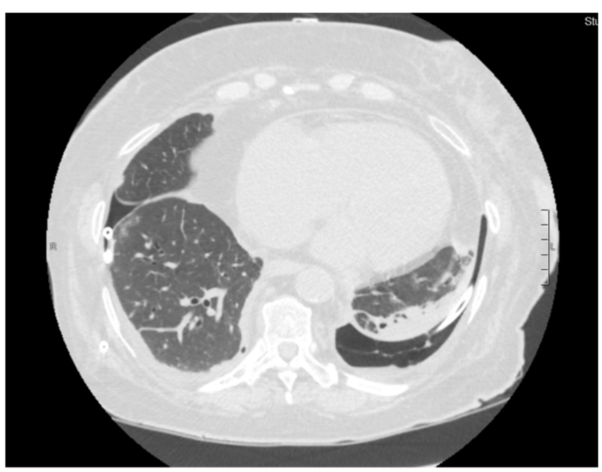

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Pleuroscopy

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Comparative Diagnostic Yields
Cancer

- Pleural fluid cytology –
  - 1st thora = 60-65%
  - 2nd thora = additional 27%
  - 3rd thora = additional 5%
- Closed pleural biopsy – 57%
- Thoracoscopy - >95%

Hooper et al Thorax 2010

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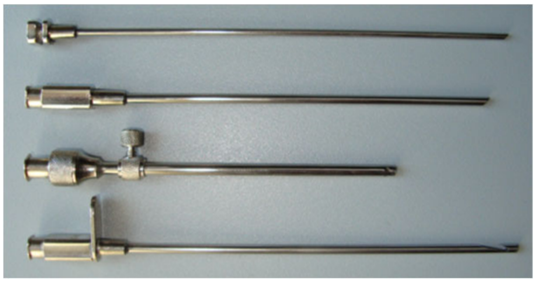
Closed Pleural Biopsy



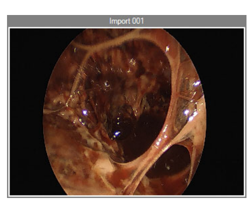
- Diagnostic sensitivity 43-59%
- Improved when done with ultrasound or CT guidance

Ferreiro et al Ann of Thor Med 2017

35

Mini VATS?

	Video Assisted Thoracic Surgery	Medical Thoracoscopy
Anesthesia	General	Moderate
Ports	~3-4	1
Setting	Admission	Typically outpatient
Indications	Biopsies, resections, pleurodesis, decortications	Biopsies, pleurodesis, washouts?



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Semi Rigid Pleuroscope

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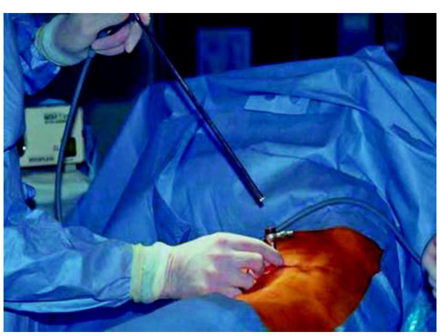
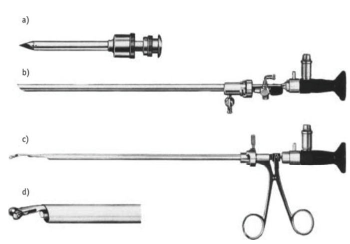
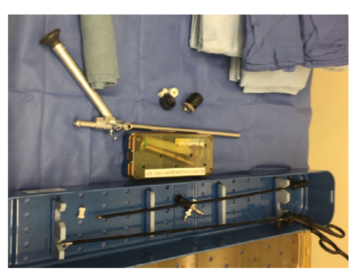
Rigid Pleuroscope







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Pleural Biopsy

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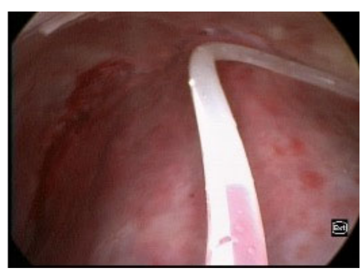
Rapid Pleurodesis Protocol

- N = 30 patient with MPE; 2 tertiary centers
- Intervention =
  - Pleuroscopy under moderate sedation
  - 5 gr Talc poudrage
  - Tunneled pleural catheter placement & 24 fr
  - 24 fr removed after 24 hrs
  - TPC removed once output <150 ml/day and no recurrence of fluid
- 92% complete pleurodesis rate at 6 months
- Median:
  - Length of hospitalization = 1.79 d
  - Length of time with TPC = 7.54 d

Reddy et al Chest 2011



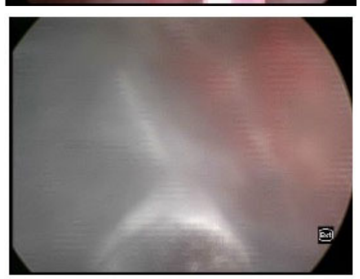


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TABLE 3. Complications of Pleuroscopy

- Prolonged air leak
- Hemorrhage
- Subcutaneous emphysema
- Postoperative fever
- Empyema
- Wound infection
- Cardiac arrhythmias
- Hypotension
- Seeding of chest wall from mesothelioma

Lee P et al J Thor Oncol 2007

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Summary

- Thoracentesis is the cornerstone of pleural disease diagnostics
- Pleural maonemetry can provide insight into the mechanical pleural physiology and complement biochemical analysis
- Pleuroscopy is a safe and minimally invasive procedure that can provide both diagnostic and therapeutic insight

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Management of Complicated Pleural Effusion and Empyema

Steve Escobar, MD
Scripps Clinic

Saturday, October 5, 2019 – 2:00 p.m. – 2:30 p.m.

Dr. Steve Escobar received his medical degree from Uniformed Services University of the Health Sciences. He completed his postgraduate medical education at Naval Medical Center San Diego and ultimately retired from the US Navy. He is currently working at Scripps Hospitals in La Jolla, California performing advanced diagnostic and therapeutic pulmonary/pleural procedures.

CALIFORNIA THORACIC SOCIETY
A chapter of the American Thoracic Society

Management of complicated pleural effusion and empyema

Steve Escobar, M.D. FCCP
Scripps Clinic Medical Group
05 October 2019

1

Disclosures

- No financial conflicts
- No Conflicts/Disclosures

2

Case 1

- 74 yo female presented to urgent care with complaints of 4-5 days of non productive cough, dyspnea, subjective fevers and right sided pleuritic chest pain. Previously underwent bronchoscopy 3 weeks prior for bronchiectasis. Denied fevers, chills, nausea or vomiting.

3

PAST MEDICAL HISTORY: Bronchiectasis, hiatal hernia, hypothyroidism, and cholecystectomy.

MEDICATIONS:
1. Albuterol.
2. Budesonide.
3. Levothyroxine.
4. Omeprazole.
5. Desvenlafaxine
6. Menest.

ALLERGIES:
1. ASPIRIN.
2. CODEINE.
3. THIMEROSAL.

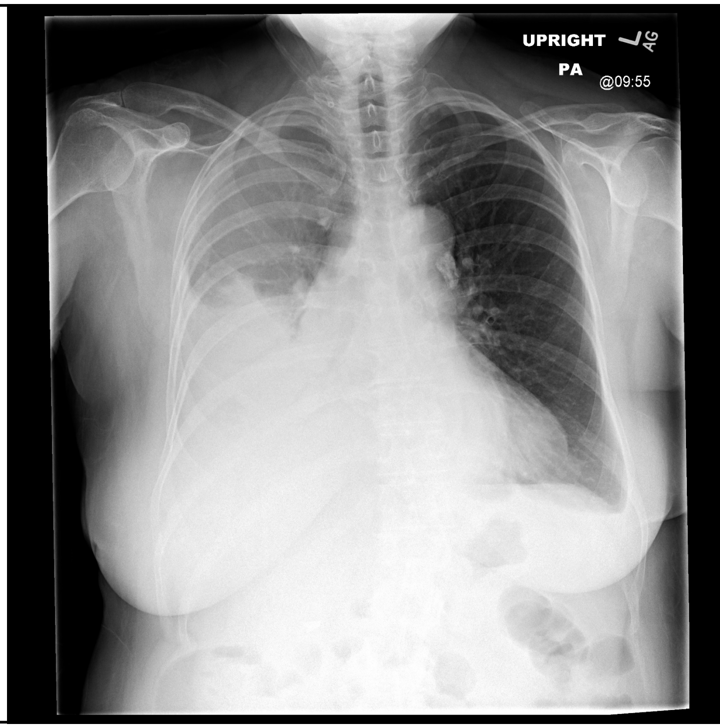
FAMILY MEDICAL HISTORY: Reviewed and noncontributory.

SOCIAL HISTORY: The patient has quit smoking after 40 years ago. Drinks alcohol very rarely. She is married. No history of recent travel.

VITAL SIGNS: Temperature is 98.5 Fahrenheit, pulse 116, respirations 20, blood pressure is 122/73, saturation 92% on room air
GENERAL: Pleasant elderly female, appearing tired, but in no acute respiratory distress.
HEENT: Eyes, pupils are equal, round, and reactive. Conjugate is intact. No scleral icterus. ENT and mouth, mucous membranes are moist.
NECK: Supple. No meningismus.
RESPIRATORY: Lungs demonstrate diminished breath sounds in the right lower lobe, with only small crackles in the right lower lobe. No clear wheezing is appreciated. Left lung base is clear.
CARDIAC: Regular. Normal S1, S2 without murmurs.
ABDOMEN: Soft, nontender, nondistended.
MUSCULOSKELETAL: There is no significant leg pain or edema noted.
SKIN: Normal turgor without rashes.
NEUROLOGIC: Cranial nerves II through XII essentially intact here. No focal motor weakness noted.
PSYCHIATRIC: Awake, alert, calm, cooperative here.

Labs:
WBC 29.8, Hgb 11.9, Hct 36.3, Plt 540 91.4 N
Na 137, K 3.3, Cl 101, Hco3 26, BUN 13, Cr 0.6, Ca 8.6, Tp 5.5, Alb 2.7

4



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What is the best next step?

a) Appropriate oral antibiotics and outpatient f/u.

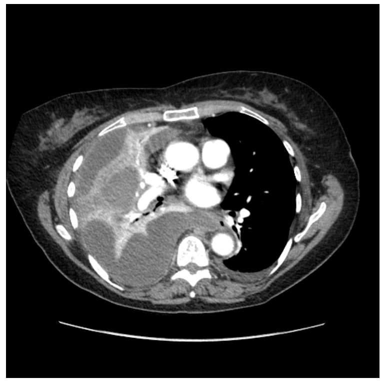
b) Admit for IV antibiotics.

c) POC ultrasound to evaluate for effusion and if present perform thoracentesis for diagnostic purposes.

d) CT angiogram.

e) POC ultrasound to evaluate for effusion and if present place small bore pleural catheter.

6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CATEGORIZING RISK FOR POOR OUTCOME IN PATIENTS WITH PARAPNEUMONIC EFFUSIONS AND EMPYEMA

Pleural Space Anatomy		Pleural Fluid Bacteriology		Pleural Fluid Chemistry	Category	Risk of Poor Outcome	Drainage
A_0: Minimal, free-flowing effusion (< 10 mm on lateral decubitus)	and	B_x: culture and Gram stain results unknown	and	C_x: pH unknown	1	Very low	No
A_1: Small to moderate free-flowing effusion (> 10 mm and < one-half hemithorax)	and	B_0: negative culture and Gram stain	and	C_0: pH ≥ 7.20	2	Low	No
A_2: Large, free-flowing effusion (≥ one-half hemithorax) loculated effusion, or effusion with thickened parietal pleura	or	B_1: positive culture and Gram stain	or	C_1: pH < 7.20 Glu <60	3	Moderate	Yes
		B_2: pus			4	High	Yes

Chest 2000; 118:1158–1171.

8

Complicated Parapneumonic effusion/empyema

- THE EMERGENCE OF PARAPNEUMONIC EMPYEMA IN THE UNITED STATES. Thorax . 2011 August ; 66(8): 663–668.
  - Empyema-related hospitalization rates increased from 3.04 /100K in 1996 to 5.98/ 100K in 2008
  - In-hospital case fatality ratio 8.0% in 1996 and 7.2% in 2008
  - Mean length of hospital stay declined from 16.5 in 1996 to 14.9 days in 2008
- Treatment failure and mortality higher with parapneumonic effusion vs pneumonia and no effusion- OR 2.7. Thorax 2004;59:960–965
  - Scoring system (RAPID). Annals ATS Volume 12 Number 9| September 2015
    - Identify patients who are at risk for a poor outcome at the time of their presentation
    - RAPID score of 5 to 7 -30% chance of dying in the subsequent 12 weeks
    - May warrant more invasive initial therapy?
- Delays in drainage are associated with substantially higher mortality

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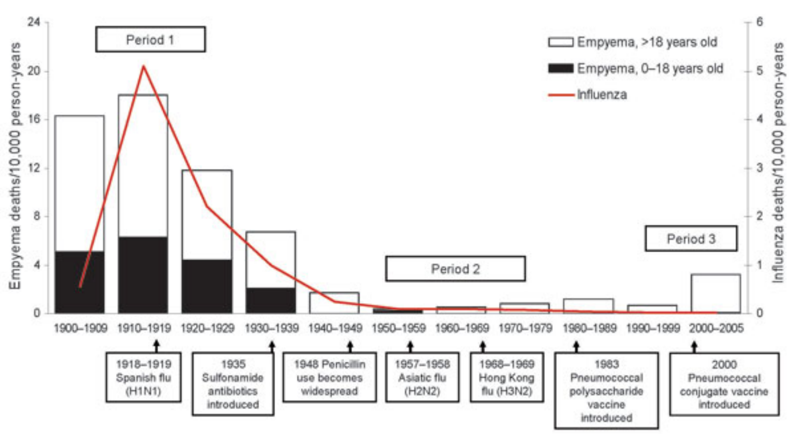
Average rates of deaths in Utah caused by parapneumonic empyema and influenza, by decade, 1900–2005.



Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 15, No. 1, January 2009

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Predicting Long-Term Outcomes in Pleural Infections
RAPID Score for Risk Stratification

Table 1. RAPID scoring system

	Value(s)	Score*	
Renal			
BUN, mmol/L	<5	0	<14 mg/dl
	5–8	1	
	>8	2	>22 mg/dl
Age, yr	<50	0	
	50–70	1	
	>70	2	
Purulence of pleural fluid			
Purulent		0	
Nonpurulent		1	
Infection source			
Community acquired		0	
Hospital acquired		1	
Dietary			
Albumin, g/L	≥27	0	
	<27	1	

Definition of abbreviations: BUN = blood urea nitrogen; RAPID = renal, age, purulence, infection source, and dietary factors.
Note: Adapted by permission from Reference 9.
*Low risk, 0–2; medium risk, 3–4; high risk, 5–7.

Table 4. Logistic regression modeling of mortality

	Mortality [*n* (%)]	Odds Ratio (95% CI)	*P* Value
Mortality at 3 mo			
Low risk (n = 67)	1 (1.5)	Ref	
Medium risk (n = 73)	13 (17.8)	14.30 (1.82–112.58)	0.01
High risk (n = 47)	21 (44.7)	53.30 (6.82–416.75)	<0.01
Mortality at 1 yr			
Low risk (n = 67)	7 (10.5)	Ref	
Medium risk (n = 73)	18 (24.7)	2.81 (1.09–7.23)	0.03
High risk (n = 47)	26 (55.3)	10.61 (4.02–28.03)	<0.01
Mortality at 3 yr			
Low risk (n = 67)	13 (19.4)	Ref	
Medium risk (n = 73)	24 (32.9)	2.04 (0.94–4.43)	0.07
High risk (n = 47)	36 (76.6)	13.59 (5.49–33.67)	<0.01
Mortality at 5 yr			
Low risk (n = 67)	15 (22.4)	Ref	
Medium risk (n = 73)	30 (41.1)	2.42 (1.15–5.07)	0.02
High risk (n = 47)	36 (76.6)	11.35 (4.68–27.53)	<0.01

Annals ATS Volume 12 Number 9| September 2015

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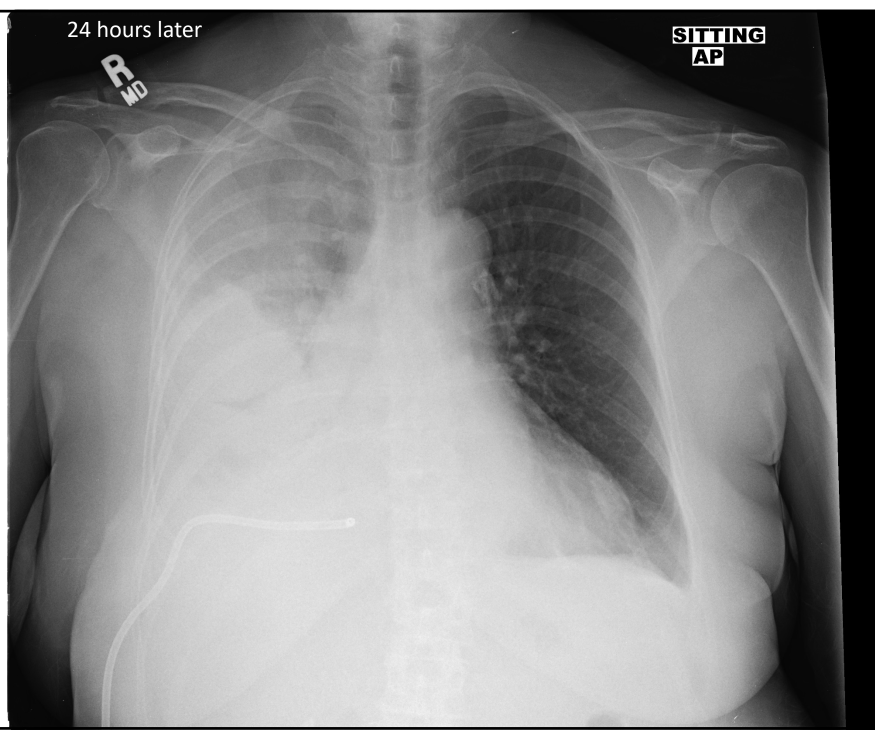
- Pleural fluid- yellow, clear
- LDH 6160, Prot 3.4, Glu- 61
- WBC- 94% N, 5% L, 1% M
- Gram stain negative

1.1 L in Atrium collection device over the first 24 hours. Almost all fluid within first hour.



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What is the best next step in addition to continuing with IV abx?

A) Continue chest drainage via catheter.

B) Start intrapleural fibrinolytics (streptokinase or tPA)

C) Insert large bore chest tube >24 Fr

D) Immediate referral for thoracic surgery (VATS)

E) Start intrapleural tPA + DNase

F) C & E

13

Cochrane Database Syst Rev. 2017 Mar

- No statistically significant difference in mortality between primary surgical and non-surgical management of pleural empyema for all age groups.
- Video-assisted thoracoscopic surgery may reduce length of hospital stay compared to thoracostomy drainage alone.
- There was insufficient evidence to assess the impact of fibrinolytic therapy.

14

Surgical management

- ~50% of patients currently undergo surgical management
- Most published studies compare open thoracotomy to VATS for outcomes

- Surgical management of primary empyema of the pleural cavity: outcome of 81 patients. Interactive CardioVascular and Thoracic Surgery 10 (2010) 565–56
  - 96% of stage II empyema patients underwent thoracoscopic drainage
  - 19% of stage III patients converted to open decortication
  - Mortality rate 0% for all procedures
  - Median length of hospital stay
    - six days for thoracoscopic debridement
    - five days for thoracoscopic decortication
    - eight days for open decortication
  - VATS debridement/decortication considered as a first choice treatment

- Thoracic Empyema: A 12-Year Study from a UK Tertiary Cardiothoracic Referral Centre PLoS ONE 1 January 2012 | Volume 7 | Issue 1 |
  - N= 406; retrospective review
  - Microbiological diagnosis- 56.4%
  - Mortality 5.7%. at 28 days
  - 68% managed by open thoracotomy and decortication
  - VATS reduced hospitalization from 10 to 7 days

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Tube Thoracostomy + thrombolytics

- A Randomized Trial of Empyema Therapy. CHEST 1997; 111:1548-51.
  - N=20.
  - VATS vs catheter-directed fibrinolytic therapy (streptokinase)
  - Treatment success 91% vs 44%,
  - Lower chest tube duration 5.8 vs 9.8 days
  - Lower number of total hospital days 8.7 vs 12.8 days
  - Hospital costs $16,642 vs $24,052

- U.K. Controlled Trial of Intrapleural Streptokinase for Pleural Infection (MIST 1) N Engl J Med 2005; 352:865-874
  - N=454
  - streptokinase (250,000 IU twice daily for three days) vs placebo
  - Combined primary outcome 31% vs 27% needed surgery or died
  - Secondary outcomes
    - 16 % vs 14% died at 3 months; 23% vs 20% died at 1 yr
    - 16 % vs 14% required surgery at 3 months;
  - Serious adverse events (CP, fever, allergy) more common with streptokinase

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Tube thoracostomy + tPA-DNase

- Intrapleural Use of Tissue Plasminogen Activator and DNase in Pleural Infection (MIST-2) N Engl J Med 2011;365:518-26
  - N=210; RCT; 2x2 factorial design
  - Primary endpoint- Change in pleural opacity −29.5 vs. −17.2% t-PA-DNase vs placebo at day 7
  - Secondary endpoints
    - Frequency of surgical referral at 3 months 4% t-PA–DNase vs. 16% placebo
      - DNase only vs placebo 39% vs 16%
    - t-PA–Dnase reduction in the hospital stay compared with placebo 11.8 vs 17 days
  - Frequency of adverse events did not differ significantly among the groups.
  - Mortality similar among groups 4, 8, 8, 13% at 3 months and 8,11,11,20% at 1 year

.

- Intrapleural Tissue Plasminogen Activator and Deoxyribonuclease for Pleural Infection. Ann Am Thorac Soc Vol 11, No 9, pp 1419–1425, Nov 2014
  - Multinational observation series; N=107
  - 92.3% managed without the need for surgical intervention.
  - Survival rates at 30 and 90 days 97.8% and 91.2%
  - Median hospital stay from first intrapleural treatment 10 days
  - Pain requiring increase analgesia 19.6%
  - Non-fatal bleeding 1.6%

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Summary of fibrinolytic regimens

Reference	Study type	Sample size	Regimen	Outcome	Complications
[67]	Randomized controlled trial	210	Sequential intrapleural administration of tPA 10 mg and DNase 5 mg twice daily for 3 days; chest drain clamped for 1 h after each drug	tPA/DNase group: greater mean reduction in pleural opacity (−29.5 ± 23.3 vs. −17.2 ± 19.6%), less surgical referral at 3 months (4 vs. 16%; odds ratio 0.17), shorter hospital stay (difference, 6.7 days) than placebo group	No significant difference on serious adverse events (intrapleural hemorrhage, hemoptysis) between tPA/DNase [3 (6%)] and placebo group [1 (2%)]
[70]	Observational, open-label study	61	tPA 5 mg, can be escalated to 10mg	58 (93.4%) successful treatment. 7 (11.5%) had dose escalation of tPA to 10 mg	3 (4.9%) received blood transfusion
[71]	Prospective observational	38	Concurrent administration of tPA 10 mg and DNase 5mg; chest drain clamped for 2 h	No significant difference on treatment success, pleural fluid drainage, median volume of pleural effusion on CT thorax	No significant difference
[72]	Retrospective	73		Successful treatment in 66 patients (90.4%); 59 (80.8%) were effectively treated with fewer than six doses of therapy; median hospital stay from the first dose of tPA/DNase to discharge was 7 days (IQR, 5–11 day)	Nonfatal pleural bleeding [4 (5.4%)], chest pain [11 (15.1%)], death because of pleural infection [2 (2.7%)]
[73]	Retrospective	39		33 (85%) treatment success	Hemorrhagic pleural effusion in one (2.5%) patient
[74]	Retrospective	55	Daily injection of tPA 10 mg and DNase 5mg	51 (92.7%) treatment success; reduction in pleural opacity	No serious adverse events
[76]	Retrospective	101	Extension of tPA 10 mg and DNase 5 mg beyond 3 days	20 (20%) had extended dosing. No significant difference on length of pleural drainage, hospital stay, surgical referral	No significant difference on complications

Curr Opin Pulm Med. 2018 Jul;24(4):367-373

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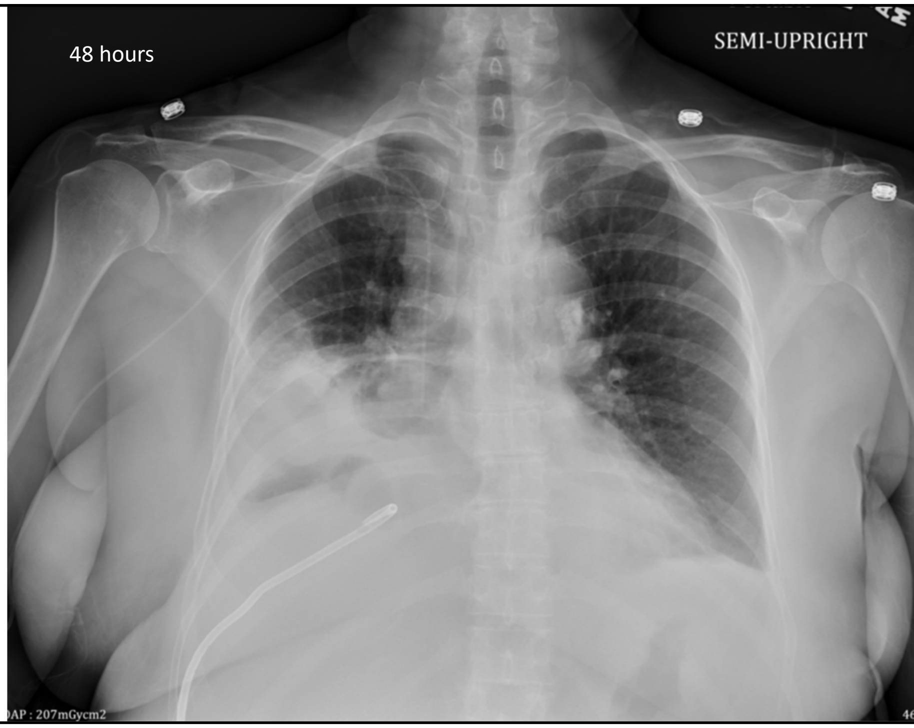

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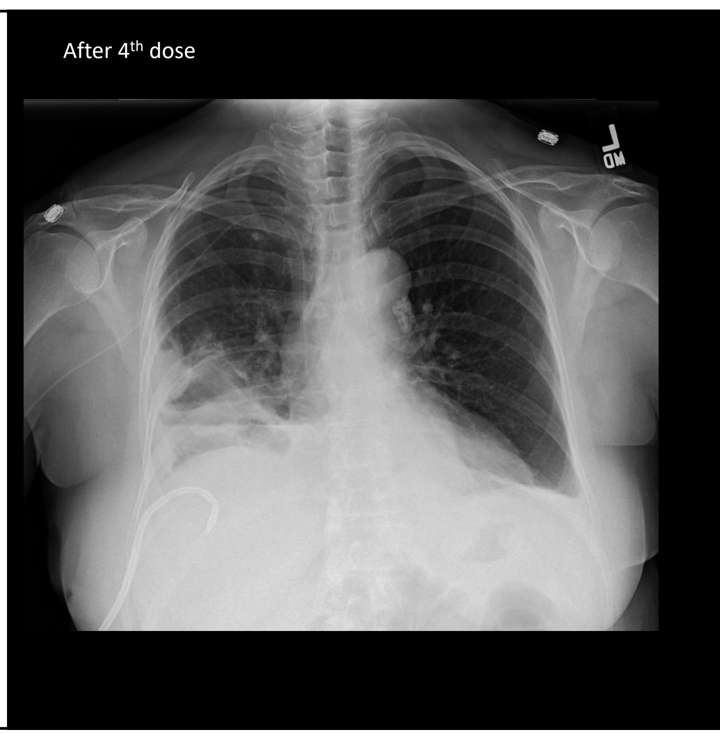

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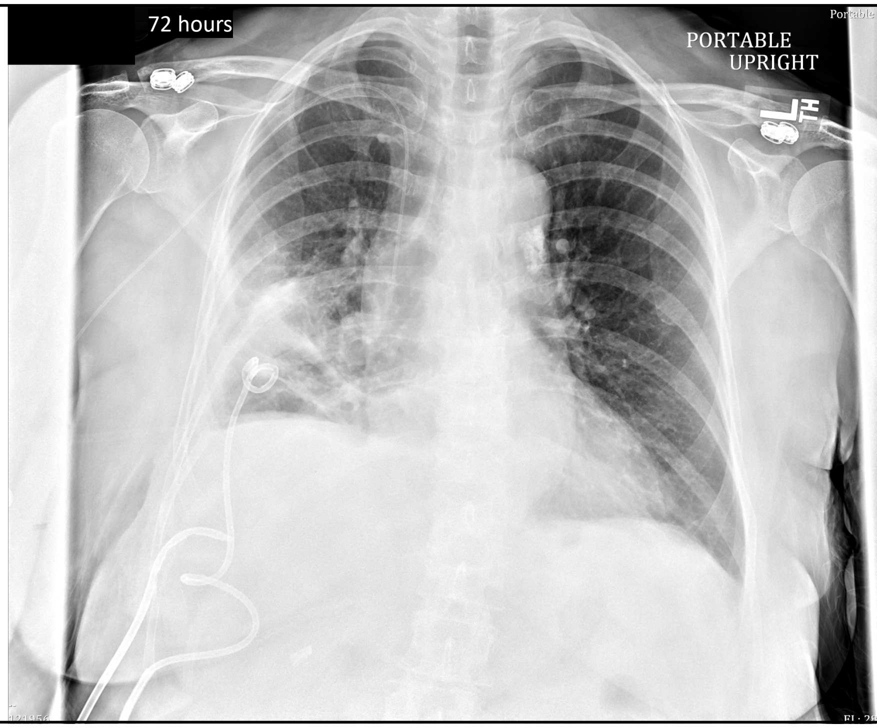

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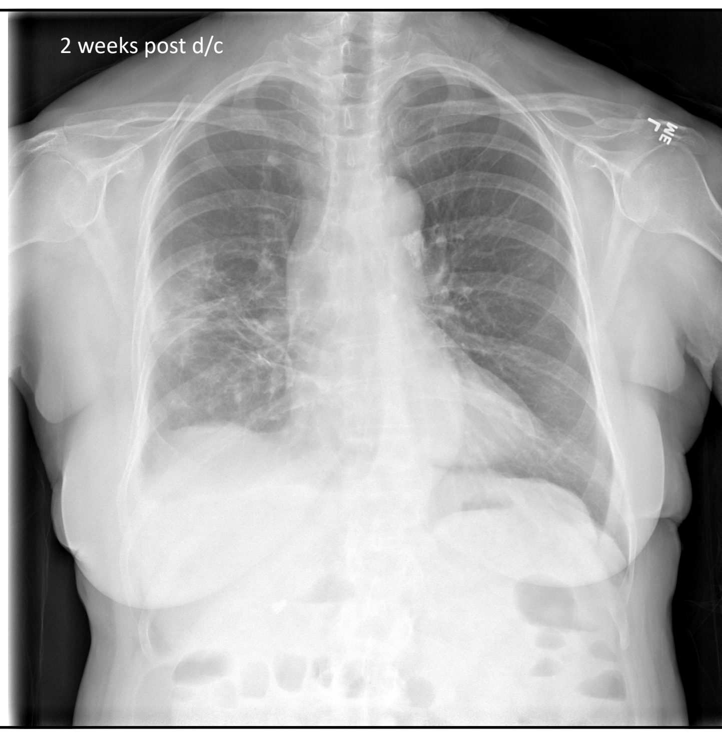

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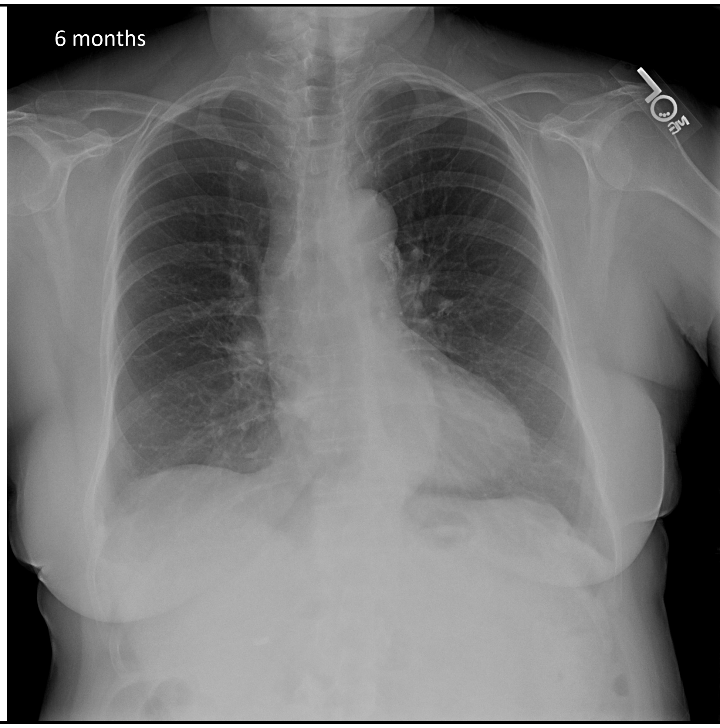

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Practical approach to managing pleural infection

Confirm diagnosis of pleural infection as per guidelines (1)
Initiate conservative therapy:
Insertion of chest tube
Small size tubes (≤16) are sufficient in the majority of cases (17,52)
Insertion should be imaging guided to ensure optimal placement
Further ICCs may be needed for distant separate locules of pleural infection
Administration of appropriate antibiotic therapy as directed by local guidelines and organism isolated
Failure of conservative therapy:
Escalation of treatment should be considered if there is:
Clinical evidence of ongoing sepsis (i.e., fever, elevated WCC and CRP) and
Persistent pleural effusion on imaging despite appropriately located ICC
The options at this point include trial of intrapleural therapy or surgery
Intrapleural treatment can be offered as alternative to surgery
Assessing bleeding risk is essential: platelet count, coagulation profile, anticoagulant medications, renal failure
Surgery is indicated if there is a contraindication to tPA/DNase (e.g., bronchopleural fistula) or tPA/DNase therapy has failed
Assess response to tPA/DNase
Daily imaging (CXR/ultrasound) to assess successful drainage of fluid
Monitoring of volume and appearance of pleural fluid drained
Monitor inflammatory markers (e.g., fever, peripheral blood leukocyte count, CRP or procalcitonin)

tPA, tissue plasminogen activator; DNase, deoxyribonuclease; WCC, white cell count; CRP, C-reactive protein; ICC, intercostal catheter; CXR, chest radiograph.

J Thorac Dis 2015;7(6):999-1008

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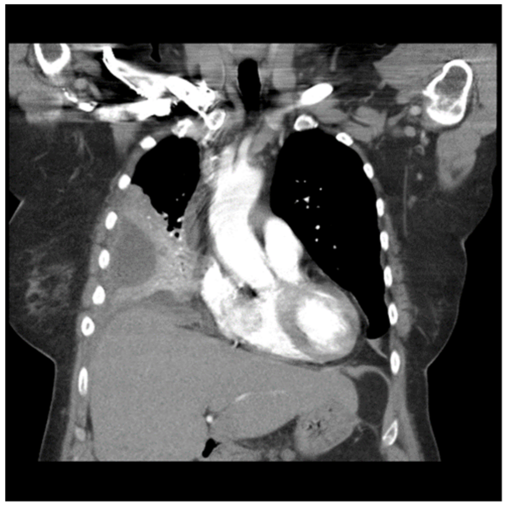
Questions?



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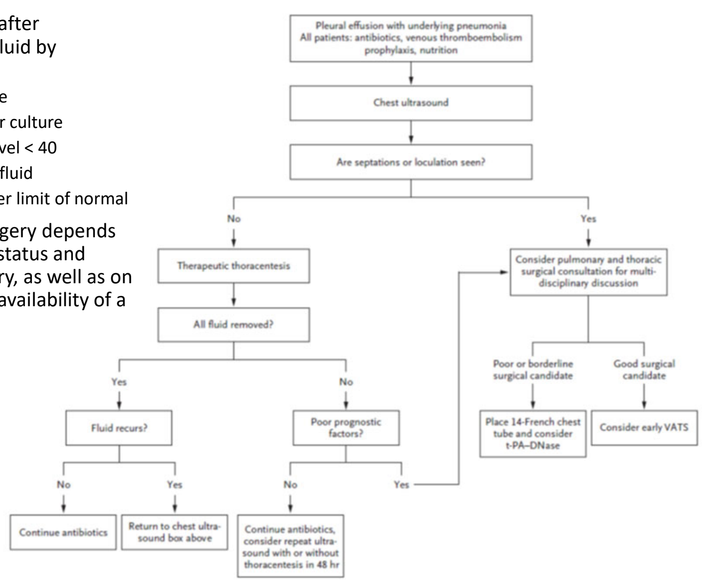
Management of Parapneumonic Effusions.

- Poor prognostic factors after incomplete removal of fluid by thoracentesis include:
  - Pus in the pleural space
  - Positive Gram's stain or culture
  - Pleural fluid glucose level < 40
  - pH < 7.15, and pleural fluid
  - LDH > 3 times the upper limit of normal
- A decision regarding surgery depends on the patient's clinical status and ability to undergo surgery, as well as on local resources and the availability of a skilled surgeon.



n engl j med 378;8 nejm.org February 22, 2018

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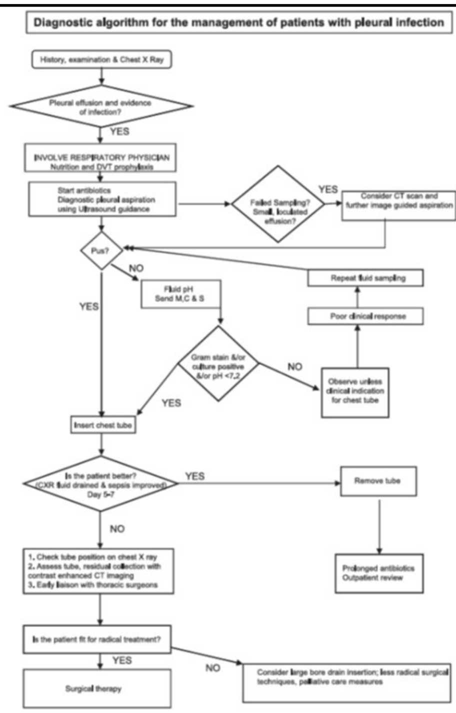
Thorax 2010;65(Suppl 2):ii1eii3.
doi:10.1136/thx.2010.137042



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Case 2

- 74 yo female presented to urgent care with complaints of right-sided chest pain and shortness of breath that came on this morning. Patient originally presented to her primary care physician 10 days ago with c/o cough, low grade fevers and right sided pleuritic CP. CXR demonstrated RLL PNA. She was prescribed doxycycline x 10 days. Patient had been compliant with her antibiotic and cough was doing much better until this morning. Otherwise no fever chills nausea vomiting headache dysuria change in bowel habit. Currently pain is on the right side and worsening with deep inspiration.

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- PMH
  - Depression
  - Syncope
  - Ectopic pregnancy
  - GERD
  - Esophageal stricture
  - Allergic rhinitis
- PSH
  - APPENDECTOMY
  - CYSTOSCOPY
  - ESOPHAGEAL DILATION
  - KNEE ARTHROSCOPY
  - OVARIAN CYST REMOVAL
  - Salpingectomy For Ectopic Pregnancy
- Allergies: Erythromycin
- Meds:
  - benzonatate (TESSALON PERLES) 100 mg capsule
  - calcium citrate-vitamin D3 (CITRACAL+D) 315-200 mg-unit per tablet
  - citalopram (CeleXA) 20 mg tablet
  - cod liver oil capsule
  - doxycycline (ADOXA) 100 mg tablet
  - estradiol (ESTRACE) 0.01 % (0.1 mg/gram) vaginal cream
  - ipratropium (ATROVENT) 0.06 % nasal spray
  - melatonin 1 mg tablet
  - temazepam (RESTORIL) 7.5 mg capsule
  - tretinoin, emollient, (RENOVA) 0.02 % cream
- FH
  - Suicide- Father
  - Cancer, Depression,HIV-Mother
- Social
  - Retired writer/editor. Lives alone. Divorced. Has one son.
  - Alcohol: none
  - Tobacco: never
  - Drugs: never
  - No sick contacts, no significant travel history recently

Physical exam

Vital Signs:

Temp: 36.5 °C (97.7 °F), Heart Rate: [51-68] 55, Resp: [18-24] 19, BP: (93-136)/(42-71) 108/61, SpO2: 94 %, O2 Flow Rate (L/min): 2 L/min

Physical Exam:

GEN: Pleasant, elderly woman, sitting in bed, no acute distress, alert, oriented x3

HEENT: Normocephalic, atraumatic. Pupils 2 mm reactive to light, EOM intact. Throat without erythema or exudate. Neck supple, no LAD.

PULM: Decreased breath sounds on right lung field. +Egophony right middle/lower lung fields. No wheezes, rales, or rhonchi.

CV: RRR. No rubs, murmurs, or gallops.

GI: Abd soft, nontender, nondistended. Normoactive BS all 4 quadrants. No pulsatile masses or hepatosplenomegaly.

EXT: No clubbing, cyanosis, or peripheral edema.

NEURO: CN 2-12 grossly intact. Strength 5/5 in all ext bilaterally. Sensation intact to light touch in all ext bilaterally. Gait normal.

SKIN: Warm and dry. No rashes or ulcerations.

Labs:

WBC- 12.6, Hbg 12.9, Hct 38.3, PLT 466, 76% -N

Na 140, K 4.0, Cl 103, Hco3 27, BUN 23, Cr 0.9, Glu 97, Ca 9.1, TP- 6.6, Alb 3.7, AST 24, ALT- 24, Bili 0.3

CRP- 133.9

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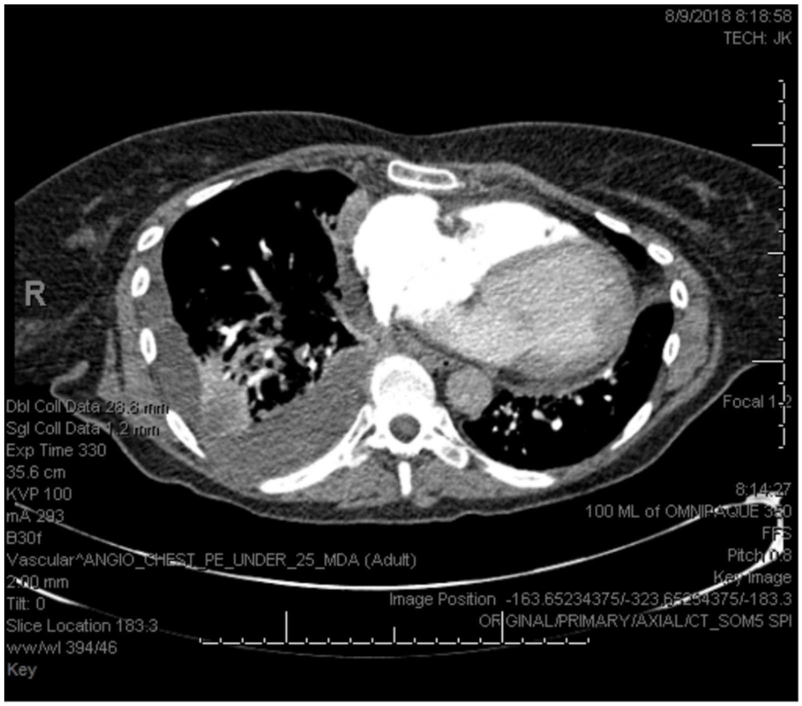
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ORIGINAL/PRIMARY/AXIAL/CT_SOM5 SPI

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32

- Pleural fluid- Orange cloudy
- Cell count WBC-37,200, 60% neutrophils, 1% lymphocytes, 37% monos, 2% eos
- LDH- 2041, Prot- 3.6, Glu- 63
- Culture- no growth
- Cyto- abundant acute inflamation

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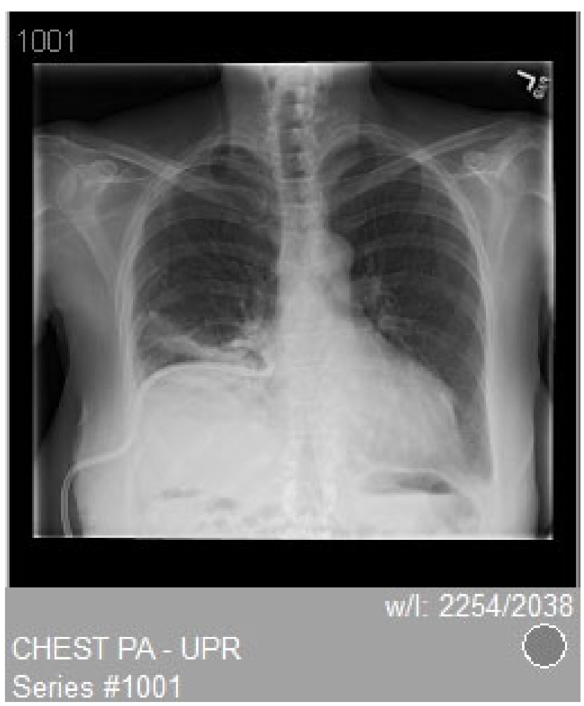

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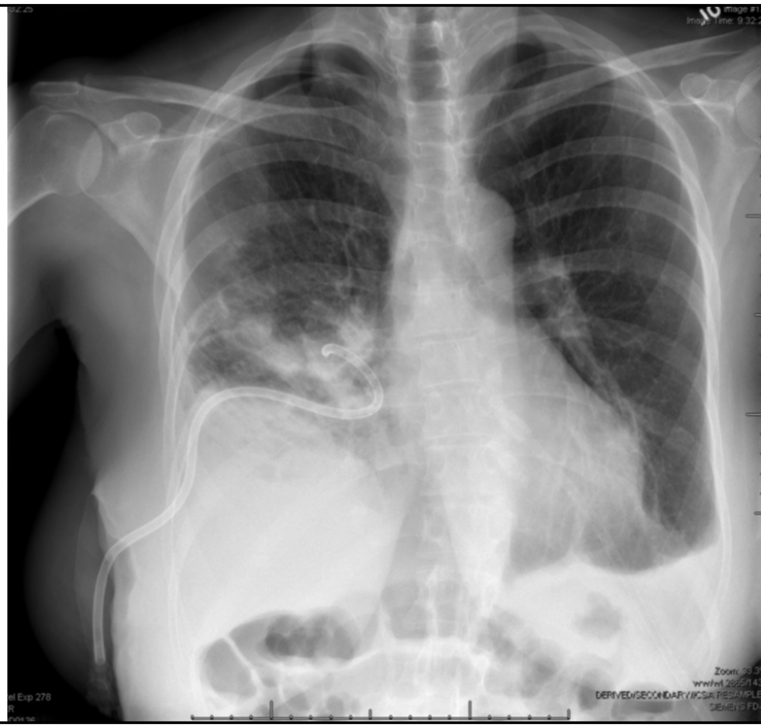

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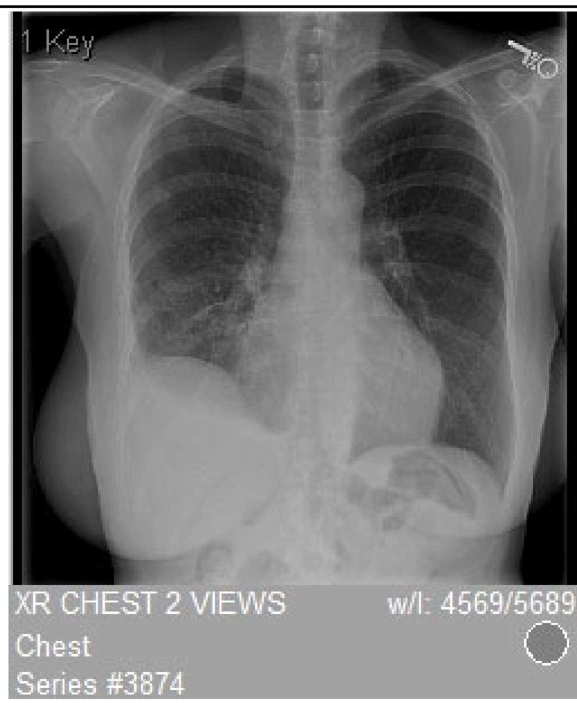

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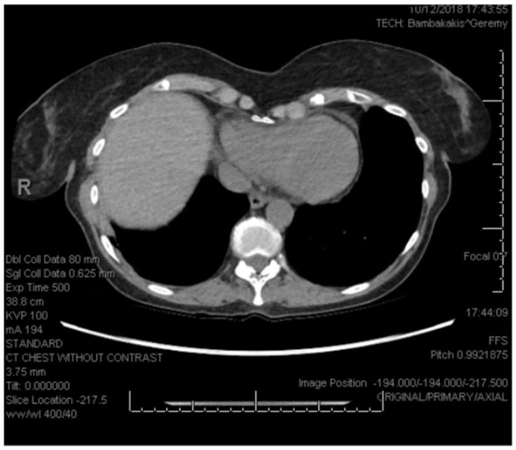
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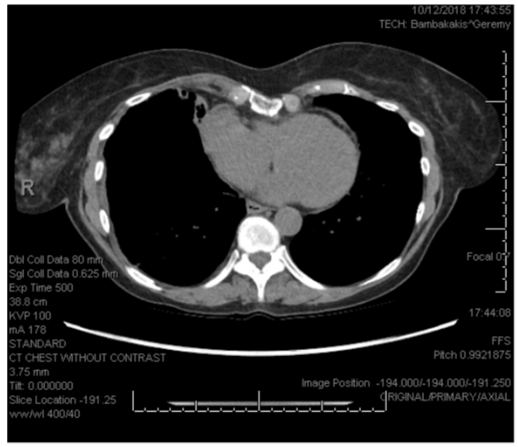
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R
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KVP 100
mA 178
STANDARD
CT CHEST WITHOUT CONTRAST
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ORIGINAL/PRIMARY/AXIAL

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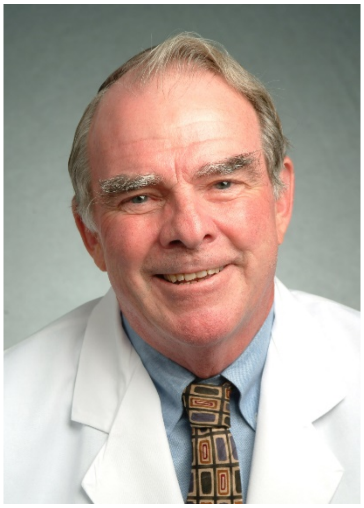
BREAK AND EXHIBITS

Saturday, October 5, 2019 – 2:30 p.m. – 2:50 p.m.



Evaluation and Management of Spontaneous and Secondary Pneumothorax

Richard Light, MD
Vanderbilt University

Saturday, October 5, 2019 – 2:50 p.m. – 3:20 p.m.

Professor Richard Light was born in Steamboat Springs, Colorado, the son of a fox and mink farmer. He then attended medical school at Johns Hopkins University, USA from 1964 to 1968 and subsequently did his training in internal medicine and pulmonary diseases at that institution. He then spent nearly 20 years at the University of California Irvine, USA where his positions included Chief of the Pulmonary Diseases Section and Associate Chief of Staff for Research at the Veterans Administration Hospital in Long Beach. Dr. Light moved to Vanderbilt University, USA 22 years ago and is presently Professor of Medicine at Vanderbilt University in Nashville, Tennessee.

Dr. Light is best known for his research on pleural disease. He developed Light's criteria for the separation of transudates and exudates in 1972. Subsequently, he has published many papers concerning the pathogenesis, diagnosis, and management of pleural disease. Dr. Light is the editor of 16 books of which the two most famous are the single authored monograph *Pleural Diseases,* which is now in its sixth edition, and *The Textbook of Pleural Disease,* which he edits in conjunction with Dr. YC Gary Lee and is in its third edition. Dr. Light has been an author on more than 450 articles and has spoken in 57 countries.

Treatment and Management of Spontaneous Primary and Secondary Pneumothorax

California Thoracic Society
Southern California
2019 Annual Educational Conference
October 4-5, 2019

Richard W. Light, M.D.
Professor Of Medicine
Vanderbilt University
rlight98@yahoo.com

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2

No conflicts of Interest

3

Primary Spontaneous Pneumothorax

- Spontaneous pneumothorax without underlying lung disease
- Etiology is thought to be rupture of subpleural blebs
- Six times more common in males
- More common in tall, thin individuals
  - 2 inches taller, 25 pounds lighter
- 92% in smokers in most countries
  - Probably subclinical lung disease
  - In China, only 50% are smokers
  - Different gene? Air pollution?
- 90% develop with patient at rest
- Usually nuisance rather than life threatening

4

Treatment For Primary Spontaneous Pt

- If small and asymptomatic – observe
  - 1.25% hemithorax absorbed daily
  - Oxygen can increase the rate by a factor of 6
- Otherwise aspirate
- If aspiration fails, tube thoracostomy or thoracoscopy
- If thoracoscopy, staple blebs and perform pleural abrasion

5

Aspiration Method

- A 16-gauge needle with an internal polyethylene catheter is inserted into the second anterior intercostal space at the midclavicular line after local anesthesia
- Attach three-way stopcock and large syringe
- Air is manually withdrawn until no more can be aspirated
  - If more than 4 L air, tube thoracostomy
- Observe for four hours then discharge
- Alternatively discharge with Heimlich valve

6

Results WITH ASPIRATION 27 PATIENTS WITH PSP

- Mean age 28 yrs ± 11.6
- Smoking status 10 current, 6 ex
- % Pneumothorax 62.1 ± 26.9
- Immediate success 16/27 (59.2%)
  - 13 discharged, 3 hospitalized (requested)
- Urgent readmissions none
- 3 recurrences during follow-up of one year
  - Noppen et al: Am J Respir Crit Care Med 2002; 165:1240
- Two other studies similar results
  - Andrivet et al. Chest 1995; 108:335
  - Harvey J et al. BMJ 1994; 309:1338

7

Possible Disadvantages Of Aspiration

- Patients might develop immediate recurrence (<48 hrs) which could be life-threatening
  - Did not happen in recent series
- The recurrence rate in the following 12 months might be greater
  - Three series combined recurrence rate in patients treated successfully was 14/64 (22%)
  - Recurrence rate in patients treated with tube thoracostomy in the same three series was 29%
- Probable that successful aspiration selects patients less likely to have recurrence

8

Advantages OF ASPIRATION

- Less expensive since hospitalization is not necessary in many patients
- Less painful
- Less time consuming for the patient and for the family

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Recurrence Rates For Spontaneous Pneumothorax

- 40 - 50% recurrence after first occurrence of primary spontaneous pneumothorax if no pleurodesis
- 60 - 70% recurrence after second occurrence
- Most recurrences within the first 90 days
- Recurrence rates with secondary spontaneous pneumothorax appear to be slightly higher

10

Predictors of Recurrence wih Spontaneous Pneumothorax

- Studied 182 patients with spontaneous pneumothorax in Guangzhou, China
- Multiple regression analysis showed that recurrences were significantly related to:
  - Secondary as opposed to primary pneumothorax
  - Patients who were taller
  - Patients who weighed less
  - Patients who did not receive chemical pleurodesis

  - Guo Y, Xie C et al. Respirology 2005; 10:378.

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Recurrence Rates After Treatment For Pneumothorax

Treatment	Recurrence %
Aspiration	50%
Tube thoracostomy	50%
Tube thoracostomy With pleurodesis	25%
Thoracoscopy with talc	5%
Thoracoscopy with Stapling and abrasion	3%
Thoracotomy	1%

12

13

Secondary Spontaneous Pneumothorax

- Most common with COPD, but can occur with most lung diseases
  - Particularly common with severe COPD
- More serious than with primary because there is less lung reserve
- Diagnosis frequently delayed in patients with severe COPD because the lung is already very dark on chest radiograph

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Treatment For Secondary Spontaneous Pneumothorax

- Tube thoracostomy for almost all patients
  - Simple aspiration is ineffective
- After the lung has expanded should attempt to create pleurodesis
  - Thoracoscopy is best, but can inject a sclerosing agent through chest tube
- If lung has not expanded or if there is a persistent airleak after 5 days, thoracoscopy should be performed
  - Blebs are treated with stapling
  - Pleural abrasion is used to create pleurodesis
  - Alternatively use blood patch

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Blood Patch for Persistent Airleak

- With this technique 2 ml/kg venous blood injected through the chest tube
- Chest tube remains unclamped for 2 hours and kept at 60 cm above the patient's chest to prevent backflow
- Underwater seal after the procedure
- Success rate was 91.7% in 109 patients with pneumothorax
  - Chambers A et al. Interact Cardiovascular and Thor Surg 2010; 11:468-472
- Also effective with post-operative airleaks
  - 92.7% success rate in 133 patients

16

Re-expansion Pulmonary Edema

- Pulmonary edema occurring when lung is expanded after being collapsed with pleural effusion or pneumothorax
- Edema fluid has high protein content
- Syndrome probably represents re-perfusion injury
- In animals occurs only if lung is collapsed for several days and high negative pressure is used
- Incidence is unknown but low

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Pneumothorax Secondary To Tuberculosis

- In the past TB was the most frequent cause of pneumothorax, but now is uncommon cause of pneumothorax in most countries
- Cavitary lesion are common among TB patients with pneumothorax
- Difficult to treat
  - Insert chest tubes in all
  - Airleaks are large and frequently take weeks to close
  - Consider Heimlich valve
- Role of thoracoscopy remains to be defined
  - Shamaei M et al: Respir Care 2011; 56:298-302

19

Catamenial Pneumothorax

- Pneumothorax in conjunction with menstruation
- Usually develops within 24 to 48 hours of beginning of menses
- Initial pneumothorax usually after age of 25
- Usually right-sided
- Recurrences are very frequent
- Pathogenesis
  - Holes in diaphragm
  - Pleural endometriosis
- Treatment
  - Suppress ovulation 50% success rate
  - Thoracoscopy with diaphragm repair and pleurodesis

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Iatrogenic Pneumothorax
Cause In 128 Cases

Procedure	#	%
Transthoracic needle asp	39	30
Subclavicular iv line	26	20
Thoracentesis	22	17
Pleural biopsy	14	11
Transbronchial biopsy	11	9
Mechanical ventilation	10	8
Supraclavicular iv line	5	4
Pericardiocentesis	1	1

21

Treatment Iatrogenic Pneumothorax

- Asymptomatic - observe
  - Oxygen if in hospital
- Symptomatic – aspirate
- Aspiration fails then small chest tube
- Small chest tube fails then large chest tube
- Most patients with iatrogenic pneumothorax are treated too aggressively
- Need not worry about preventing recurrence

22

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Tension Pneumothorax

- A tension pneumothorax is a pneumothorax in which the pleural pressure is positive throughout the respiratory cycle
- To get positive pressure throughout the respiratory cycle, must have positive pressure applied to airway (mechanical ventilation or resuscitation) or invoke a one-way valve type mechanism

24

Diagnosis Of Tension Pneumothorax

- Tension pneumothorax is a medical emergency
- If time is spent confirming the diagnosis radiologically, the patient is likely to die
- The physical examination strongly suggests the diagnosis in most cases
- The diagnosis confirmed when aspiration yields air

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Aspiration for the Treatment of Tension Pneumothorax

- 60 ML syringe with 3cc saline attached to a three way stopcock and a needle-catheter system
- After the needle catheter is inserted into the pleural space, withdraw the needle and attach to stopcock and syringe
- Remove plunger from syringe and open stopcock
  - Bubbling through stopcock confirms the diagnosis of tension pneumothorax
  - If saline goes into the thorax, wrong diagnosis

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Summary

- Treat primary spontaneous and iatrogenic pneumothoraces initially with aspiration
- Treat secondary spontaneous pneumothorax with tube thoracostomy plus attempt to create pleurodesis
- Think of catamenial pneumothorax in women who are ovulating
- Tension pneumothorax is a medical emergency and the diagnosis should be made with the physical exam

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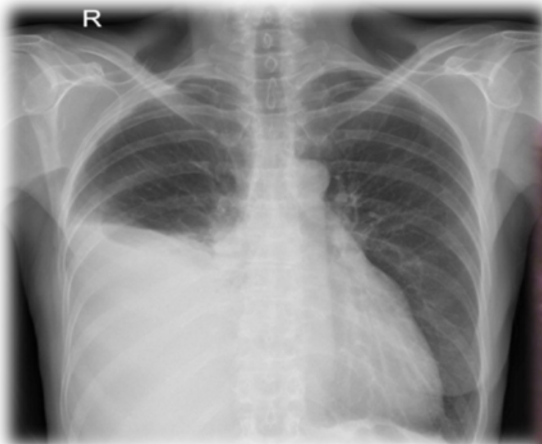
Management of Recurrent Malignant Pleural Effusions

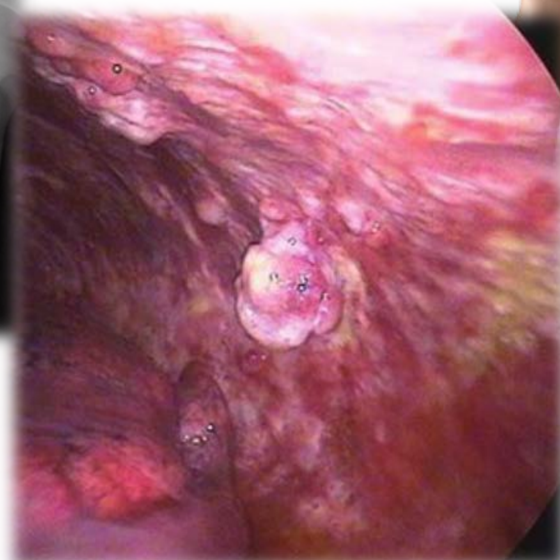
Ara Chrissian, MD
Loma Linda University

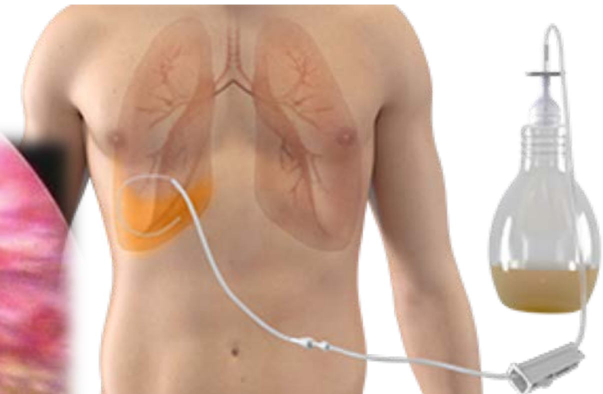
Saturday, October 5, 2019 – 3:20 p.m. –3:50 p.m.

Dr. Chrissian received his medical degree from the University of California, San Diego. He completed fellowship in Pulmonary and Critical Care Medicine at Washington University, St. Louis and dedicated subspecialty training in Interventional Pulmonology at Henry Ford Hospital in Detroit. He is currently the Director of Adult Bronchoscopy and Interventional Pulmonology at Loma Linda University Medical Center, where he also serves as Associate Professor of Medicine and an Associate Director for the Pulmonary and Critical Care Fellowship. In addition to a busy clinical practice, Dr. Chrissian is heavily involved in medical education.

Management of recurrent malignant pleural effusion







Ara A. Chrissian, MD, FCCP, DAABIP
Director, Adult Bronchoscopy and Interventional Pulmonology
Associate Professor of Medicine
Associate Fellowship Director
Division of Pulmonary, Critical Care, Hyperbaric, Sleep, and Allergy Medicine
Loma Linda University

No relevant financial disclosures

Goals and objectives

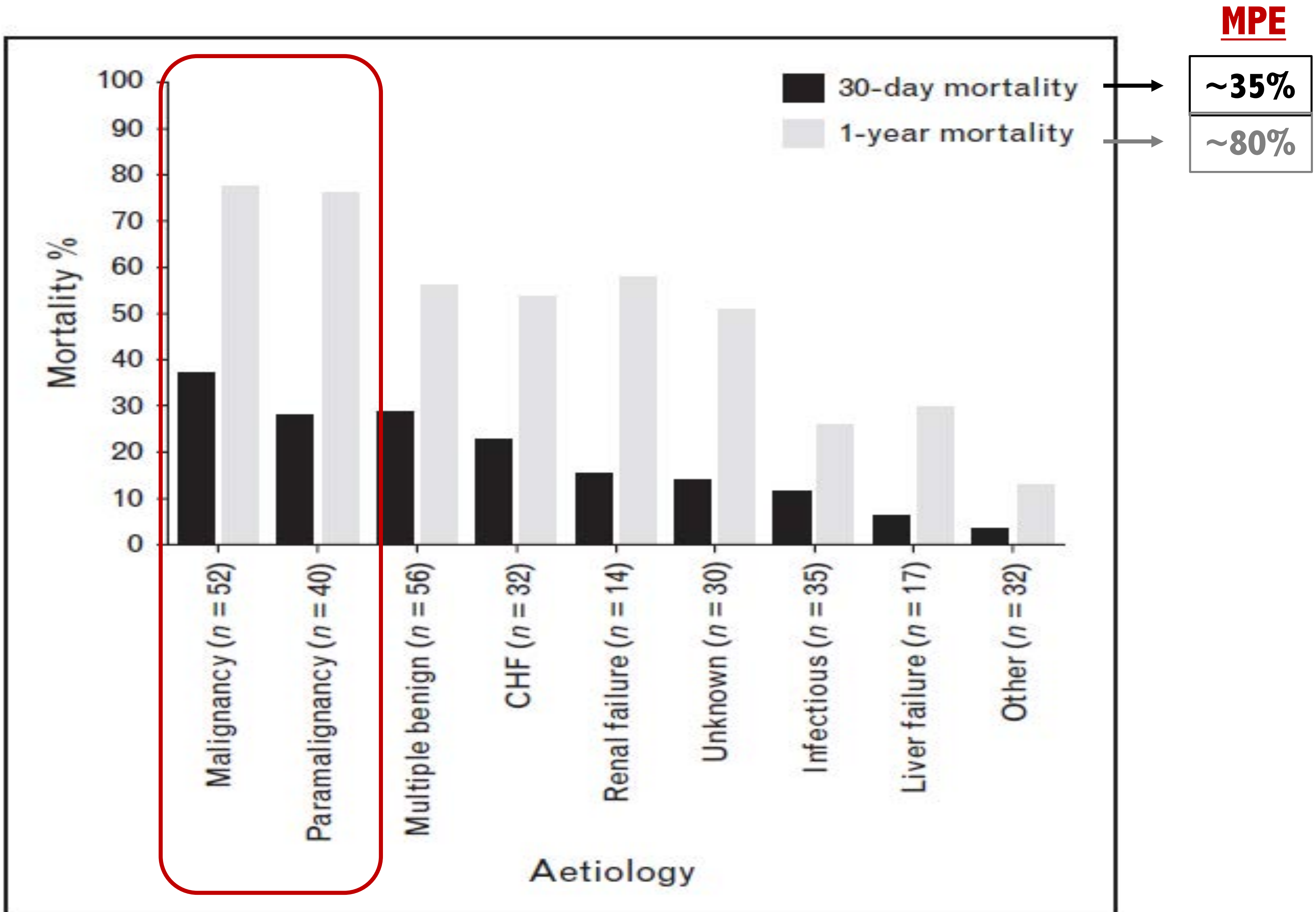
- Understand the basic pathophysiology and impact of malignant pleural effusion (MPE)
- Identify the therapeutic options available for managing MPE
- Apply an evidence-based and patient-centered approach to managing MPE

Malignant pleural effusion (MPE) is common

Congestive heart failure	500,000
Parapneumonic effusion	300,000
Malignant Pleural effusion	200,000
Lung	60,000
Breast	50,000
Lymphoma	40,000
Other	50,000
Pulmonary embolization	150,000
Viral disease	100,000
Cirrhosis with ascites	50,000
Postcoronary artery bypass graft surgery	50,000
Gastrointestinal disease	25,000
Tuberculosis	2,500
Mesothelioma	2,300
Asbestos exposure	2,000

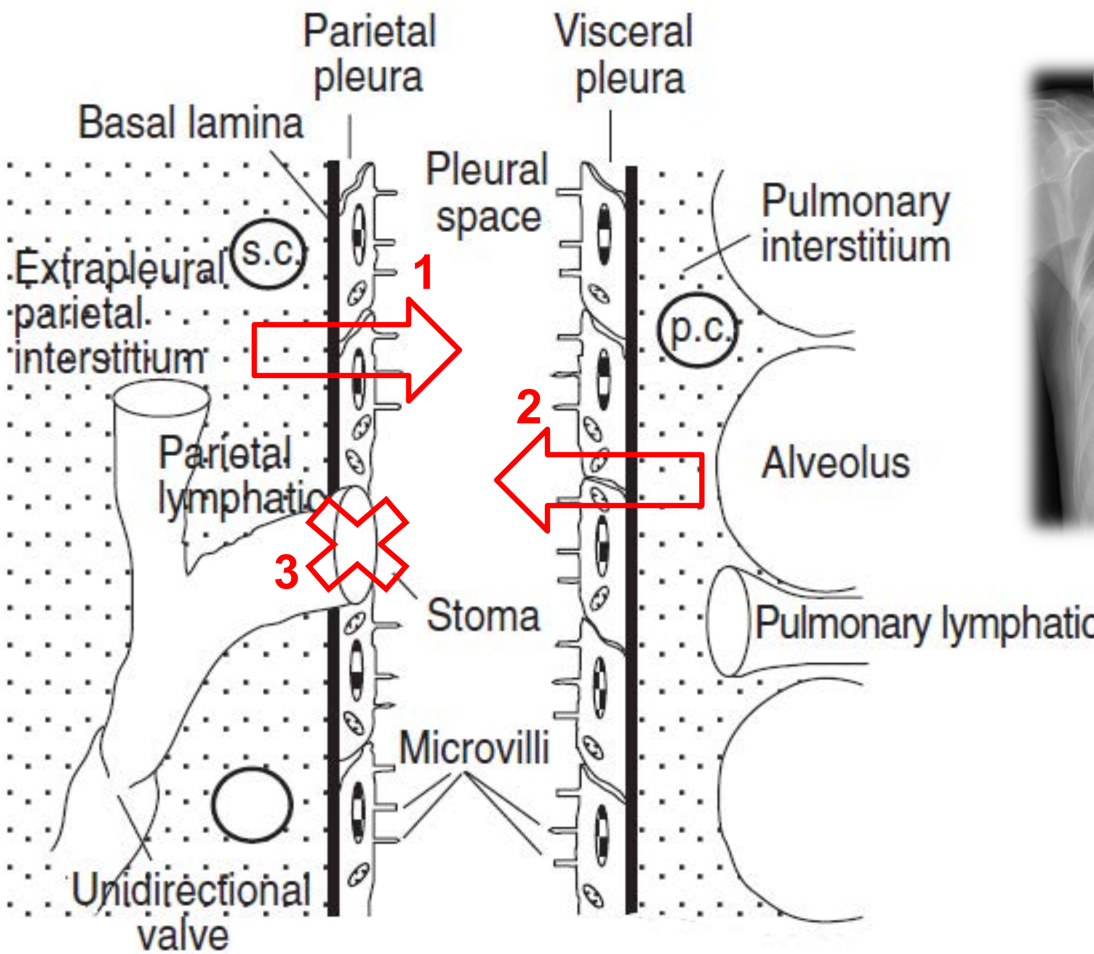
Light, 2007; Kookoolis, 2014

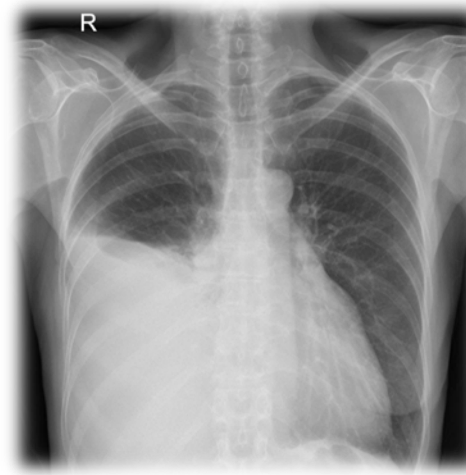
MPE predicts a poor prognosis



Eur Respir J 2015; 46: 495–502

Increased pleural fluid production + decreased clearance
= Pleural effusion

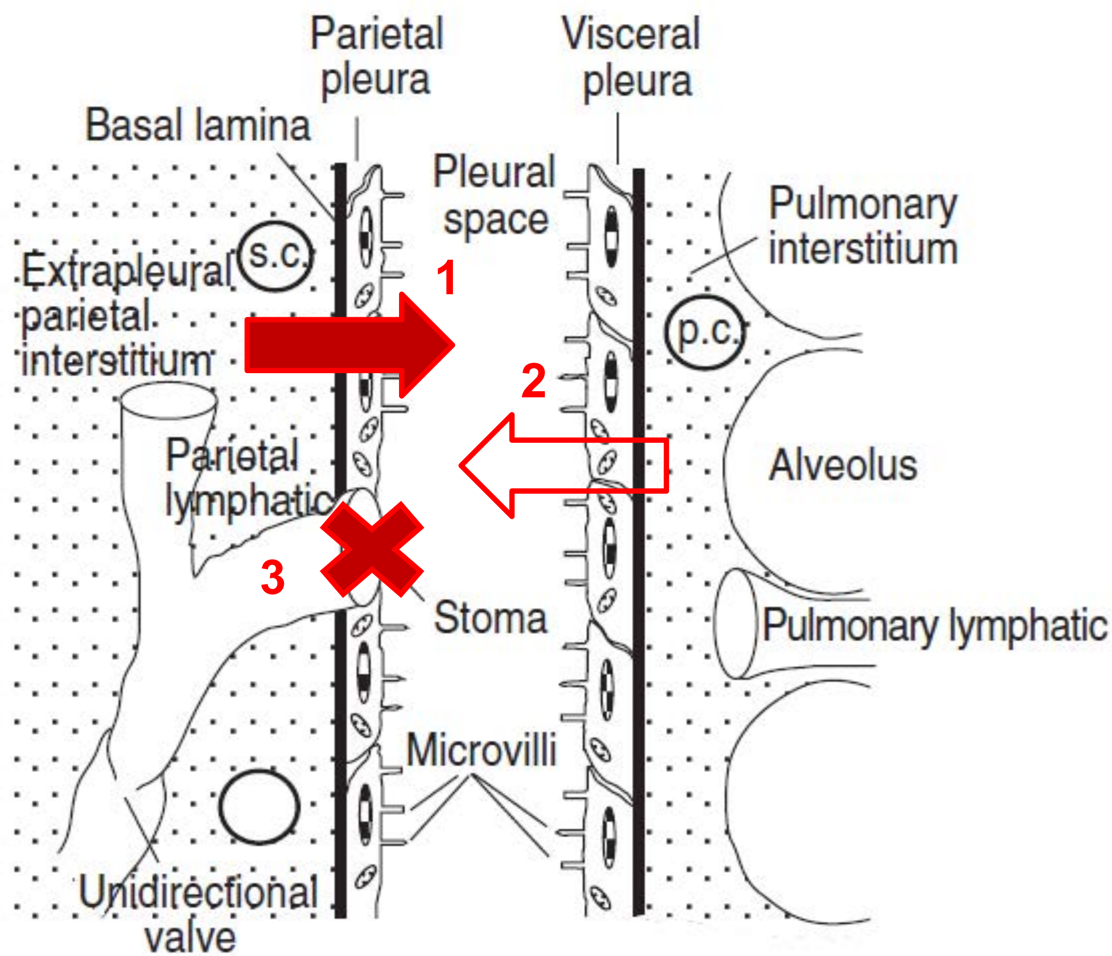




$$\text{Flow} = k \times [(P1 - P2) - s(\pi1 - \pi2)]$$

1- Local inflammatory response:

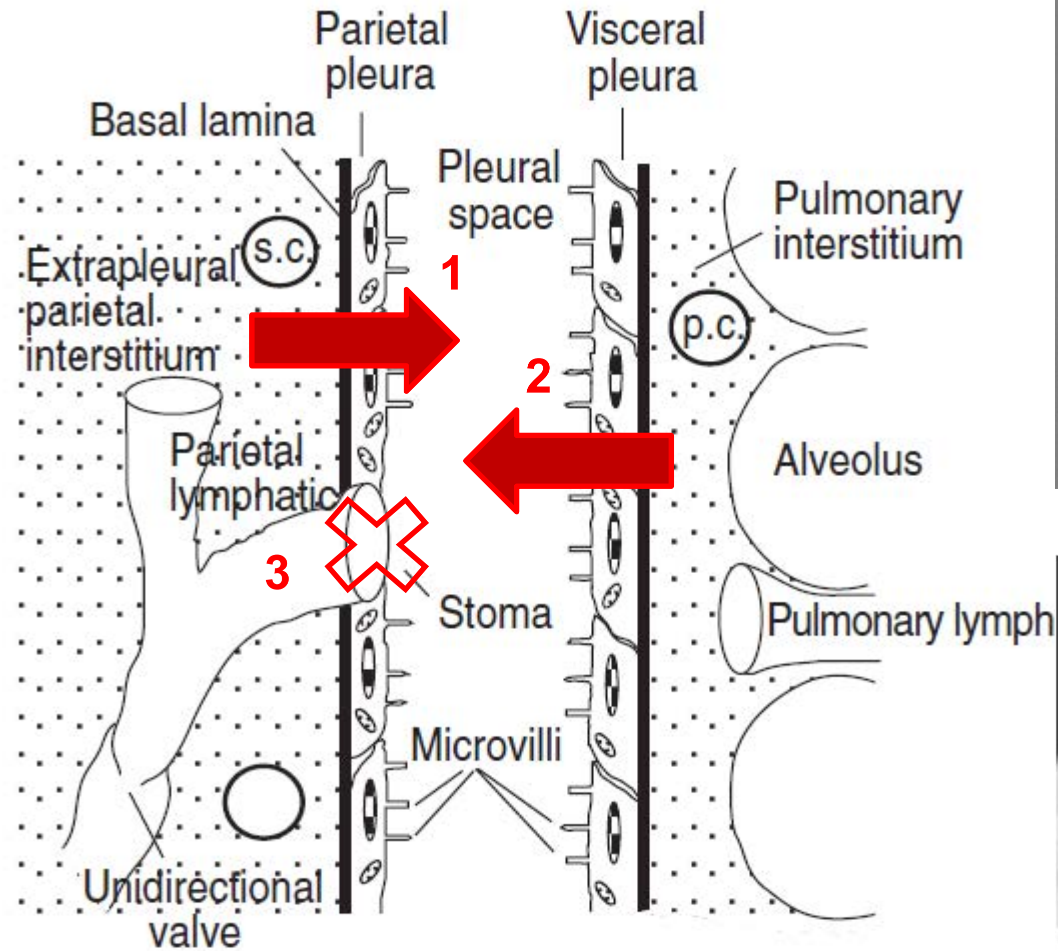
Increased mesothelial permeability, parietal lymph obstruction



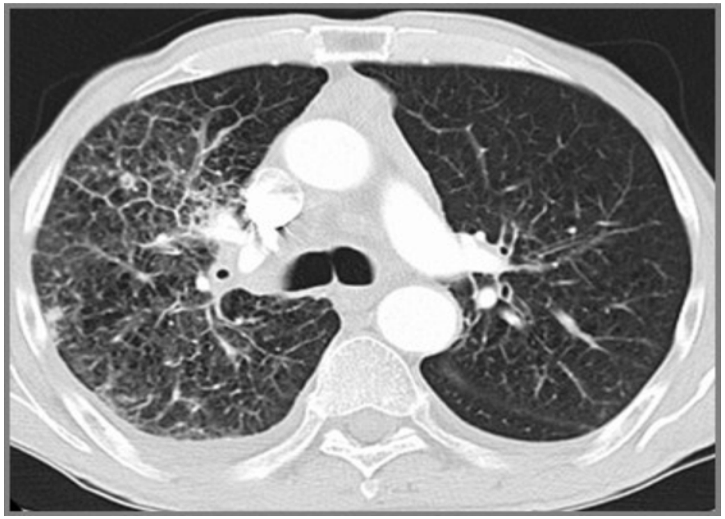
Flow = k x [(P1 - P2) - s (π1 - π2)]

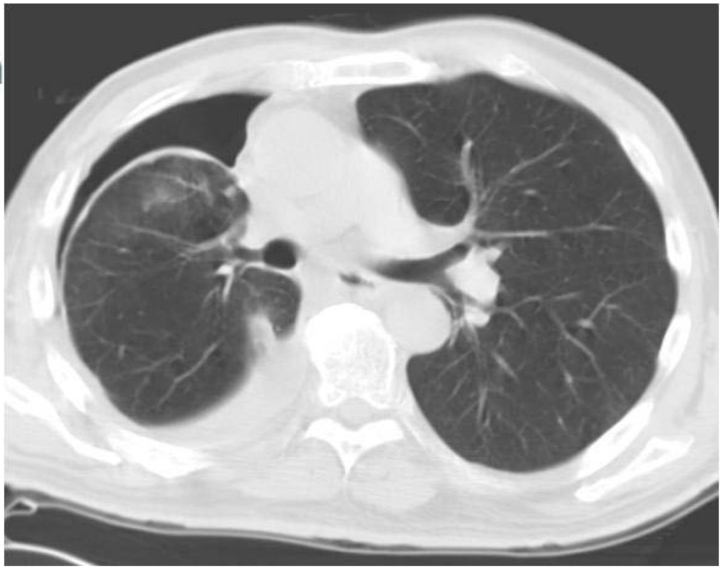
2- Change in local hydraulic forces:

Lymphangitic carcinomatosis, SVC syndrome, trapped lung



$$\text{Flow} = k \times [(P1 - P2) - s(\pi 1 - \pi 2)]$$

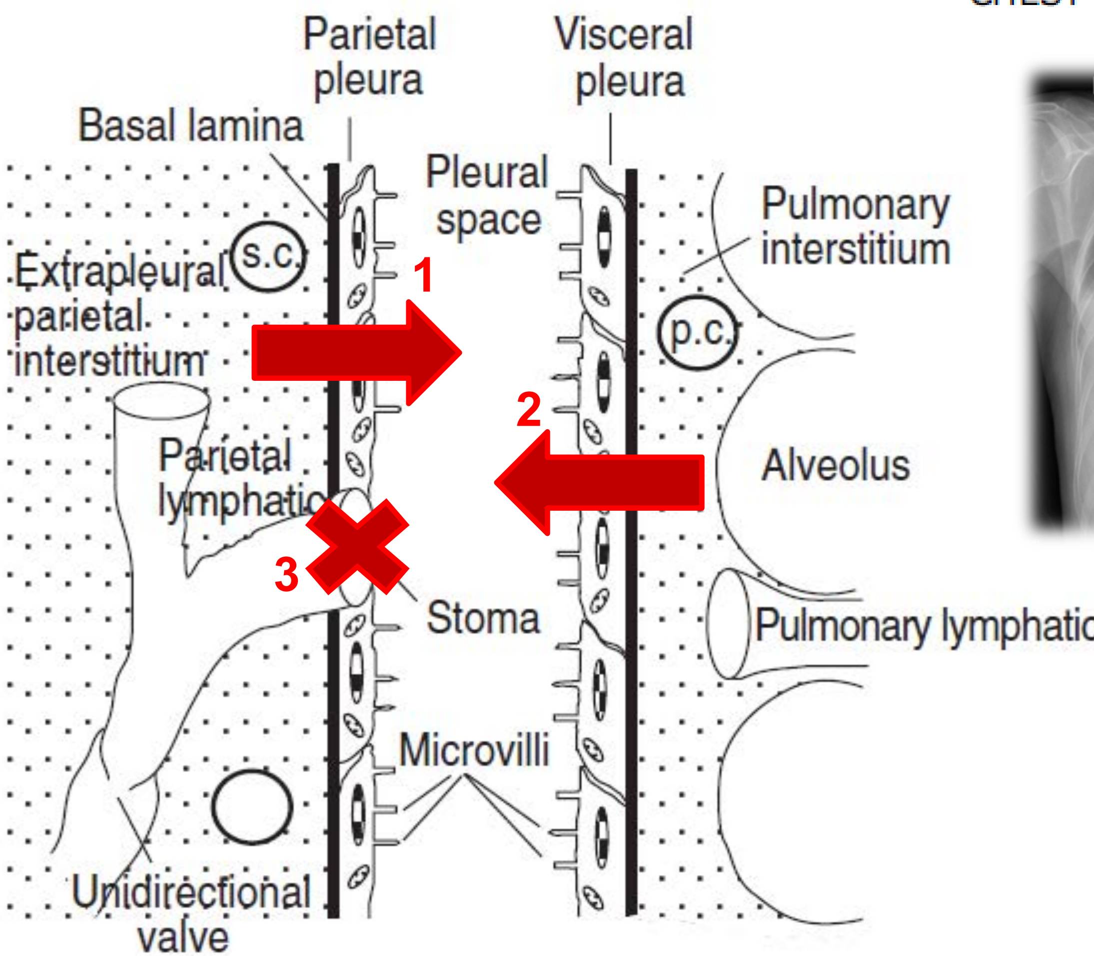


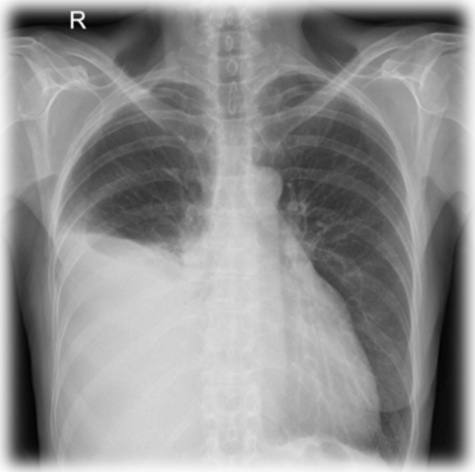


MPE: multifactorial pathophysiology

= large, rapidly recurrent (median 9 days, IQR 3-32)

CHEST 2018; 153(2):438-452

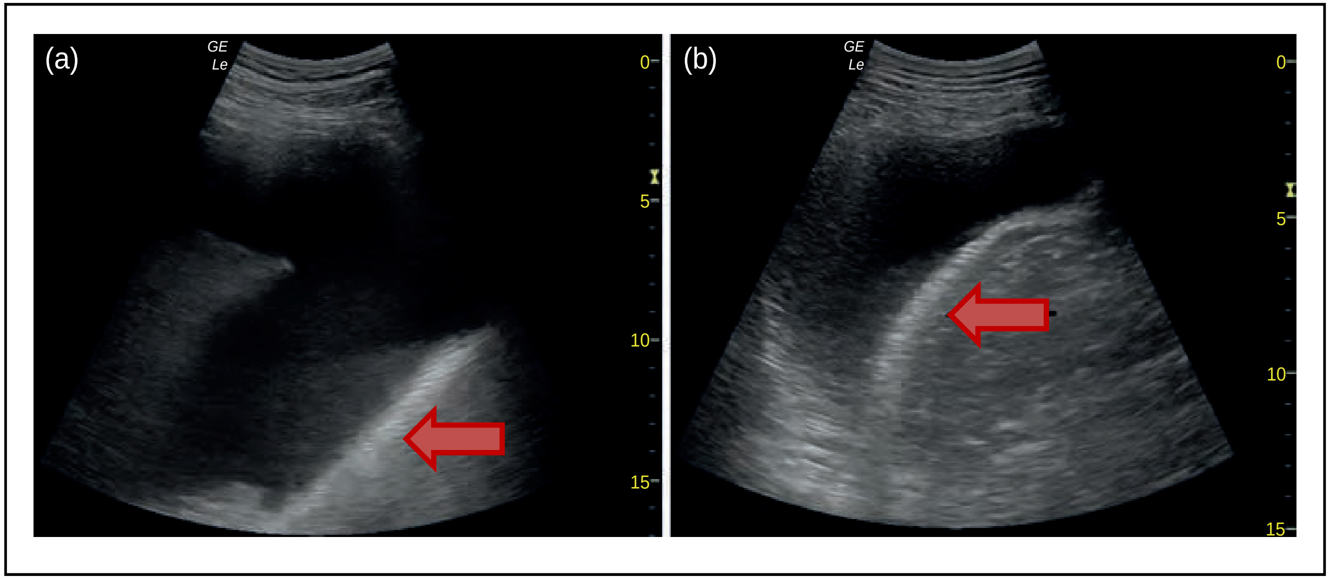




↑↑↑Flow = ↑k x ↑[(P1 - P2) - ↓s (π1↓- π2)]

MPE: Significant morbidity

- Patients often symptomatic
- Drainage offers a substantial palliative benefit in a majority of patients



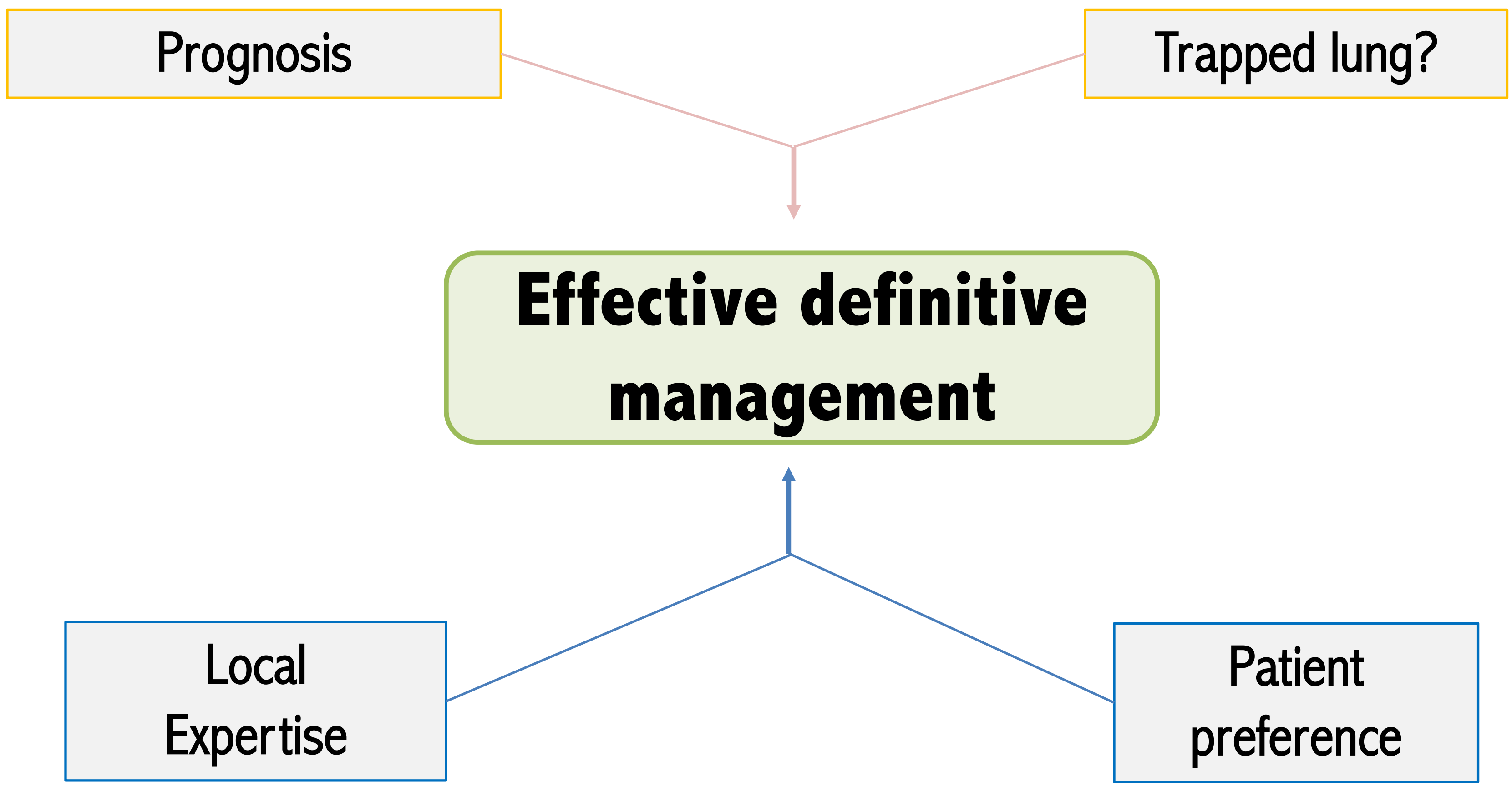
a) Flattening of diaphragm due to large pleural effusion, restored to more normal 'dome' contour after thoracentesis (b)

Management of Malignant Pleural Effusions

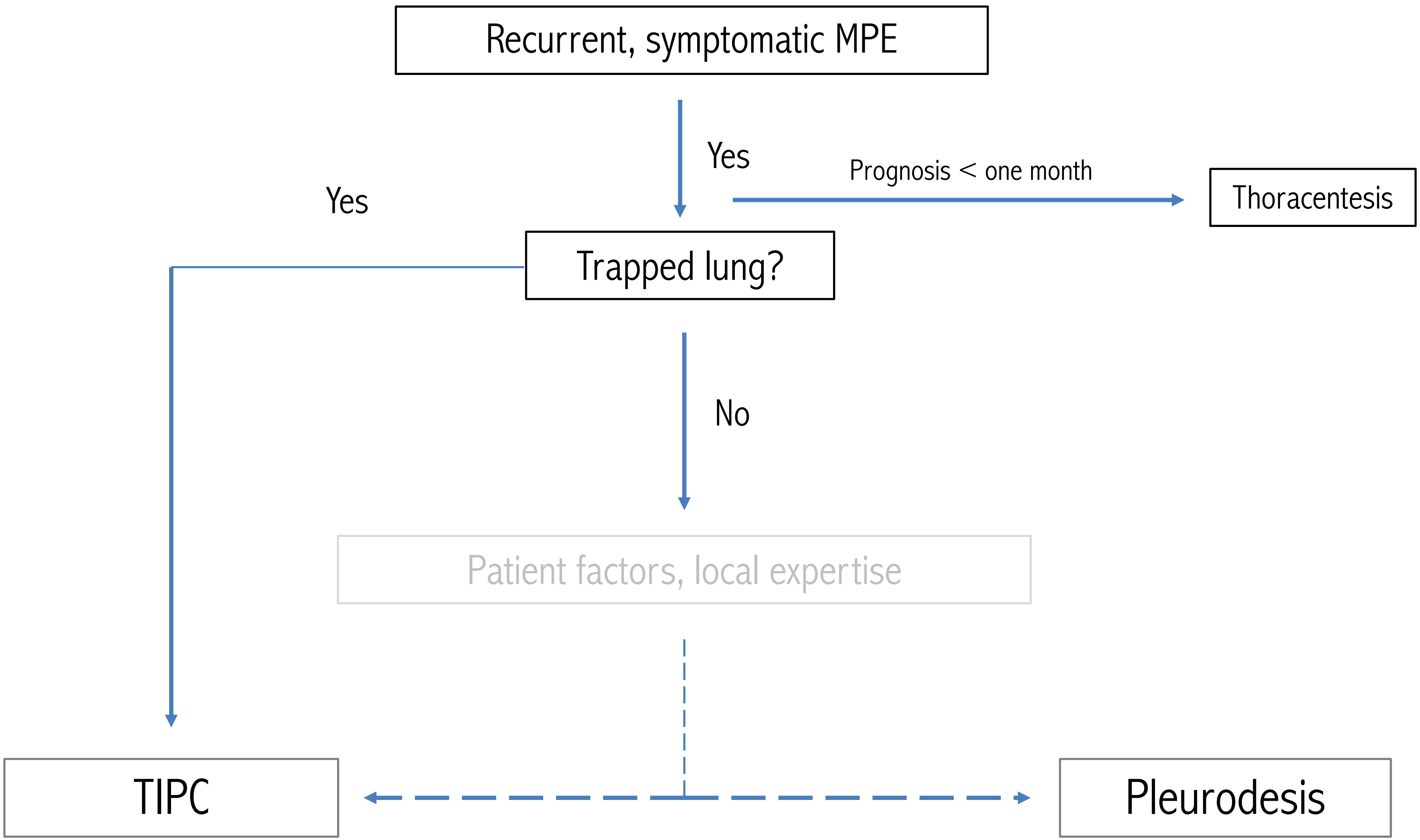
An Official ATS/STS/STR Clinical Practice Guideline

David J. Feller-Kopman*, Chakravarthy B. Reddy*, Malcolm M. DeCamp, Rebecca L. Diekemper, Michael K. Gould, Travis Henry, Narayan P. Iyer, Y. C. Gary Lee, Sandra Z. Lewis, Nick A. Maskell, Najib M. Rahman, Daniel H. Sterman, Momen M. Wahidi, and Alex A. Balekian; on behalf of the American Thoracic Society, Society of Thoracic Surgeons, and Society of Thoracic Radiology

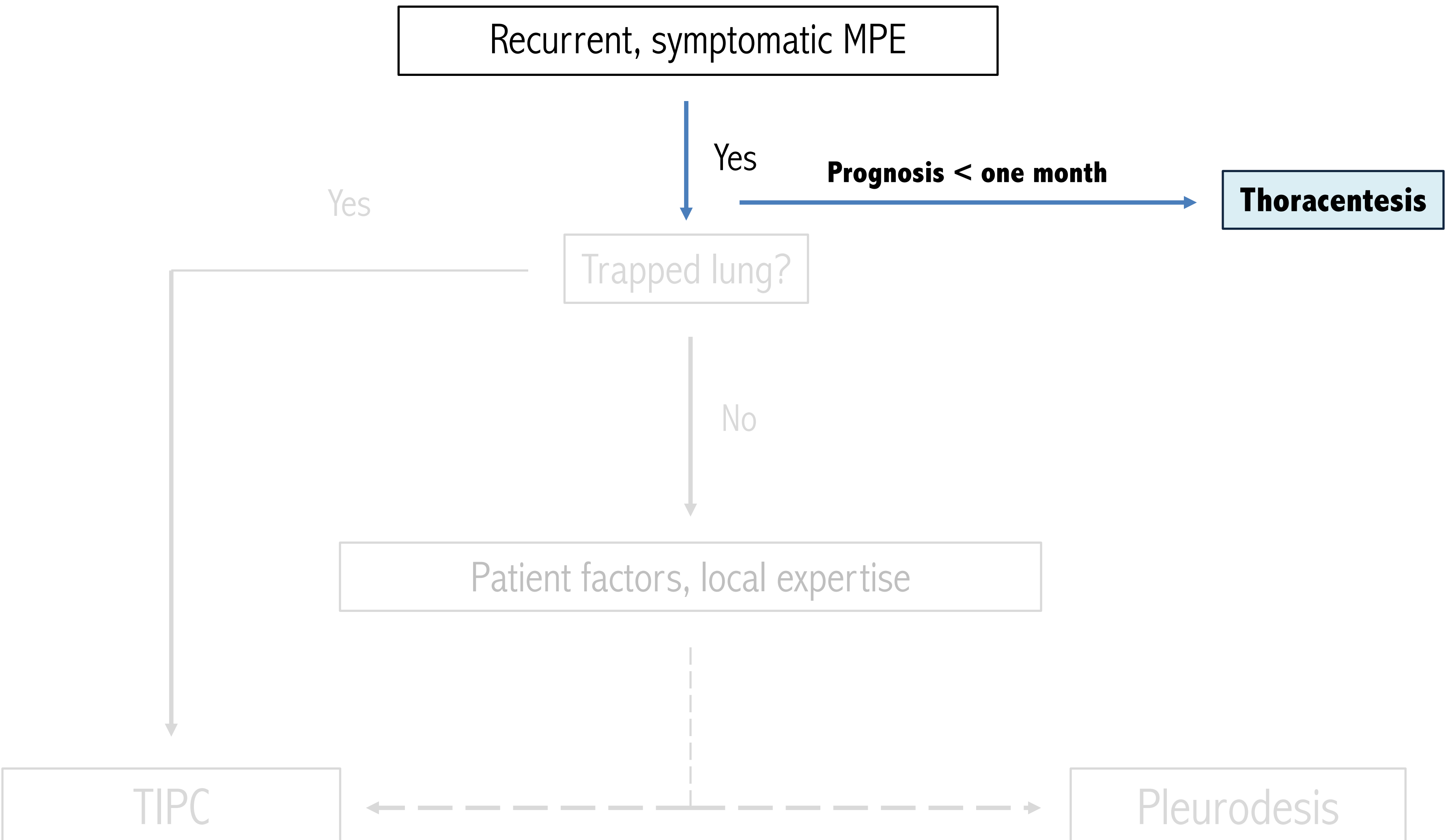
Managing the *recurrent, symptomatic* (MPE)



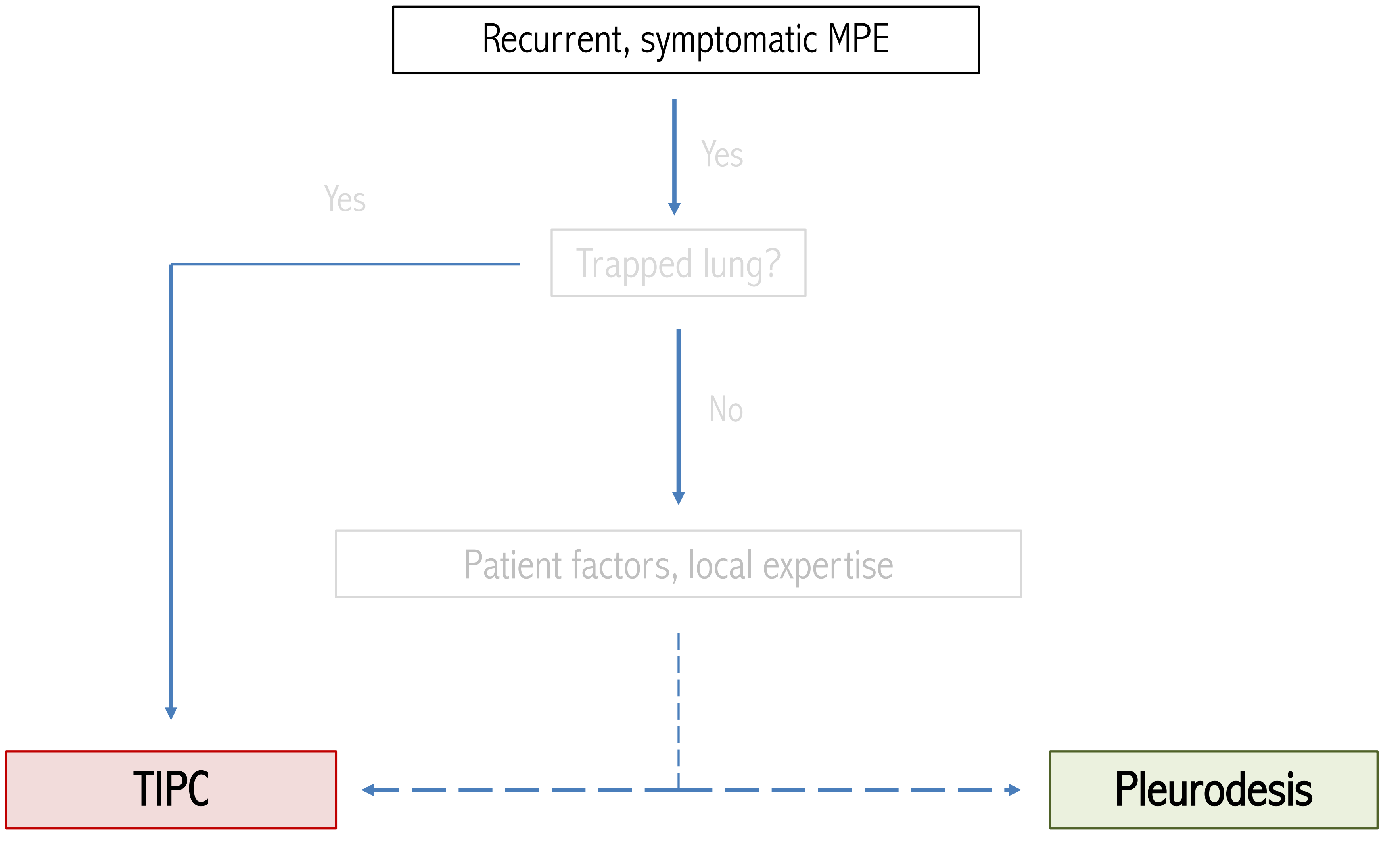
Definitive management for MPE



Definitive management for MPE



Definitive management for MPE



Pleurodesis: Obliteration of pleural space

Mesothelial injury

Inflammation

Coagulation

Fibrosis

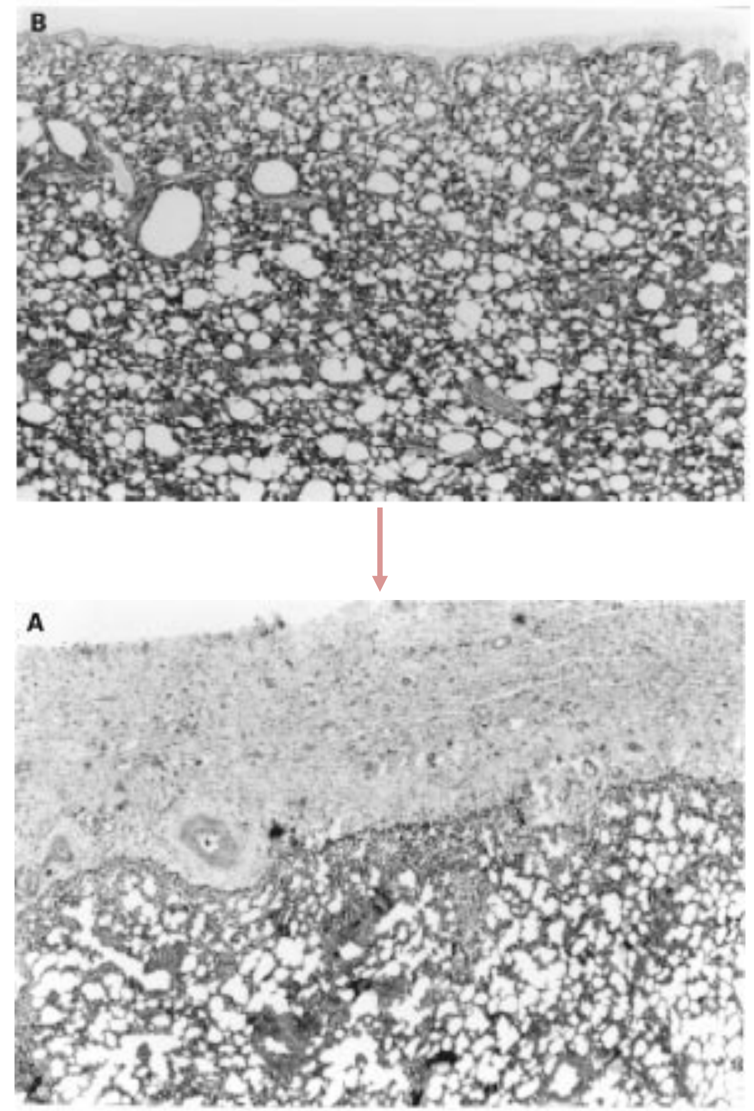
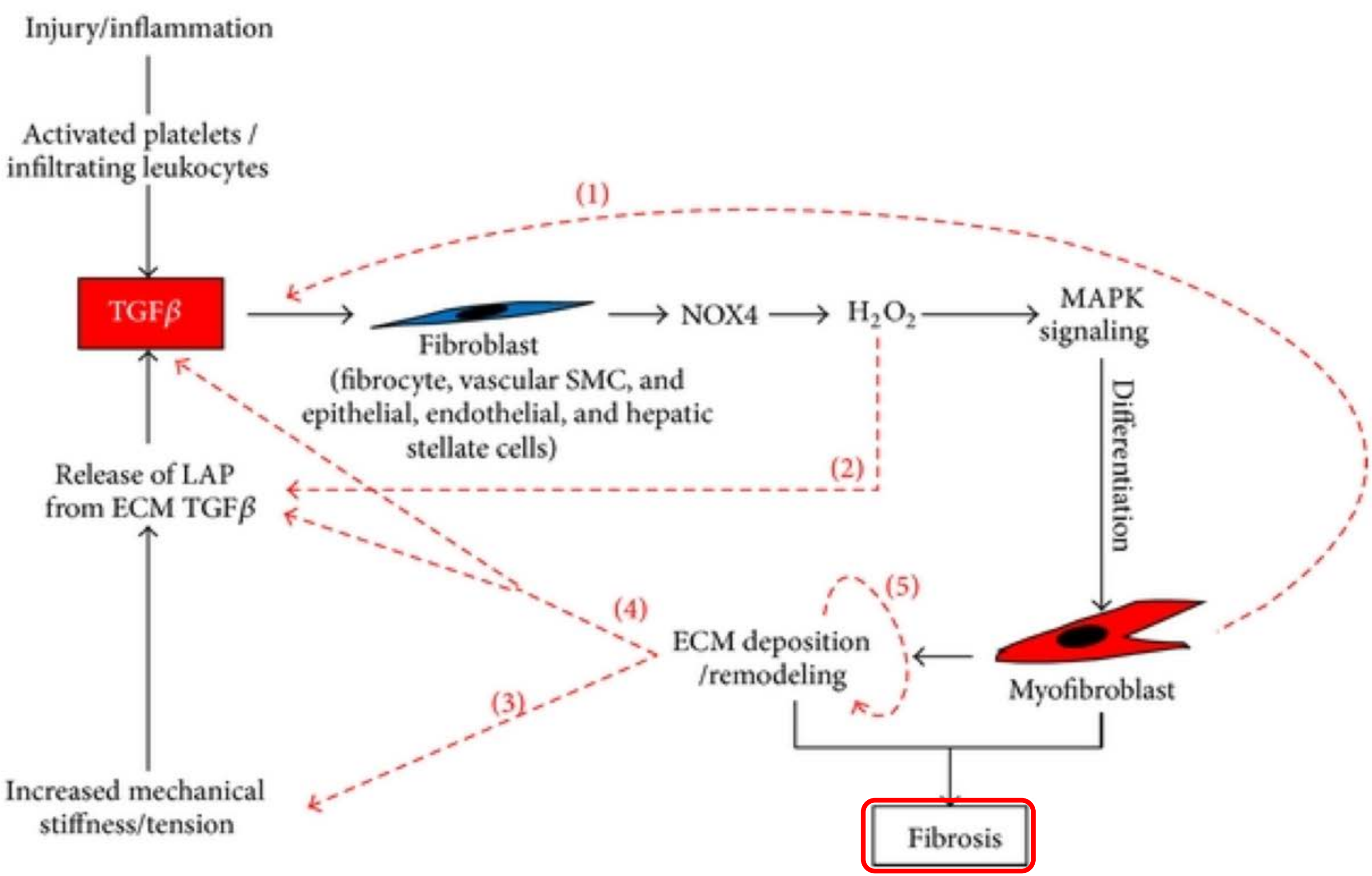


Figure adapted and modified from Lee, et al *Thorax* 2000;**55**:1058–1062

TGF-β promotes pleural fibrosis



BioMed Research International
Volume 2014, Article ID 131737, 14 pages
http://dx.doi.org/10.1155/2014/131737

Chemical pleurodesis

Sclerosant **(Talc, TCN)**

↓

Mesothelial injury

Inflammation

Coagulation

Fibrosis

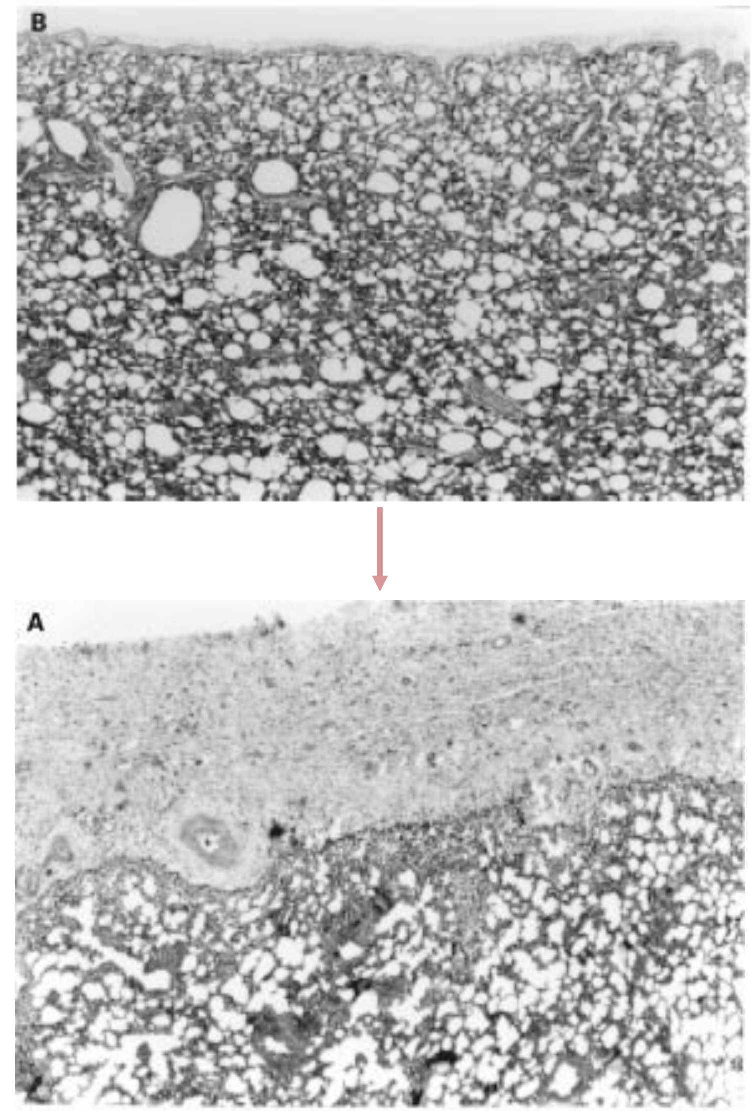


Figure adapted and modified from Lee, et al *Thorax* 2000;**55**:1058–1062

Bedside chemical pleurodesis

Hospitalization

↓

Chest tube drainage, 1-2 days

↓

Instillation of sclerosant

↓

Chest tube drainage, 1-2 days

↓

Discharge home

Thoracoscopic talc poudrage

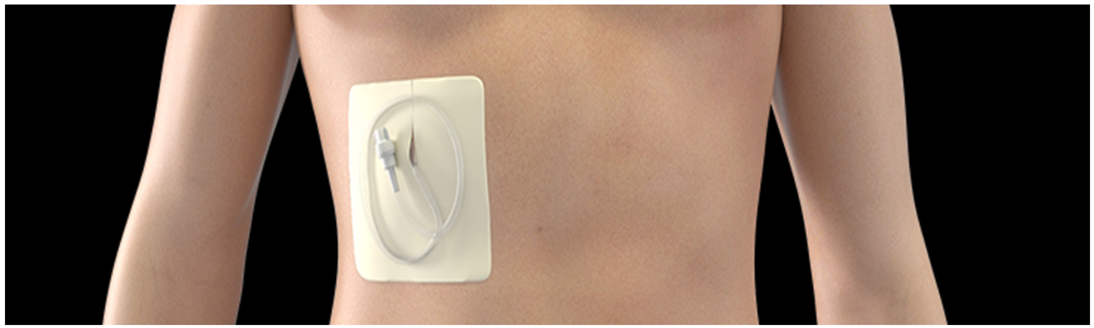
Which agent to use?

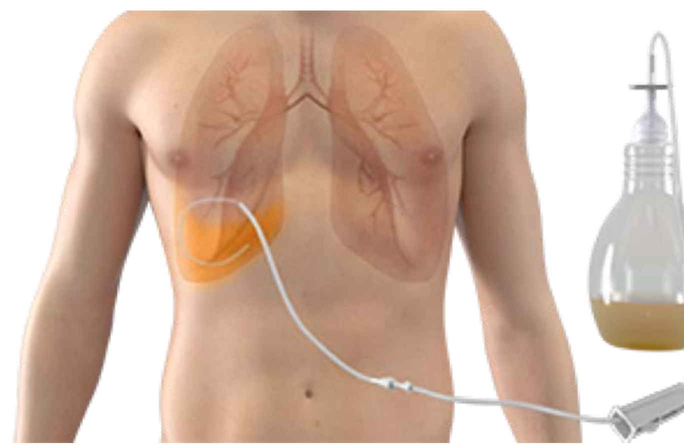
Efficacy and Safety of Talc Pleurodesis for Malignant Pleural Effusion: A Meta-Analysis

	Success rate:	Talc	Comparator	
Talc vs Bleomycin				
	Hamed/1989	10/10	10/15	1.45 (1.00–2.12)
	Lynch/1996	8/17	10/14	0.66 (0.36–1.20)
	Zimmer/1997	17/19	11/14	1.14 (0.83–1.56)
	Diacon/2000	13/15	6/17	2.46 (1.25–4.82)
	Ong/2000	16/18	14/20	1.27 (0.91–1.77)
	Haddad/2004	30/37	23/34	1.20 (0.91–1.59)
	Overall	94/116	74/114	1.25 (1.06–1.46)
Talc vs Tetracycline				
	Fentiman/1986	11/12	10/21	1.92 (1.19–3.11)
	Lynch/1996	8/17	8/15	0.88 (0.44–1.76)
	Overall	19/29	18/36	1.36 (0.62–2.97)
Talc vs Povidone iodine				
	Das/2008	19/24	24/28	0.92 (0.72–1.19)
	Mohsen/2011	19/22	17/20	1.02 (0.79–1.30)
	Overall	38/46	41/48	0.97 (0.81–1.15)

Overall talc success= 79%

Tunneled Indwelling Pleural Catheter (TIPC)





Placement of IPC

Outpatient procedure suite

+/- Instillation of sclerosant

Patient advised to drain regularly

Efficacy and Safety of Tunneled Pleural Catheters in Adults with Malignant Pleural Effusions: A Systematic Review

Margaret E. M. Van Meter, MD[1], Kanako Y. McKee, MD[2], and R. Jeffrey Kohlwes, MD, MPH[2,3]

J Gen Intern Med 26(1):70–6

Outcome	Number of Studies	Percent with Outcome: *Combined Results*	*Single Study Minimum*	*Single Study Maximum*	% Combined participants with outcome
Without complication	10	**87.5** (517/591)	54.5 (6/11)	100 (55/55)	
Symptomatic improvement	12	**95.6** (628/657)	86.2 (50/58)	100 (100/100)	

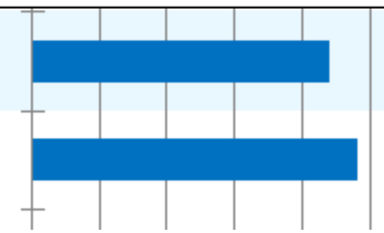
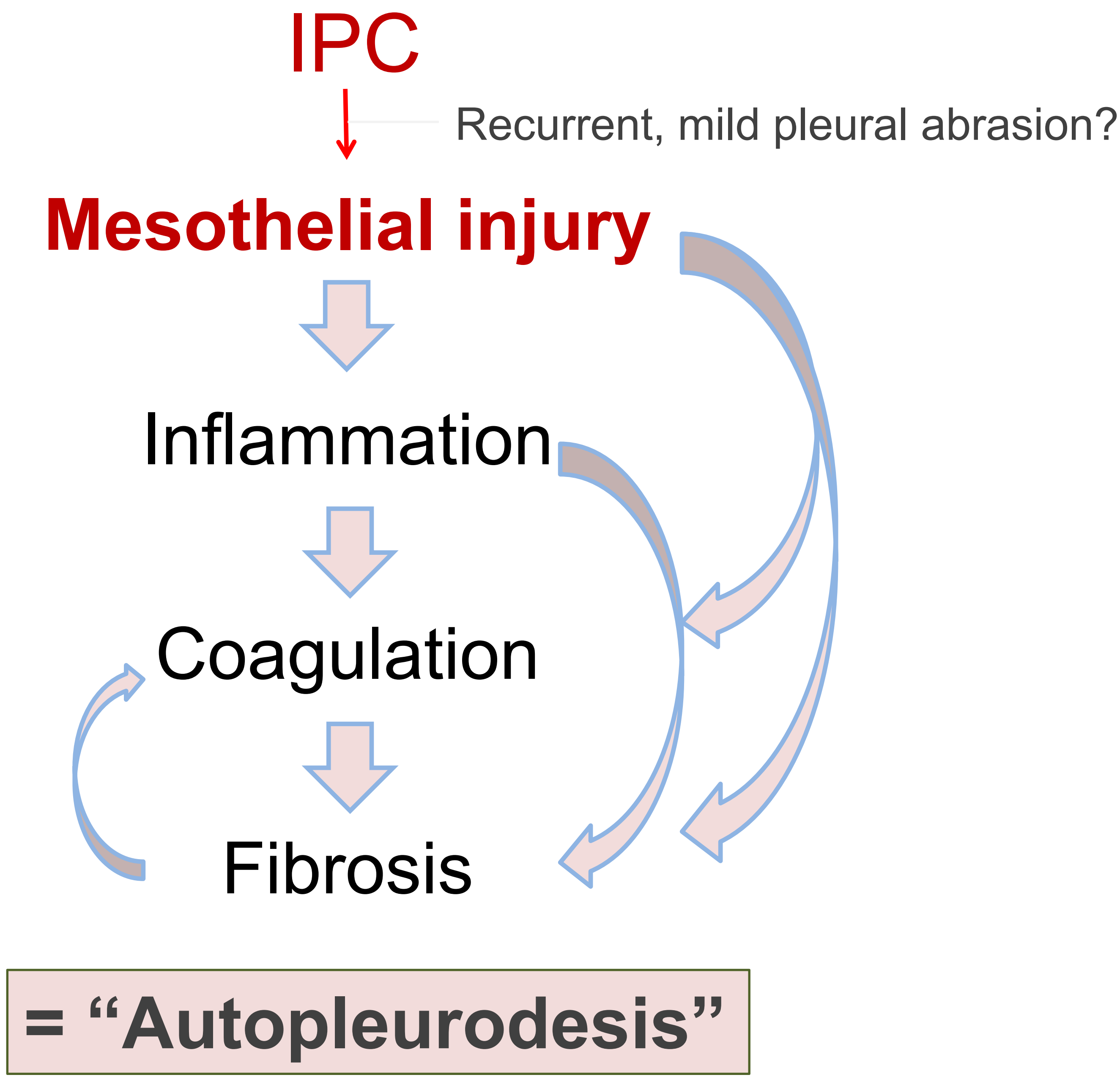


*Figure 2. Outcomes reported in patients treated with the TIPC

*Figure adapted from Van Meter, et al. JGIM 2011


IPC
Recurrent, mild pleural abrasion?
Mesothelial injury
Inflammation
Coagulation
Fibrosis
= “Autopleurodesis”

Transforming Growth Factor-β1 Rise in Pleural Fluid After Tunneled Pleural Catheter Placement

Pilot Study

Semira Shojaee, MD, Norbert Voelkel, MD, Laszlo Farkas, MD, Marjolein de Wit, MD, and Hans J. Lee, MD

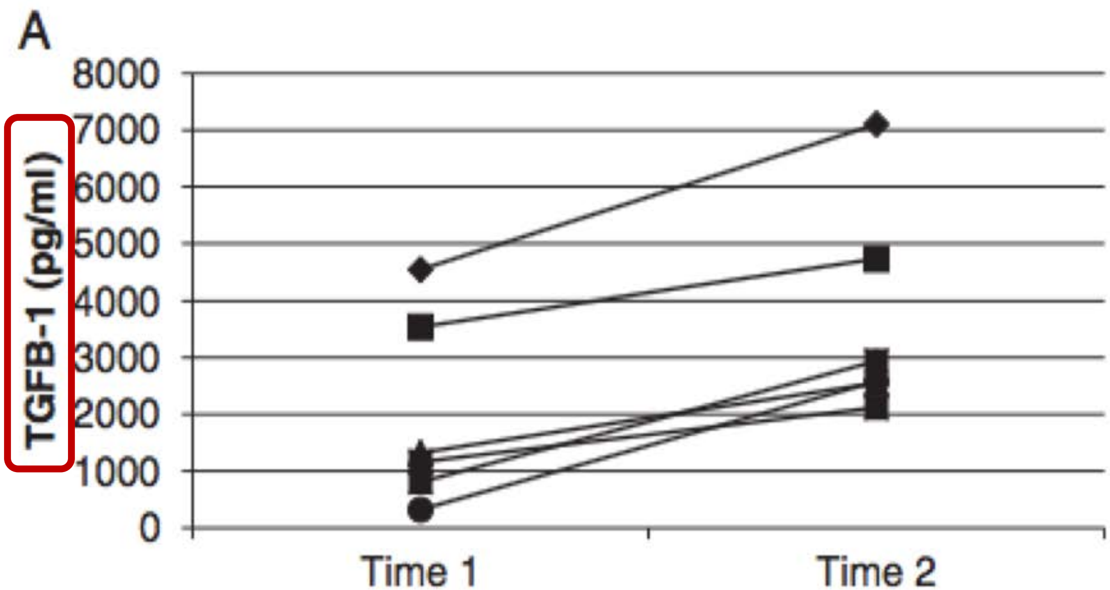


FIGURE 1. A, Increase in TGF-β depicted in graphs when comparing TGF-β at the time of insertion of TPC (T1) and 2 weeks after insertion (T2). B, No significant relation between TPC placement and VEGF from T1 to T2. C, Increase in PAI-1 depicted in graphs when comparing PAI-1 at T1 and T2, although not statistically significant. PAI-1 indicates plasminogen activator inhibitor-1; T1, time 1; T2 time 2; TGF-β1, transforming growth factor-β1; TPC, tunneled pleural catheters; VEGF, vascular endothelial growth factor.

(*J Bronchol Intervent Pulmonol* 2013;20:304–308)

Efficacy and Safety of Tunneled Pleural Catheters in Adults with Malignant Pleural Effusions: A Systematic Review

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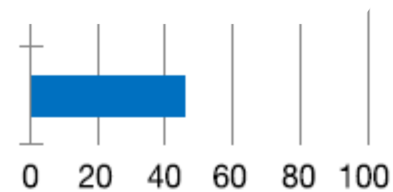
J Gen Intern Med 26(1):70–6

Outcome	Number of Studies	Percent with Outcome: *Combined Results*	*Single Study Minimum*	*Single Study Maximum*	% Combined participants with outcome
Spontaneous pleurodesis	12	**45.6** (430/943)	11.8 (4/34)	76.4 (42/55)	

* **Figure 2.** Outcomes reported in patients treated with the TIPC

*Figure adapted from Van Meter, et al. JGIM 2011

Selected summary of IPC-related autopleurodesis rates

Study	Design	Total sample	AP rate	Time to AP
Putnam, et al Cancer 1999	**RCT, IPC vs doxycycline, efficacy and safety comparison**	**91 patients**	**46%**	**27 days**
Tremblay, et al. Eur Resp J 2007	Retrospective analysis of IPC efficacy fit for pleurodesis	109 IPCs	70%	90 days
Warren, et al. Ann Thor Surg 2008	Retrospective review of IPC morbidity and efficacy	202 IPCs	58%	NR
Suzuki, et al JTO 2011	Retrospective analysis of IPC efficacy, AP rate	418 IPCs	26%	44 days
Davies, et al. JAMA 2012	**RCT, IPC vs talc for dyspnea relief**	**49 patients**	**51%**	**NR**
Wahidi, et al. AJRCCM 2016	**RCT, IPC, daily vs standard drainage**	**149 patients**	**47% 24%**	**54 90**

Abbreviations: AP= autopleurodesis; RCT=randomized controlled trial; IPC= indwelling pleural catheter; NR= not reported

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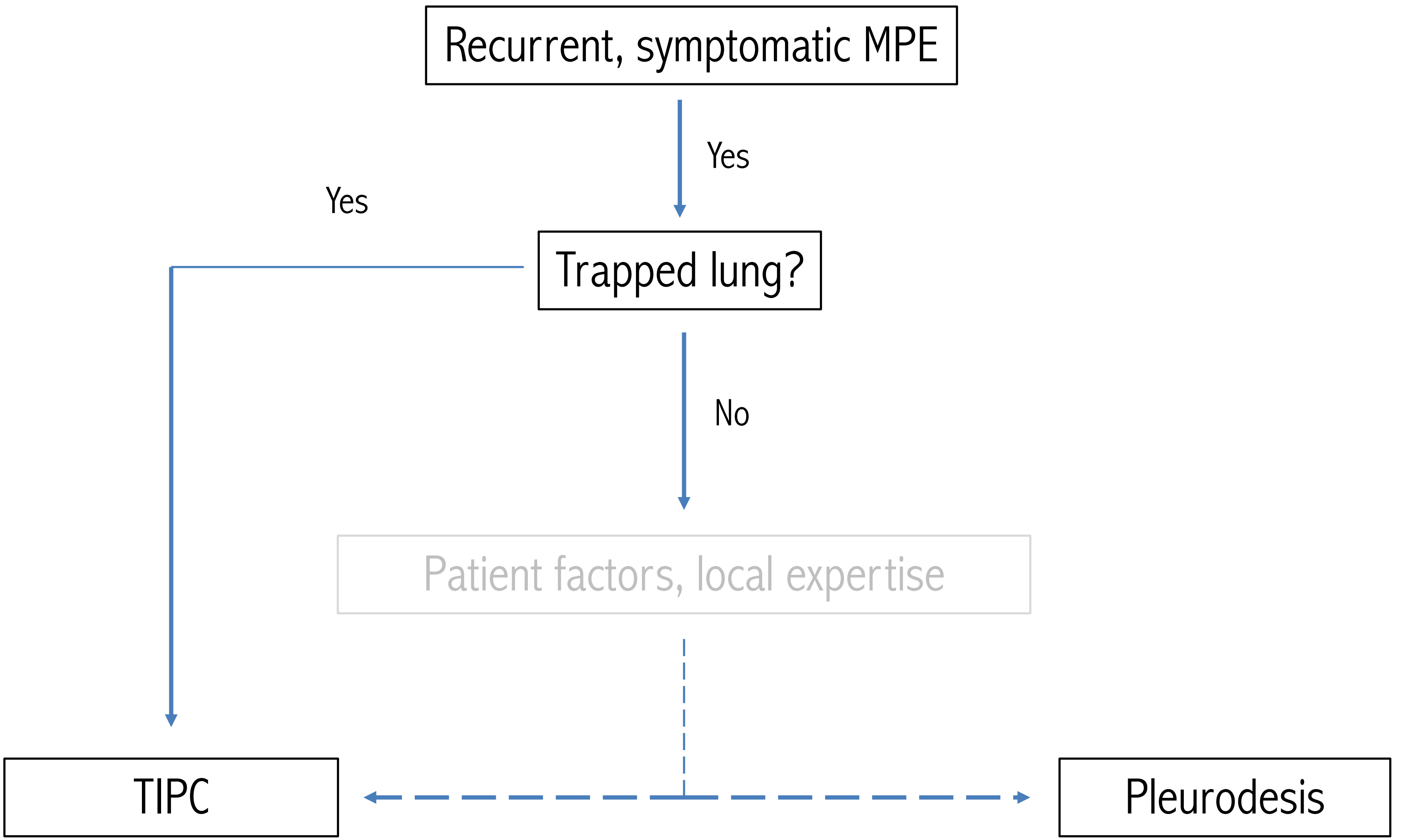
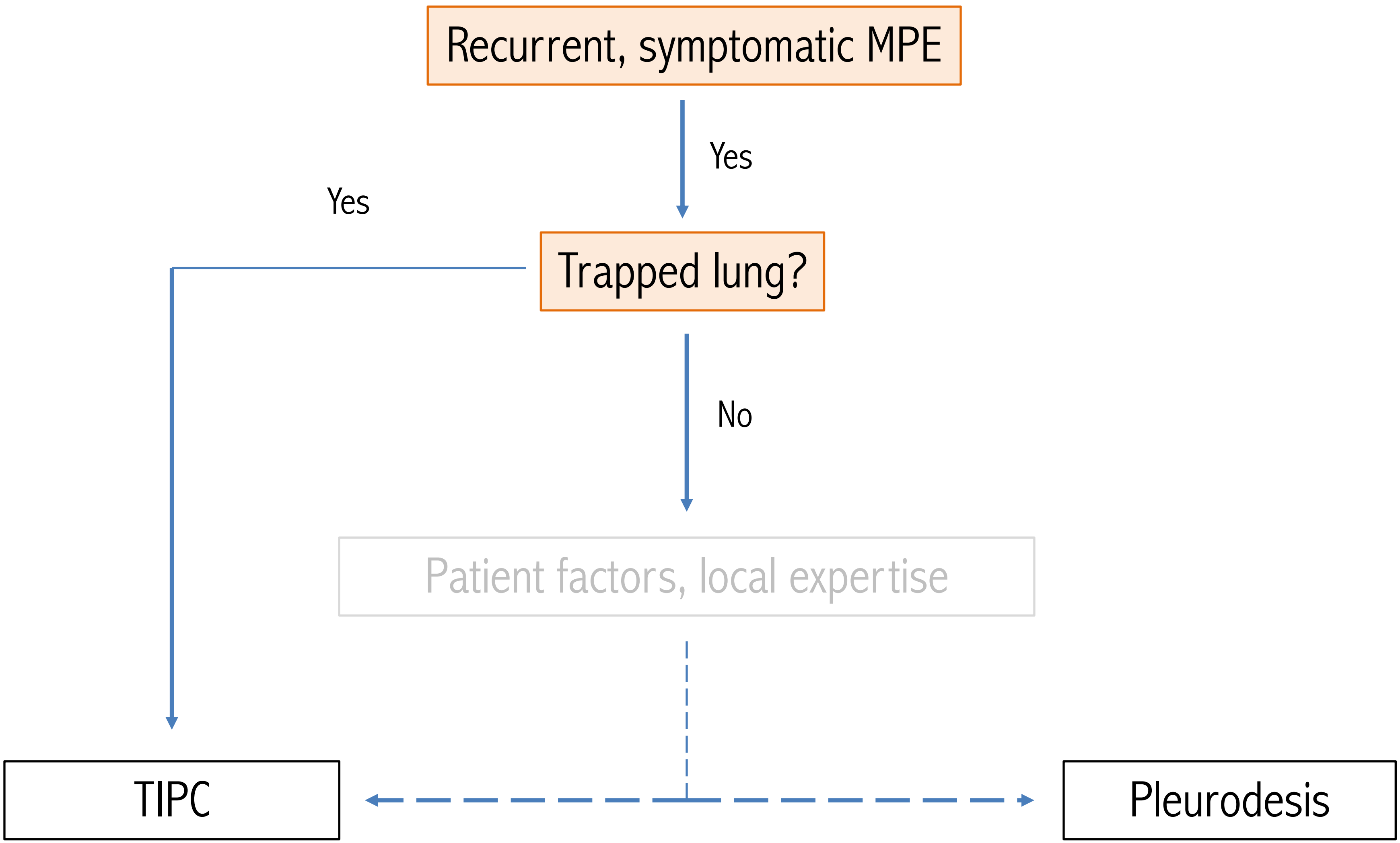
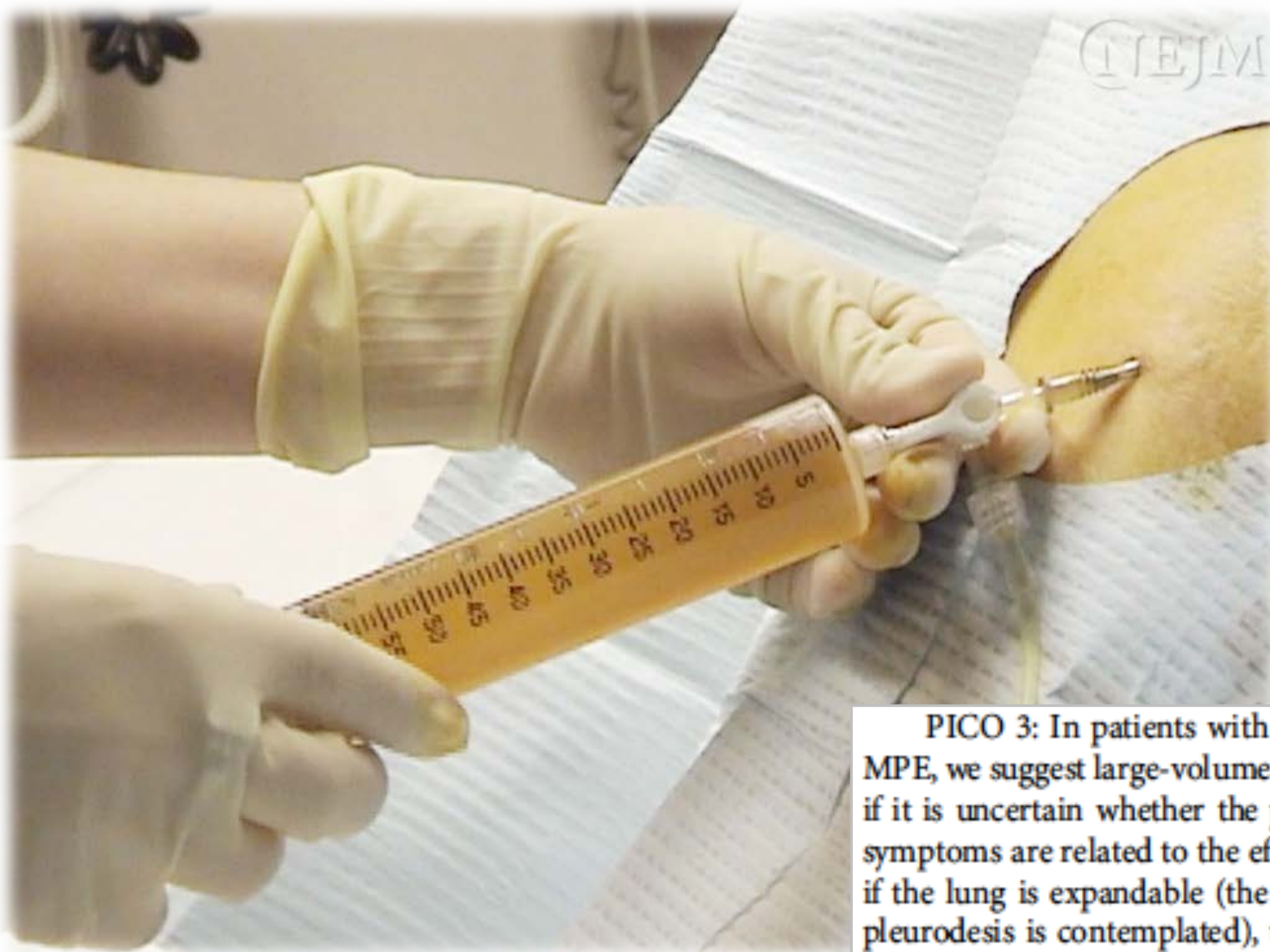
Definitive management for MPE



Definitive management for MPE



Assesses for symptomatic relief, trapped lung

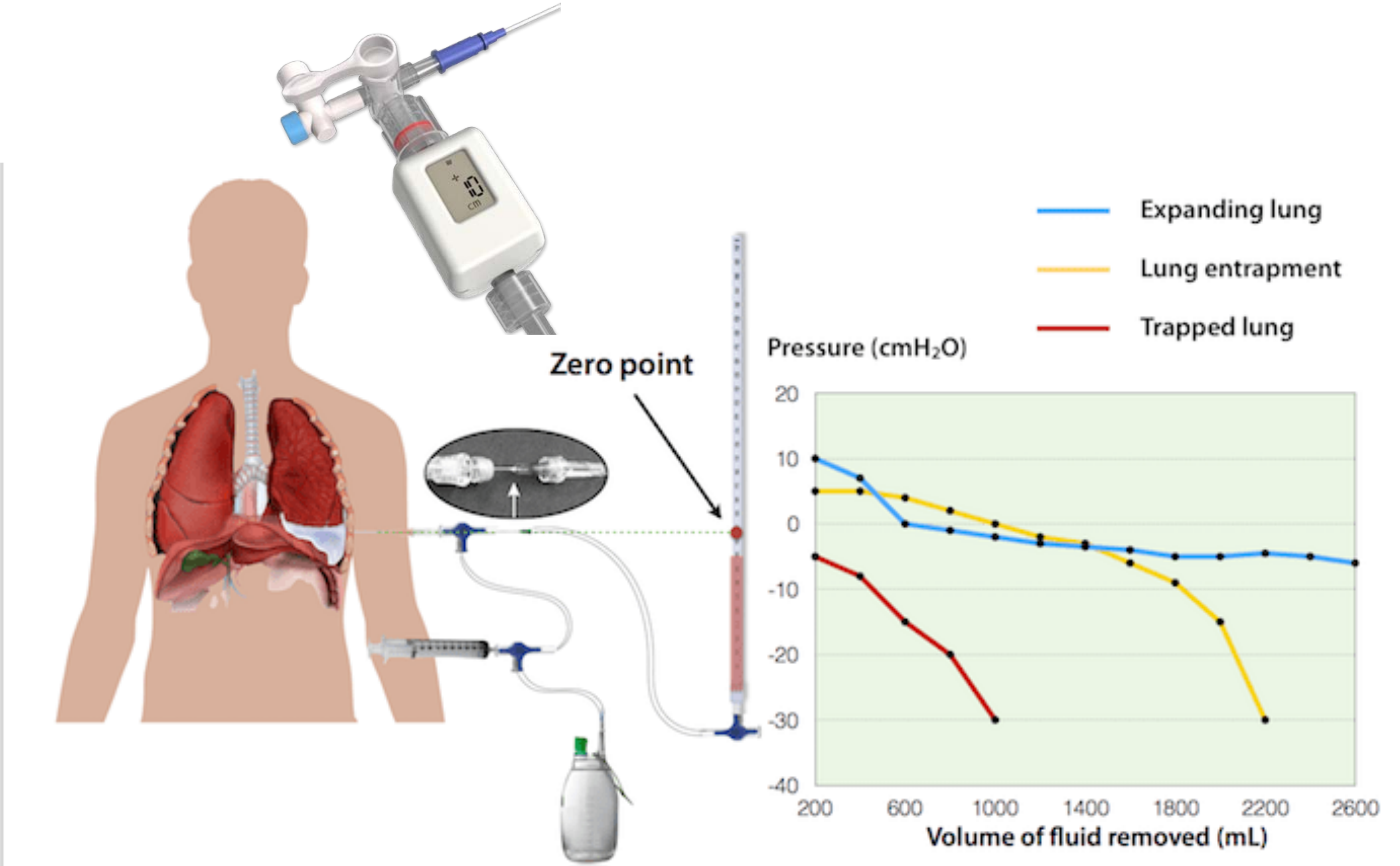


PICO 3: In patients with symptomatic MPE, we suggest large-volume thoracentesis if it is uncertain whether the patient's symptoms are related to the effusion and/or if the lung is expandable (the latter if pleurodesis is contemplated), to assess lung expansion.

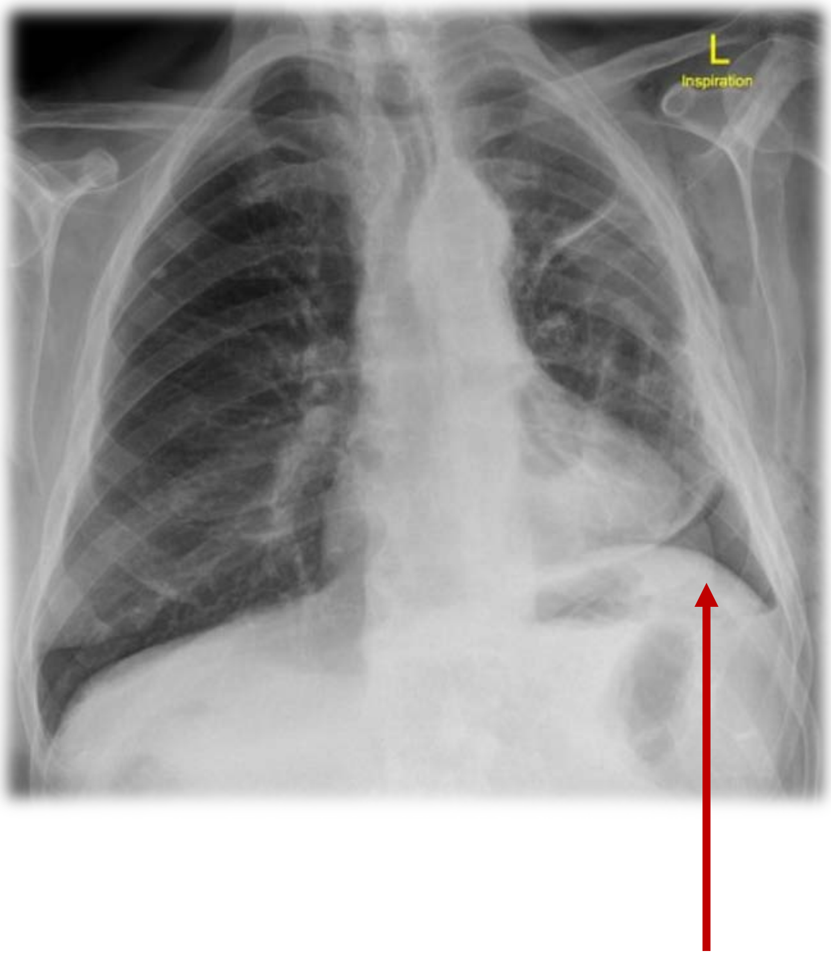
American Journal of Respiratory and Critical Care Medicine Volume 198 Number 7 | October 1 2018

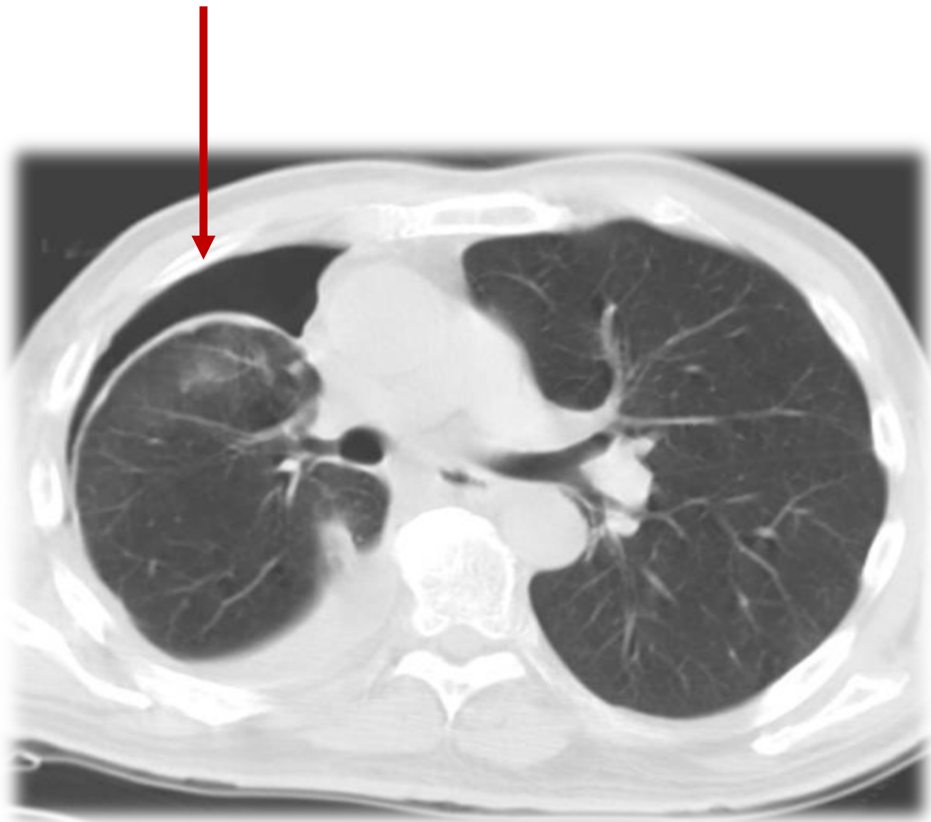
Pleural manometry

Pleural elastance (dP/dV) curve obtained during thoracentesis

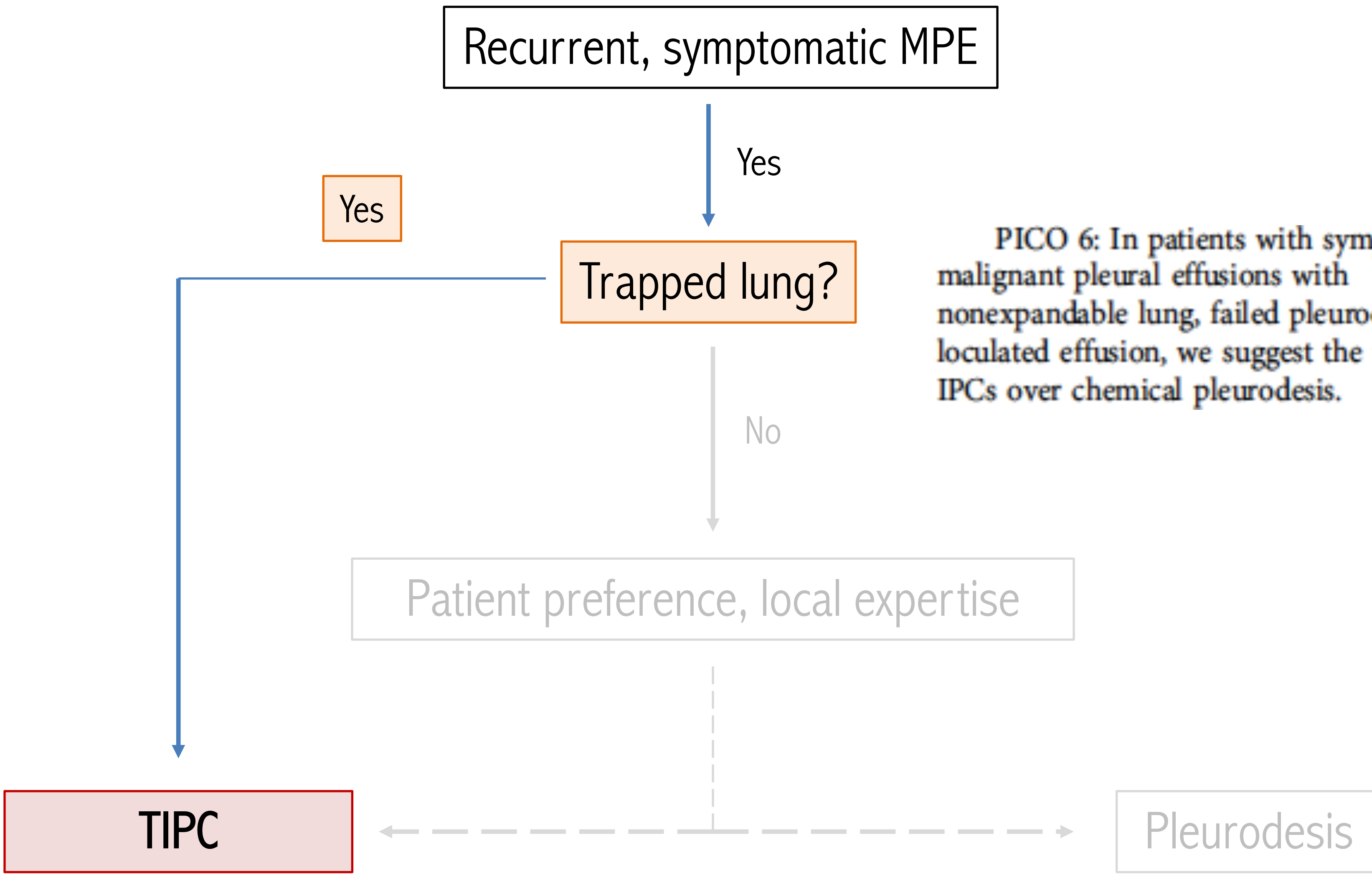


Trapped lung: imaging





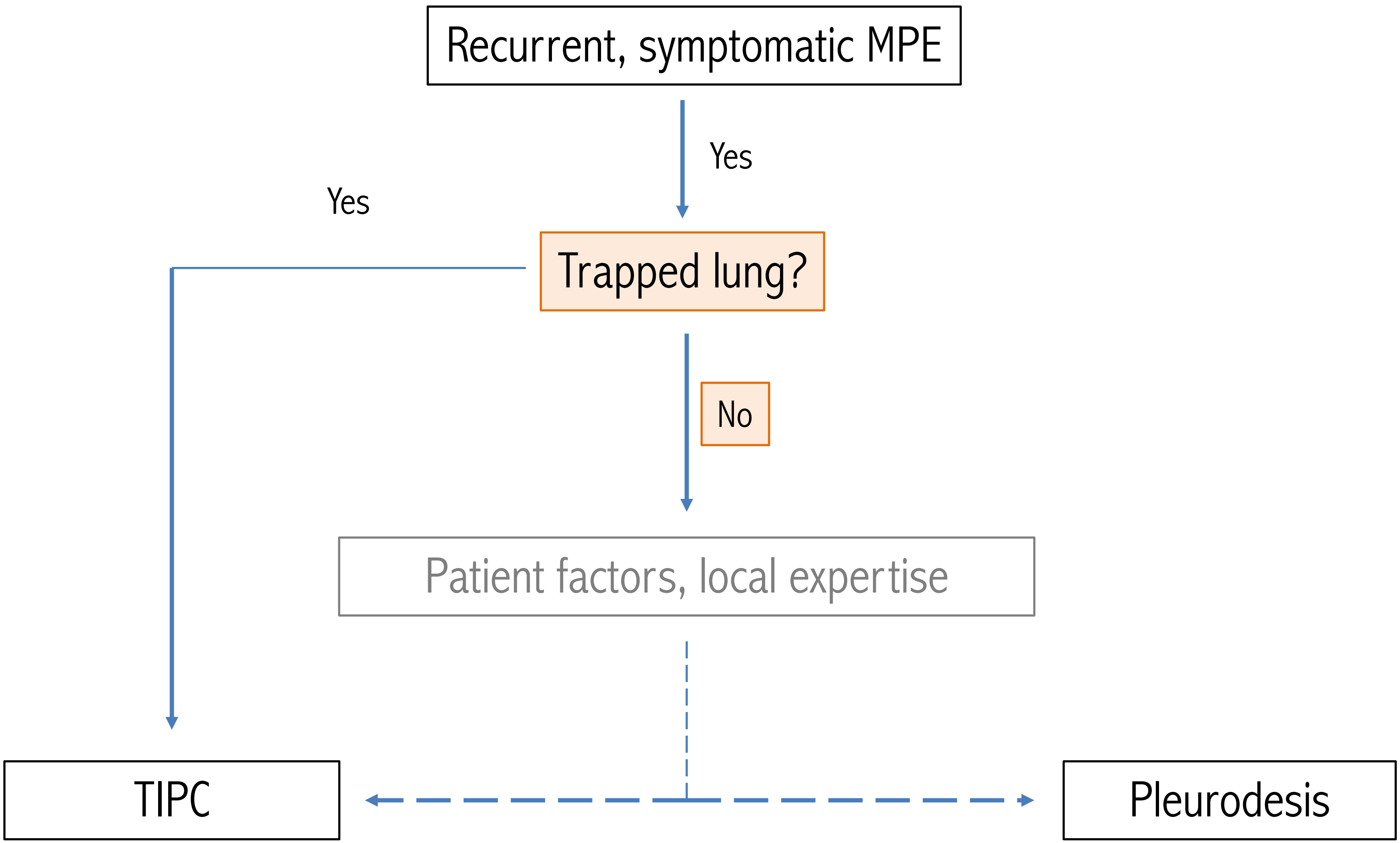
Basic management algorithm for MPE



PICO 6: In patients with symptomatic malignant pleural effusions with nonexpandable lung, failed pleurodesis, or loculated effusion, we suggest the use of IPCs over chemical pleurodesis.

American Journal of Respiratory and Critical Care Medicine Volume 198 Number 7 | October 1 2018

Basic management algorithm for MPE



IPC vs pleurodesis
Comparing important outcomes

Indwelling Pleural Catheter versus Pleurodesis for Malignant Pleural Effusions

A Systematic Review and Meta-Analysis

Narayan P. Iyer[1], Chakravarthy B. Reddy[2], Momen M. Wahidi[3], Sandra Z. Lewis[4], Rebecca L. Diekemper[4], David Feller-Kopman[5], Michael K. Gould[6], and Alex A. Balekian[7]

AnnalsATS Volume 16 Number 1| January 2019

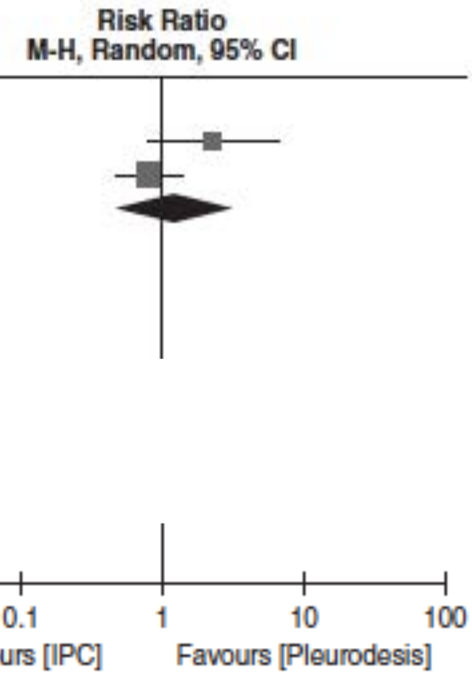
IPC vs pleurodesis

Mortality: equivalent risk

Study or Subgroup	IPC Events	IPC Total	Pleurodesis Events	Pleurodesis Total	Weight	Risk Ratio M-H, Random, 95% CI
3.1.1 Mortality, 3 months post procedure						
Davies 2012	9	28	4	29	40.3%	2.33 [0.81, 6.71]
Demmy 2012	16	51	20	52	59.7%	0.82 [0.48, 1.39]
Subtotal (95% CI)		**79**		**81**	**100.0%**	**1.25 [0.45, 3.45]**
Total events	25		24			

Heterogeneity: $Tau^2 = 0.38$; $Chi^2 = 3.08$, df = 1 (P = 0.08); $I^2 = 67\%$

Test for overall effect: Z = 0.42 (P = 0.67)



AnnalsATS Volume 16 Number 1| January 2019

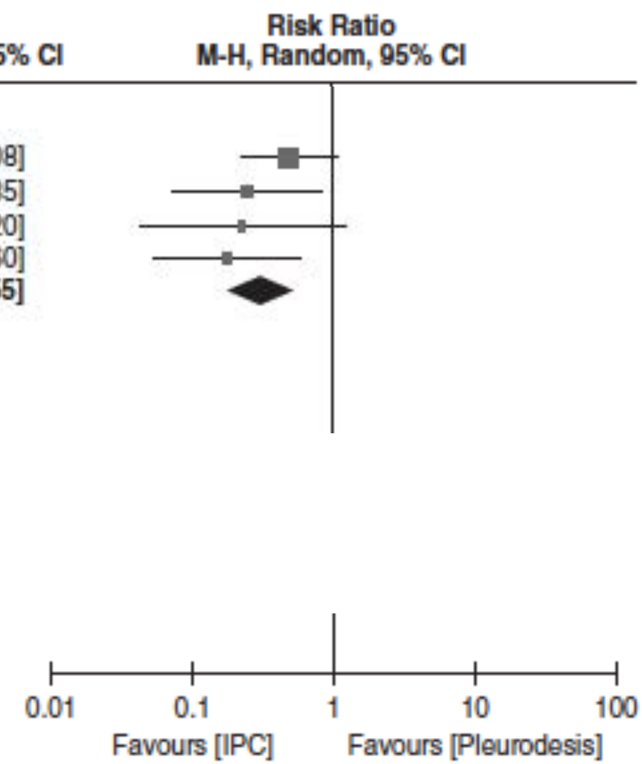
IPC vs pleurodesis

<u>Repeat interventions</u>: favors IPC

Study or Subgroup	IPC Events	IPC Total	Pleurodesis Events	Pleurodesis Total	Weight	Risk Ratio M-H, Random, 95% CI
3.1.2 Repeat pleural procedures						
Boshuizen 2017	7	43	15	45	47.4%	0.49 [0.22, 1.08]
Davies 2012	3	51	12	52	20.6%	0.25 [0.08, 0.85]
Putnam 1999	2	94	4	43	10.9%	0.23 [0.04, 1.20]
Thomas 2017	3	73	16	71	21.1%	0.18 [0.06, 0.60]
Subtotal (95% CI)		**261**		**211**	**100.0%**	**0.32 [0.18, 0.55]**
Total events	15		47			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.30$, df = 3 (P = 0.51); $I^2 = 0\%$

Test for overall effect: Z = 4.09 (P < 0.0001)



IPC = 5.7%
Pleurodesis = 22.3%

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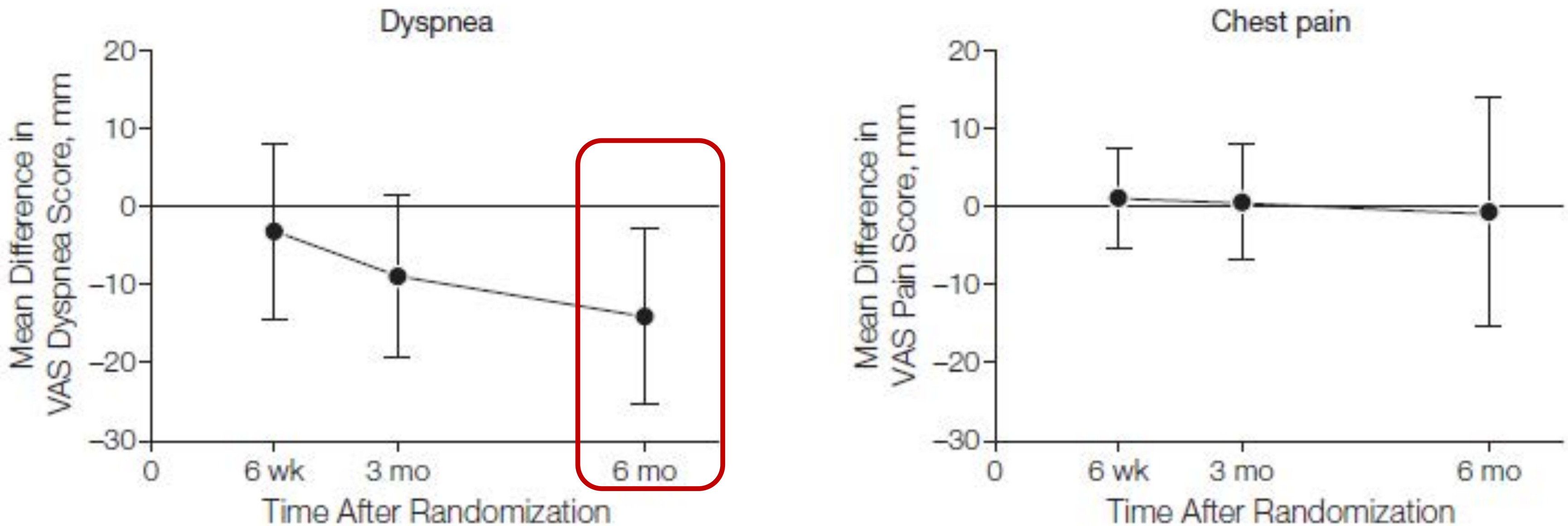
TIME-2 trial

Dyspnea control may favor IPC at 6 months

Figure 3. Mean Difference in Visual Analog Scale (VAS) Score for Dyspnea and Chest Pain



No. of patients

	6 wk	3 mo	6 mo
Talc	32	26	21
IPC	30	31	22

No. of patients

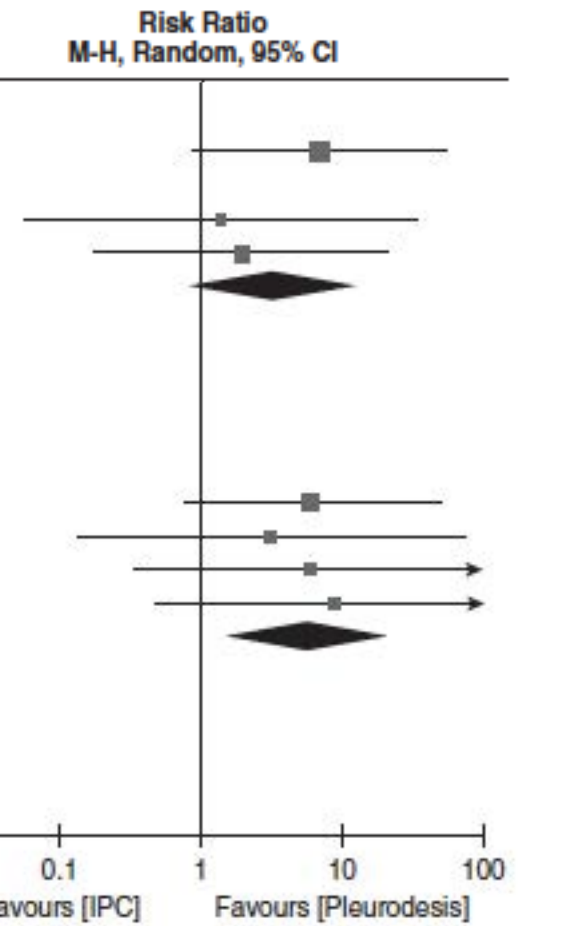
	6 wk	3 mo	6 mo
Talc	32	26	21
IPC	30	31	22

JAMA, June 13, 2012—Vol 307, No. 22

IPC vs pleurodesis

<u>Infection risk</u>: favors pleurodesis

Study or Subgroup	IPC Events	IPC Total	Pleurodesis Events	Pleurodesis Total	Weight	Risk Ratio M-H, Random, 95% CI
3.1.3 Pleural infection						
Davies 2012	7	51	1	52	46.1%	7.14 [0.91, 55.96]
Demmy 2012	0	28	0	29		Not estimable
Putnam 1999	1	94	0	43	19.3%	1.39 [0.06, 33.43]
Thomas 2017	2	73	1	71	34.6%	1.95 [0.18, 20.98]
Subtotal (95% CI)		**246**		**195**	**100.0%**	**3.32 [0.82, 13.44]**
Total events	10		2			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.04$, df = 2 (P = 0.60); $I^2 = 0\%$						
Test for overall effect: Z = 1.68 (P = 0.09)						
3.1.4 Cellulitis						
Davies 2012	6	51	1	52	40.3%	6.12 [0.76, 49.04]
Demmy 2012	1	28	0	29	17.5%	3.10 [0.13, 73.12]
Putnam 1999	6	94	0	43	21.4%	6.02 [0.35, 104.52]
Thomas 2017	4	73	0	71	20.7%	8.76 [0.48, 159.73]
Subtotal (95% CI)		**246**		**195**	**100.0%**	**5.83 [1.56, 21.87]**
Total events	17		1			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.23$, df = 3 (P = 0.97); $I^2 = 0\%$						
Test for overall effect: Z = 2.61 (P = 0.009)						



IPC = 10.9% (empyema = 4.1%)
Pleurodesis = 1.5% (1.0%)

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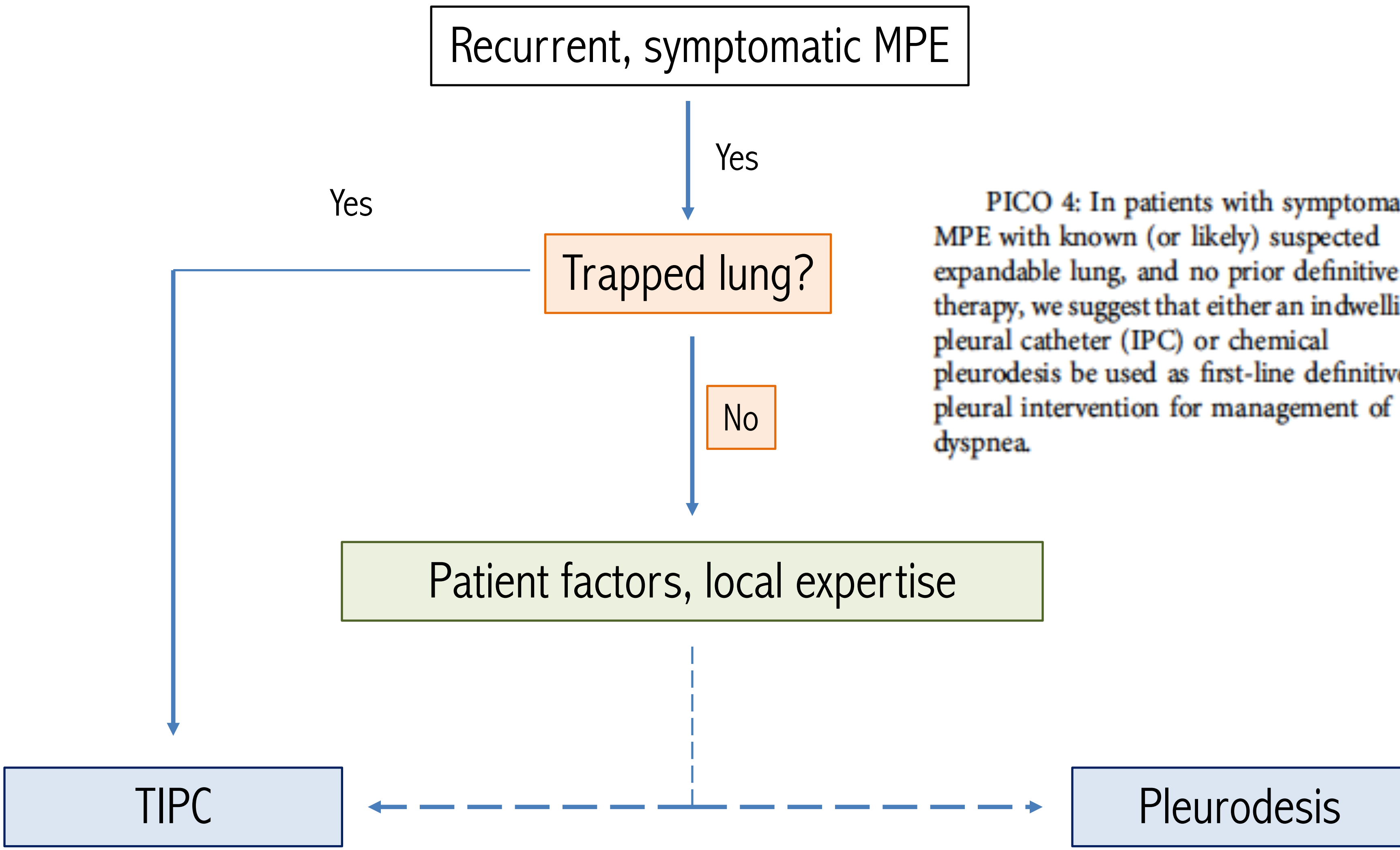
Definitive management for MPE



PICO 4: In patients with symptomatic MPE with known (or likely) suspected expandable lung, and no prior definitive therapy, we suggest that either an indwelling pleural catheter (IPC) or chemical pleurodesis be used as first-line definitive pleural intervention for management of dyspnea.

Fine-tuning your practice

- Patient prognosis

- Logistics
  - Outpatient pleural clinic
  - Access to pleuroscopy

- Patient preferences

Fine-tuning your practice

- **Patient prognosis**

- Logistics
  - Outpatient pleural clinic
  - Access to pleuroscopy

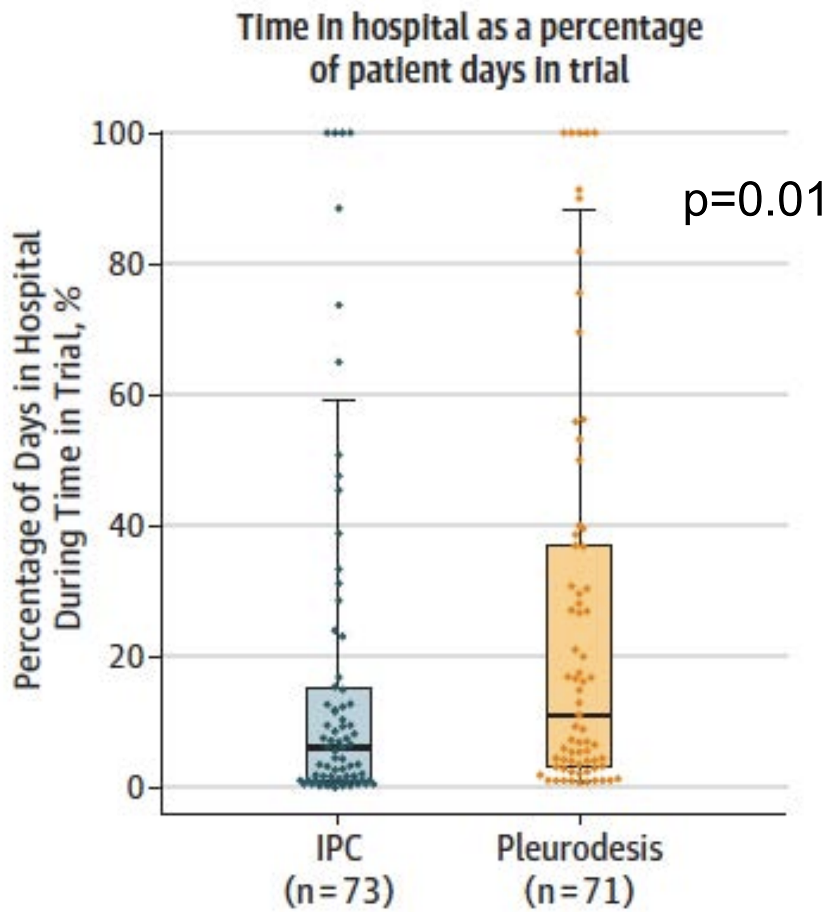
- Patient preferences

Effect of an Indwelling Pleural Catheter vs Talc Pleurodesis on Hospitalization Days in Patients With Malignant Pleural Effusion
The AMPLE Randomized Clinical Trial

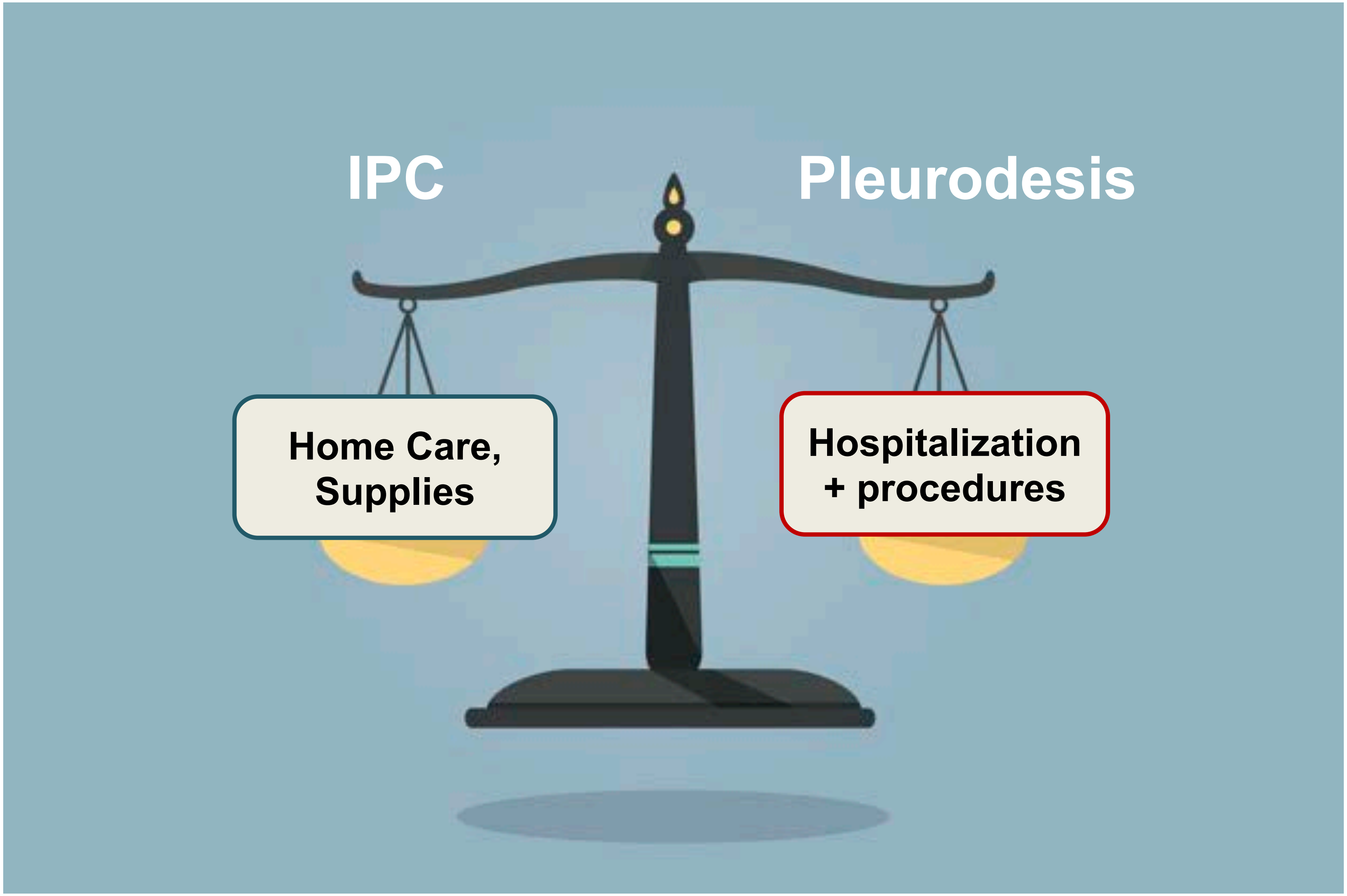
Time spent in hospital

	IPC	Pleurodesis
Median	**6.2%**	**11.1%**
IQR	1.1-15%	3.2-37%

***Patients undergoing pleurodesis spent a significantly higher percentage of their lifespan in the hospital**



Financial considerations



Comparing Cost of Indwelling Pleural Catheter vs Talc Pleurodesis for Malignant Pleural Effusion

TABLE 4] Resource Use, Mean Cost, and Mean Cost Difference Between IPC and Talc in US$

Category	IPC		Talc	
	Resources Used	Cost, Mean (SD), $	Resources Used	Cost, Mean (SD), $
Initial intervention				
Intervention procedures	51	797 (36)	53	476 (47)
Mean LOS,[a] d	2.49 (7)	1,147 (2,961)	4.98 (4)	2,461 (1,834)
	N = 51		N = 51	
Day-case visit	32 visits	325 (260)	0 visits	0
Total initial intervention costs, $	2,276 (2,849)		2,939 (1,844)	
Total ongoing drainage costs, $	1,011 (732)		57 (213)	
Adverse events				
Outpatient visits[b]	33	336 (694)	41	401 (1,440)
Inpatient visits[b]	15	1,188 (4,453)	30	871 (2,327)
Procedures[b]	3	19 (76)	46	227 (694)
Diagnostic imaging[c]	34	43 (106)	66	52 (137)
	6		2	
Total adverse events costs, $	1,653 (4,693)		1,555 (3,737)	
Total cost, $	4,993 (5,529)		4,581 (4,359)	
Difference in costs, $				
Total cost[d]				
Mean differ				
95% CI				
Adverse eve				
Mean diffe				
95% CI				
Combined initial intervention and ongoing drainage cost[d]				
Mean difference[e]	316			
95% CI	(−603 to 1,426)			

TIPC more cost efficient in patients with limited survival (<14 weeks)

CHEST 2014; 146(4):991-1000

Predicting prognosis: the LENT score

High risk: poor performance status, inflammatory state, lung cancer

Table 3 The LENT score calculation

	Variable	Score
L	LDH level in pleural fluid (IU/L)	
	<1500	0
	>1500	1
E	ECOG PS	
	0	0
	1	1
	2	2
	3–4	3
N	NLR	
	<9	0
	>9	1
T	Tumour type	
	Lowest risk tumour types	0
	▶ Mesothelioma	
	▶ Haematological malignancy	
	Moderate risk tumour types	1
	▶ Breast cancer	
	▶ Gynaecological cancer	
	▶ Renal cell carcinoma	
	Highest risk tumour types	2
	▶ Lung cancer	
	▶ Other tumour types	

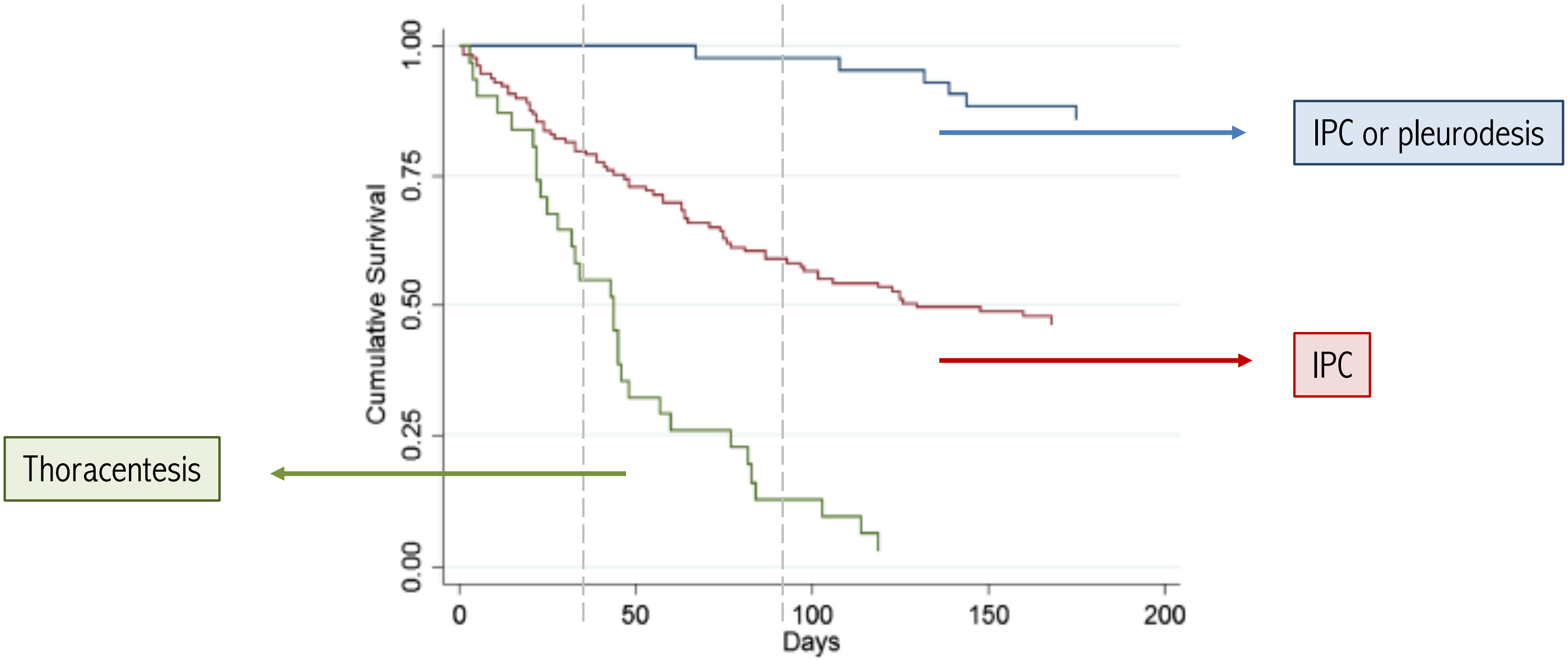
Risk categories	Total score
Low risk	0–1
Moderate risk	2–4
High risk	5–7

ECOG PS, Eastern Cooperative Oncology Group performance score; LDH, lactate dehydrogenase; NLR, neutrophil-to-lymphocyte ratio.

Clive AO, *et al*. *Thorax* 2014;**69**:1098–1104. doi:10.1136/thoraxjnl-2014-205285

Predicting prognosis: the LENT score

High risk: poor performance status, inflammatory state, lung cancer



Number at risk					
Low risk	43	43	42	38	36
Moderate risk	129	94	73	63	57
High risk	31	10	4	1	1

	MS (IQR) days	HR (95% CI)
Low risk	319 (228-549)	-
Moderate risk	130 (47-467)	1.49 (1.03-2.15)
High risk	44 (22-77)	5.97 (3.58-9.97)

Clive AO, *et al.* *Thorax* 2014;**69**:1098–1104. doi:10.1136/thoraxjnl-2014-205285

Fine-tuning your practice

- Worse prognosis
  - > consider IPC over pleurodesis
- Logistics
  - Outpatient pleural clinic
  - Access to pleuroscopy
- Patient preferences

Fine-tuning your practice

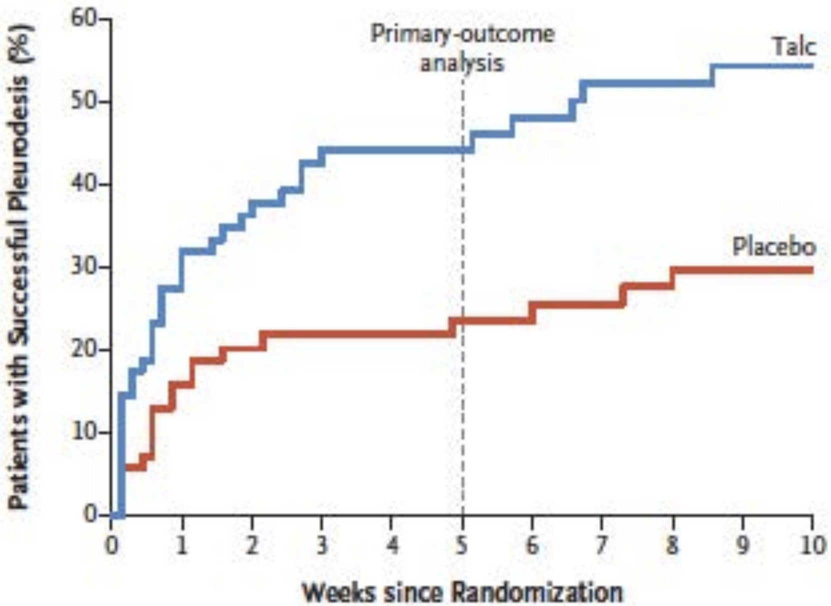
- Worse prognosis
  - > consider IPC over pleurodesis

- **Logistics**
  - **Outpatient pleural clinic**
  - **Access to pleuroscopy**

- Patient preferences

Outpatient Talc Administration by Indwelling Pleural Catheter for Malignant Effusion

N ENGL J MED 378;14 NEJM.ORG APRIL 5, 2018



No. at Risk											
Talc	69	50	43	35	32	29	27	24	23	21	10
Placebo	70	58	52	47	45	43	41	37	33	30	16

Figure 2. Survival Curve for Primary-Outcome Results and Rates of Successful Pleurodesis at Day 70 after Randomization.

A total of 30 of 69 patients (43%) in the talc group had successful pleurodesis by day 35 (primary-outcome analysis), as compared with 16 of 70 (23%) in the placebo group (hazard ratio, 2.20; 95% CI, 1.23 to 3.92; P=0.008). At day 70, successful pleurodesis occurred in 35 of 69 patients (51%) in the talc group, as compared with 19 of 70 (27%) in the placebo group (hazard ratio, 2.24; 95% CI, 1.31 to 3.85; P=0.003).

IPC-PLUS trial

IPC+talc
= faster pleurodesis vs only IPC

Talc slurry vs Poudrage: efficacy

Efficacy and Safety of Talc Pleurodesis for Malignant Pleural Effusion: A Meta-Analysis

Table 3. Subgroup analysis of success rates between talc pleurodesis and different control group

Comparison Groups	Study	Talc pleurodesis (n/N)	Control Therapies (n/N)	RR (95% CI)	P (Z)
Talc poudrage *vs* Talc slurry					
	Yim/1996	27/28	26/29	1.08 (0.93–1.24)	
	Dresler/2005	119/152	92/130	1.11 (0.96–1.27)	
	Stefani/2006	59/72	23/37	1.32 (1.00–1.73)	
	Terra/2009	25/30	26/30	0.96 (0.78–1.19)	
	Overall	230/282	167/226	1.12 (1.01–1.23)	0.026

Talc Poudrage = 82% vs Slurry = 74%

Fine-tuning your practice

- Worse prognosis and higher tumor burden
  - >consider IPC over pleurodesis

- Logistics
  - Outpatient pleural clinic
  - Access to pleuroscopy

Consider combined approaches

- Patient preferences

Fine-tuning your practice

- Worse prognosis and higher tumor burden
  - >consider IPC over pleurodesis
- Logistics
  - Outpatient pleural clinic
  - Access to pleuroscopy

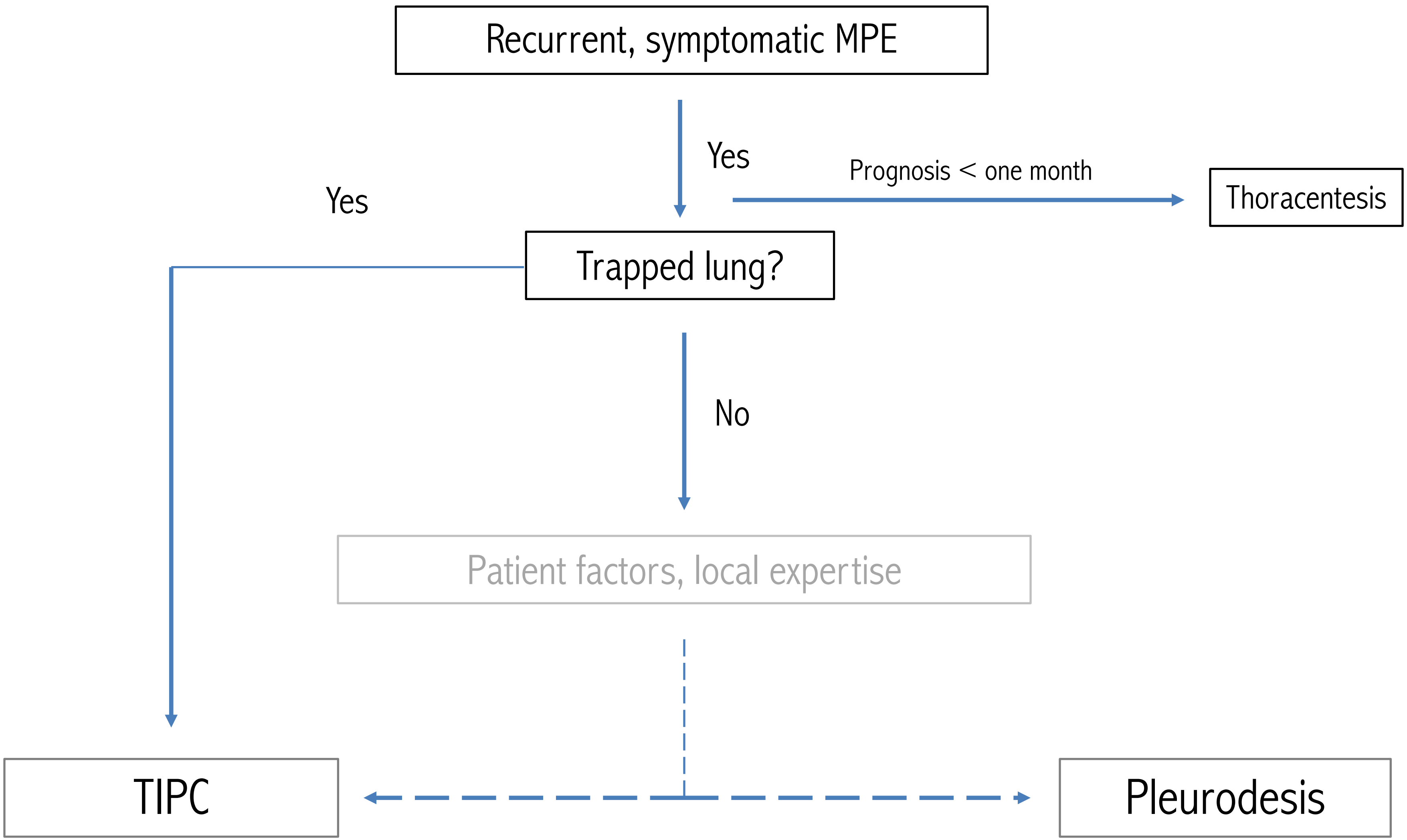
Consider combined approaches

- **Patient preferences**

Common patient questions and concerns

	IPC	Pleurodesis
Will the procedure hurt?	No	Possibly
Will I have to stay in the hospital?	No	Depends on approach
What will be my limitations?	No water submersion	None
Will I need a caregiver?	Yes	No
What are the chances I will need more procedures?	Less than 10%	Up to 25%
What are the chances of infection?	About 10% or less	Negligible
Can I still get chemotherapy?	Yes	Yes*
Can the catheter come out, and when?	About a 50% chance within 3 months	--------

Definitive management for MPE



Thank you, Questions??

Ara A. Chrissian, MD, FCCP, DAABIP

Director, Adult Bronchoscopy and Interventional Pulmonology

Associate Director, Pulmonary and Critical Care Fellowship

Associate Professor of Medicine

Loma Linda University Medical Center

achrissian@llu.edu

Management of Non-Malignant Recurrent Pleural Effusions (including Rare Pleural Diseases: Chylothorax, Urinothorax, Hepatic Hydrothorax, and Pancreatic Fistula Effusions)

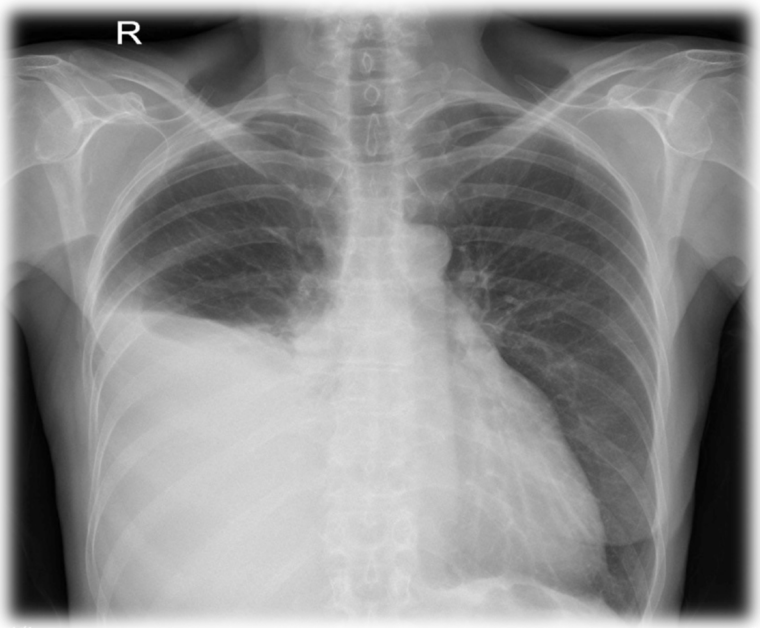
Ara Chrissian, MD
Loma Linda University

Saturday, October 5, 2019 – 3:50 p.m. – 4:10 p.m.

Dr. Chrissian received his medical degree from the University of California, San Diego. He completed fellowship in Pulmonary and Critical Care Medicine at Washington University, St. Louis and dedicated subspecialty training in Interventional Pulmonology at Henry Ford Hospital in Detroit. He is currently the Director of Adult Bronchoscopy and Interventional Pulmonology at Loma Linda University Medical Center, where he also serves as Associate Professor of Medicine and an Associate Director for the Pulmonary and Critical Care Fellowship. In addition to a busy clinical practice, Dr. Chrissian is heavily involved in medical education.

Managing the non-malignant pleural effusion

NOT "Just Another Thoracentesis"



Ara A. Chrissian, MD, FCCP, DAABIP

Director, Adult Bronchoscopy and Interventional Pulmonology

Associate Fellowship Director

Associate Professor of Medicine

Division of Pulmonary, Critical Care, Hyperbaric, Sleep, and Allergy Medicine

Loma Linda University

Goals and objectives

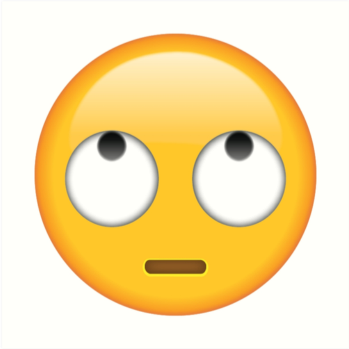
- Understand the importance of obtaining the correct diagnosis in recurrent non-malignant effusions (NMPE)

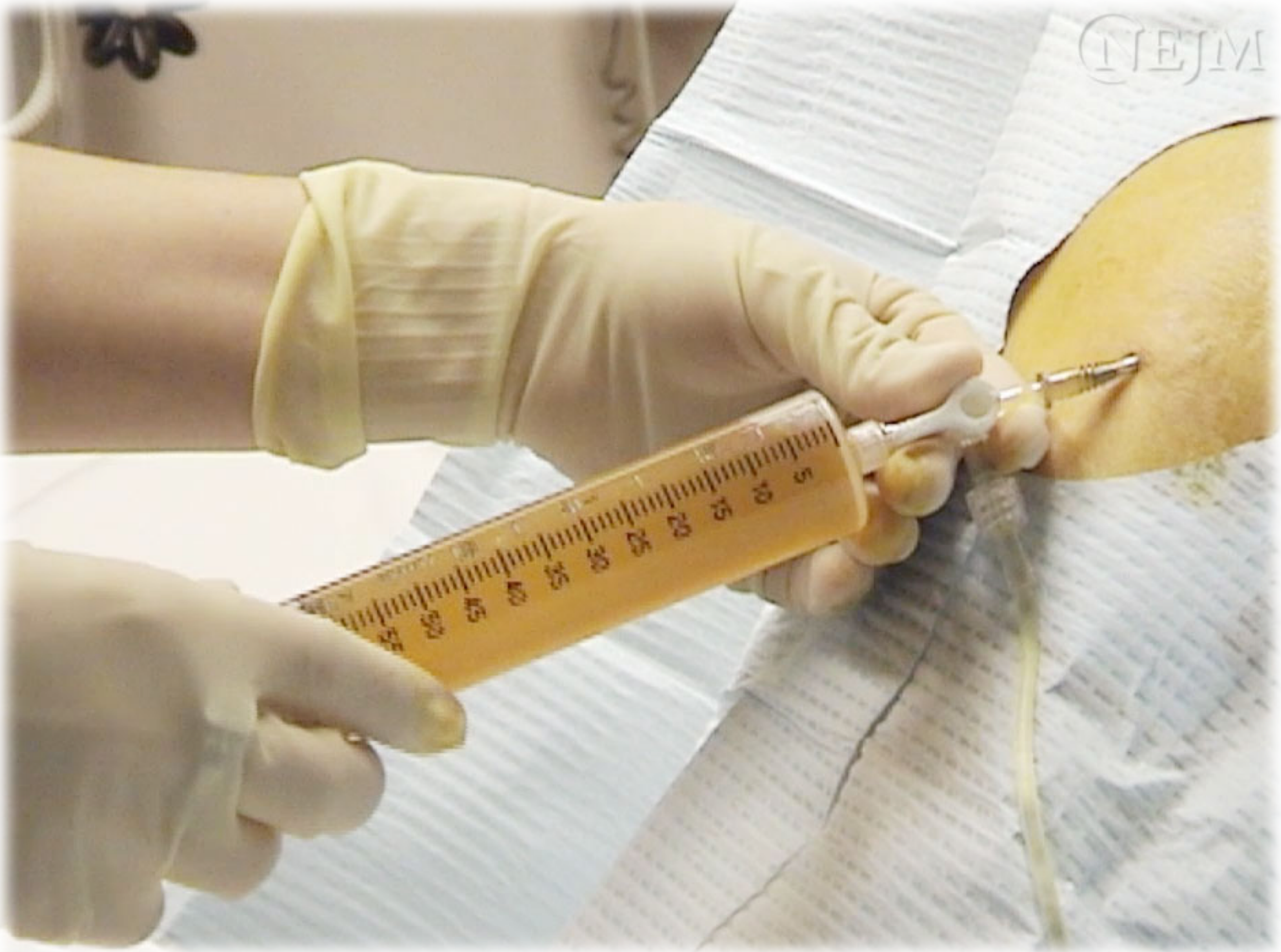
- Brief review of uncommon causes of NMPEs

- Identify options available for managing NMPEs

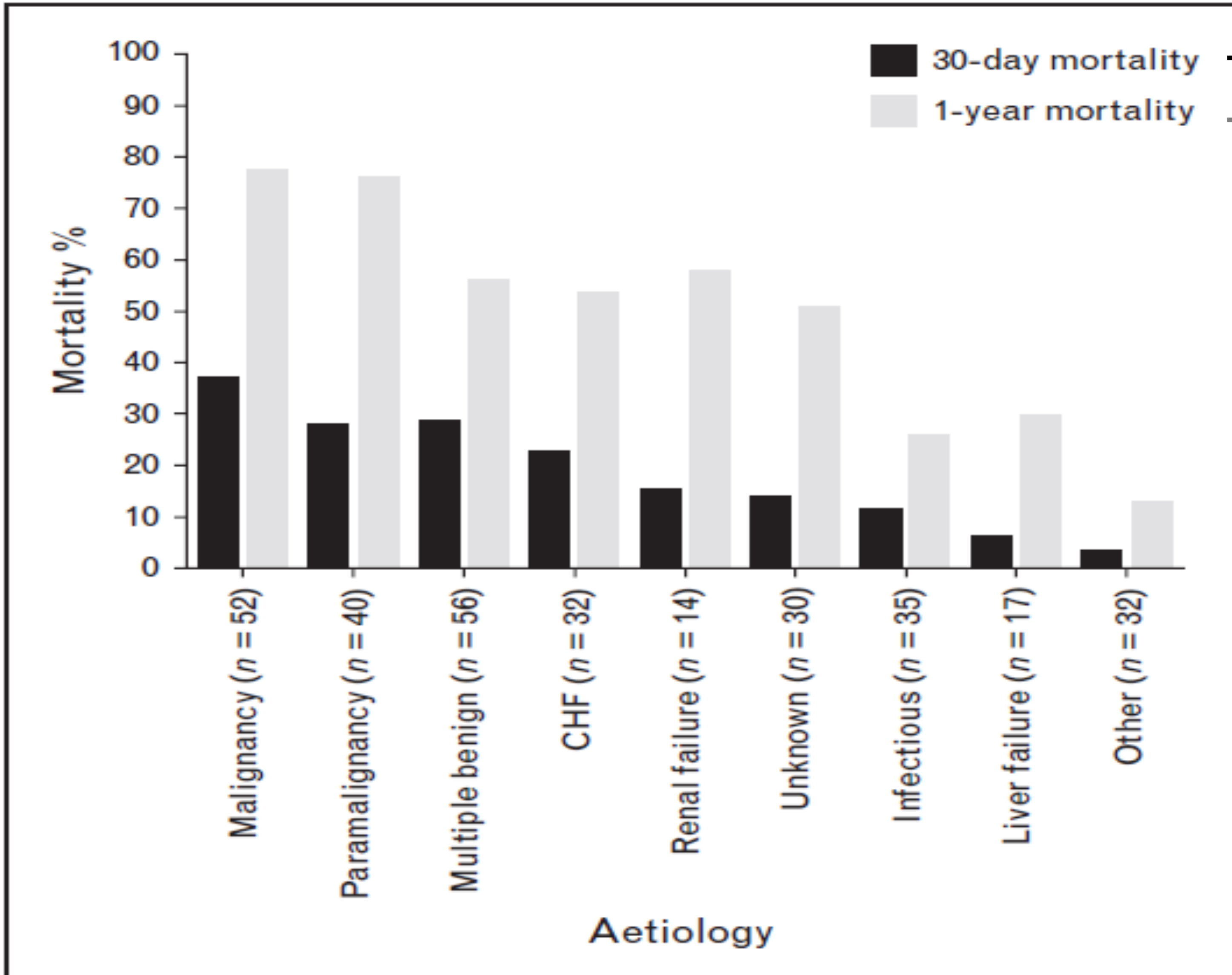
No relevant financial disclosures

Pleural effusion, so what?





Pleural effusion: a marker of disease severity



Overall

21%
51%

Eur Respir J 2015; 46: 495–502

‘Benign’ pleural effusions are NOT BENIGN

Nonmalignant Pleural Effusions

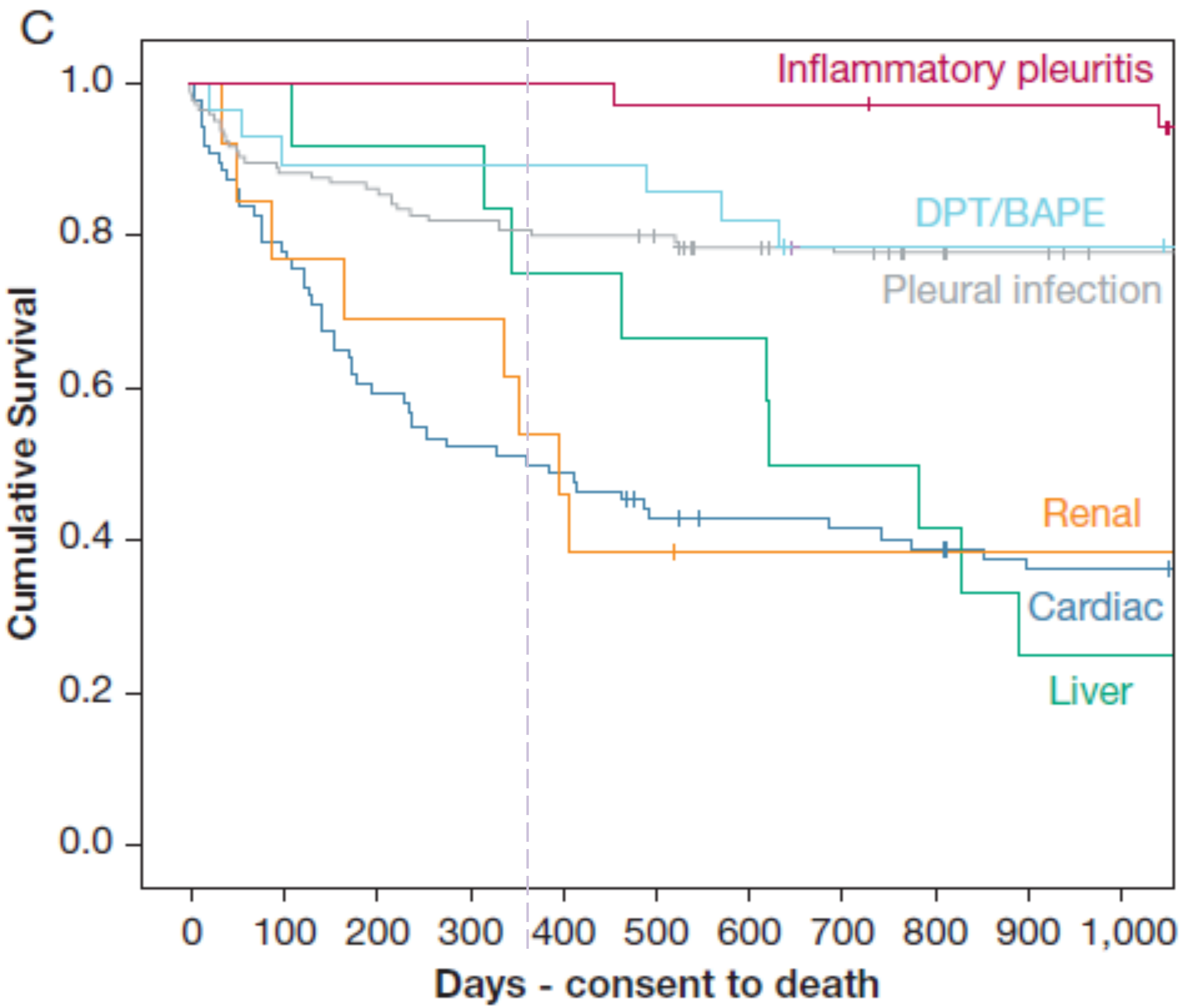
A Prospective Study of 356 Consecutive Unselected Patients

TABLE 3] Mortality Rates and Multivariate Predictors of Mortality in Nonmalignant Pleural Effusion Cohort

	6-Month Mortality			1-Year Mortality		
Variable	Mortality (%)	HR (95% CI)	P Value	Mortality (%)	HR (95% CI)	P Value
Characteristic						
Bilateral[a]	43	3.44 (2.00-5.93)	< .001	57	3.55 (2.22-5.68)	< .001
Transudates[b]	33	2.81 (1.71-4.62)	< .001	43	2.78 (1.81-4.28)	< .001

CHEST 2017; 151(5):1099-1105

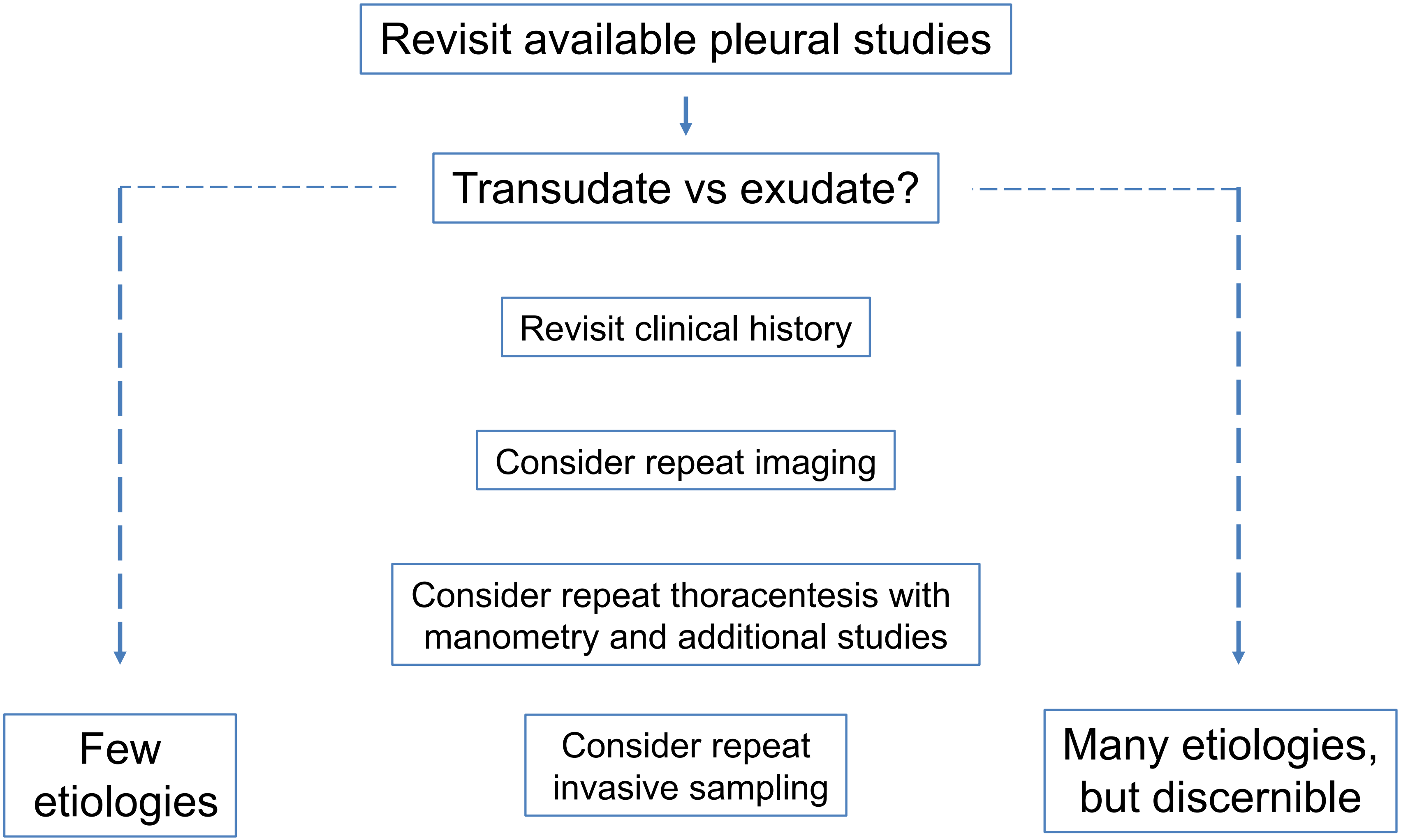
‘Benign’ pleural effusions are **NOT BENIGN**



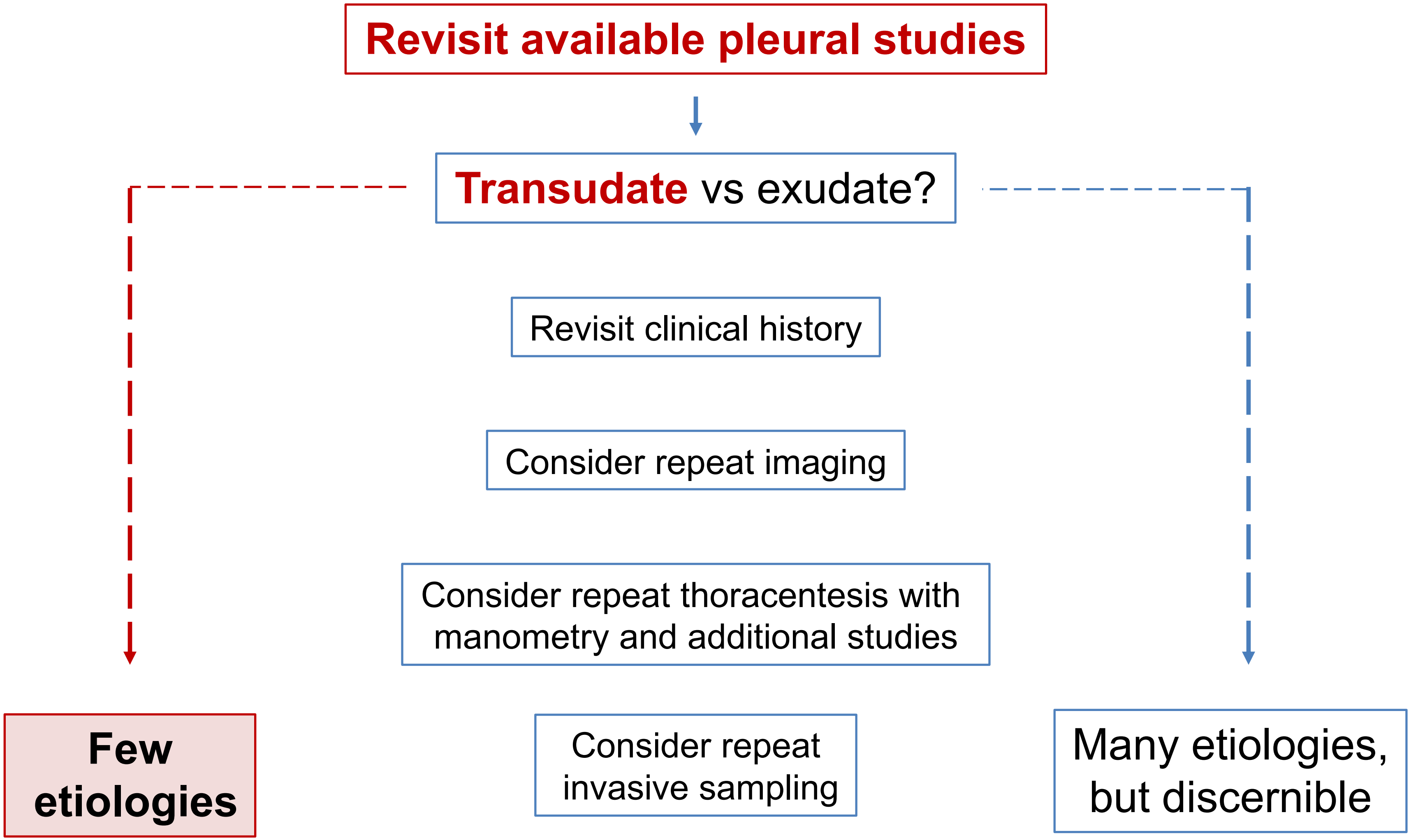
CHEST 2017; 151(5):1099-1105

Managing the recurrent pleural effusion

Do you have the right diagnosis?



Managing the recurrent pleural effusion
Do you have the right diagnosis?



Misdiagnosed transudate:
Clinical – testing discordance

- **It's not a (one of the 'big-3') transudate because…**
  - *"It's an exudate– it's not the heart"*
  - *"There's no ascites and the effusion is on the left"*
  - *"We've dialyzed the patient daily for a week"*

Are Light's Criteria Imperfect?

- Review of misclassified transudates: 27%

- In one series: 107 **misclassified** heart failure-related effusions had:
  - Median protein ratio = **0.51**
  - Median LDH ratio = **0.63**

JM Porcel. Curr Opin Pulm Med 2013;19(4):362-67
Bielsa S et al. Respirology 2012;17:721-26

Studies Examining Misclassified Transudates

Table 2. Published reports examining misclassified transudates[a]

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)

- 62% of false exudates uncovered by protein gradient >3.1 g/dL
- **80.5% of false exudates uncovered by serum-pleural albumin gradient (SPAG) >1.2 g/dL**

JM Porcel. Curr Opin Pulm Med 2013;19(4):362-67

SPAG particularly helpful in hepatic hydrothorax

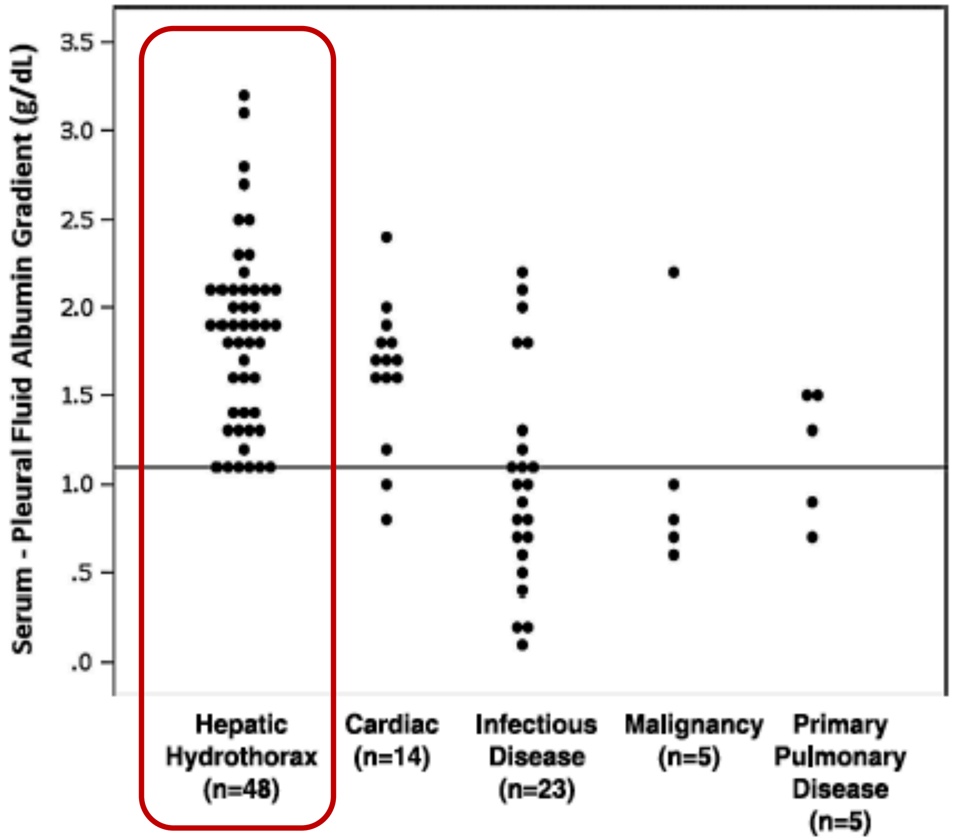


FIGURE 5. SPAG in patients with cirrhosis and hepatic hydrothorax or cirrhosis and other causes of pleural effusion. Each patient's SPAG value is represented by a single dot (that is, for patients with hepatic hydrothorax, n = 48). Levels are segregated according to the cause of pleural effusion, shown in the x axis. Units are g/dL and a horizontal line is placed at a value of 1.1 g/dL for reference.

Hepatic Hydrothorax

Clinical Features, Management, and Outcomes in 77 Patients and Review of the Literature

TABLE 2. Clinical Presentation and Imaging Results

	n	No. of Reported Symptoms (% of Patients) or No. of Patients (%)
Pleural effusion	77	
Laterality		
Right-sided only		56 (73%)
Left-sided only		13 (17%)
Bilateral		8 (10%)
Size	77	
Small		2 (3%)
Moderate		19 (25%)
Large		55 (71%)
Not reported		1 (1%)

Ascites

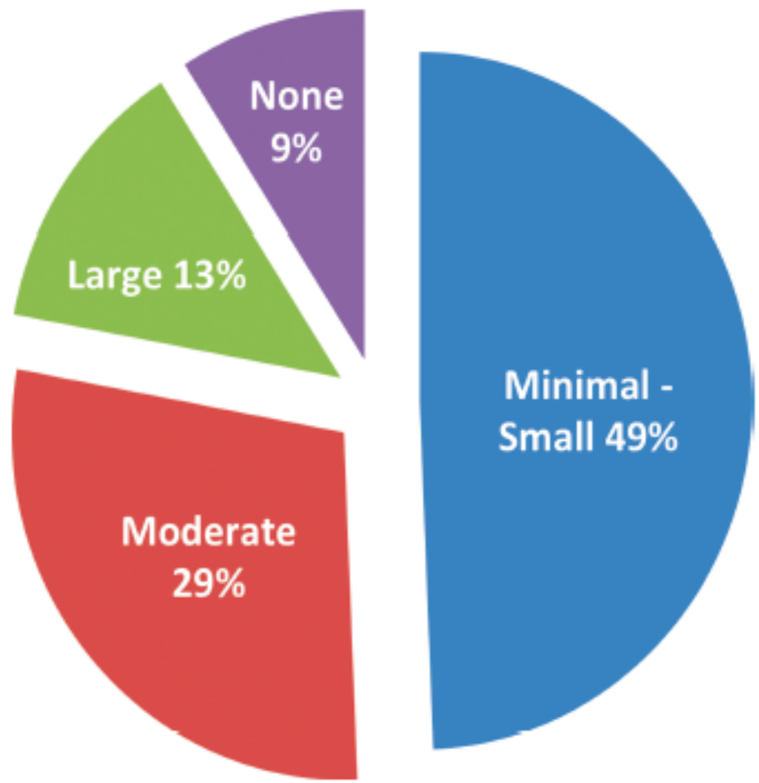
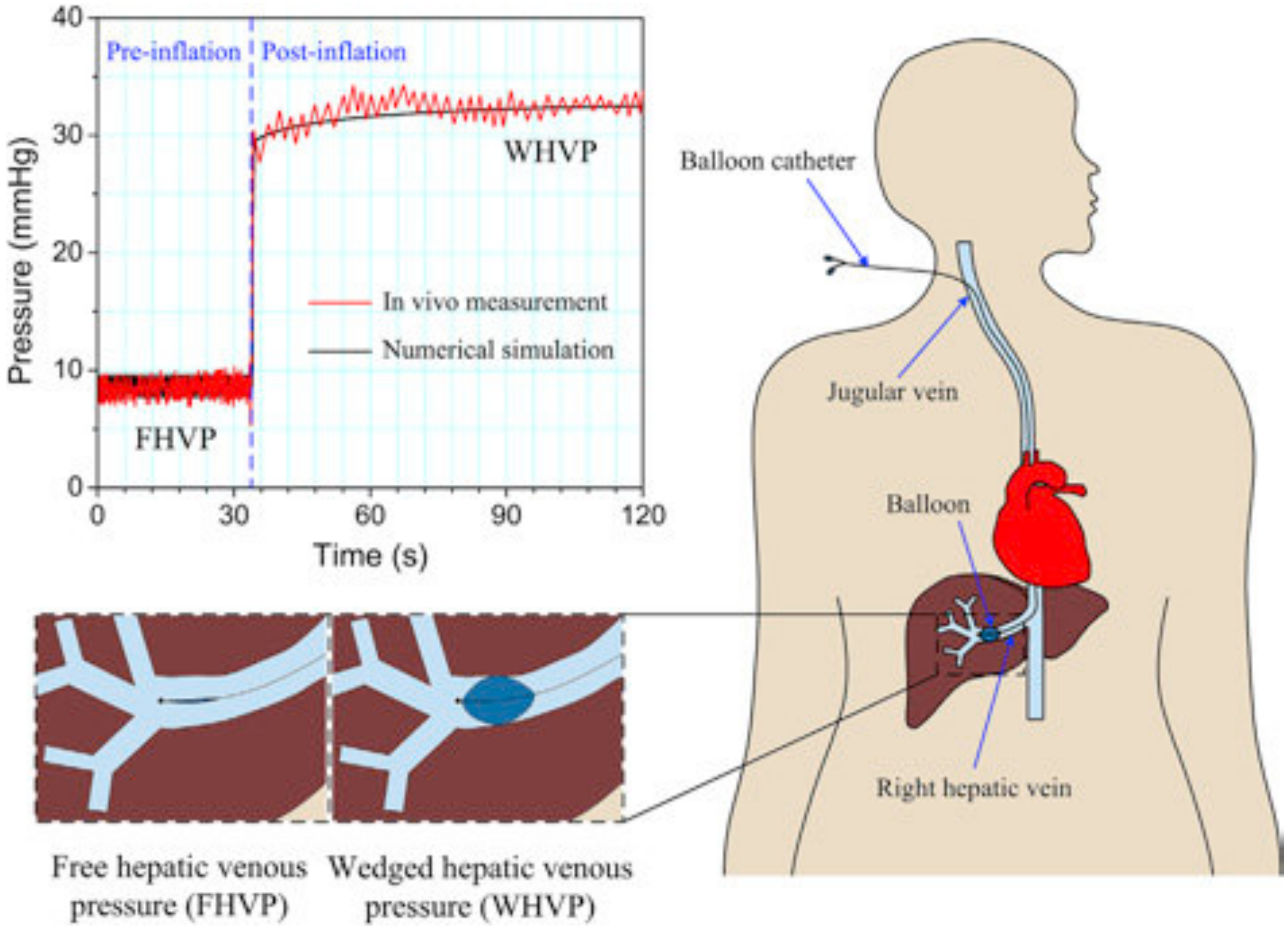


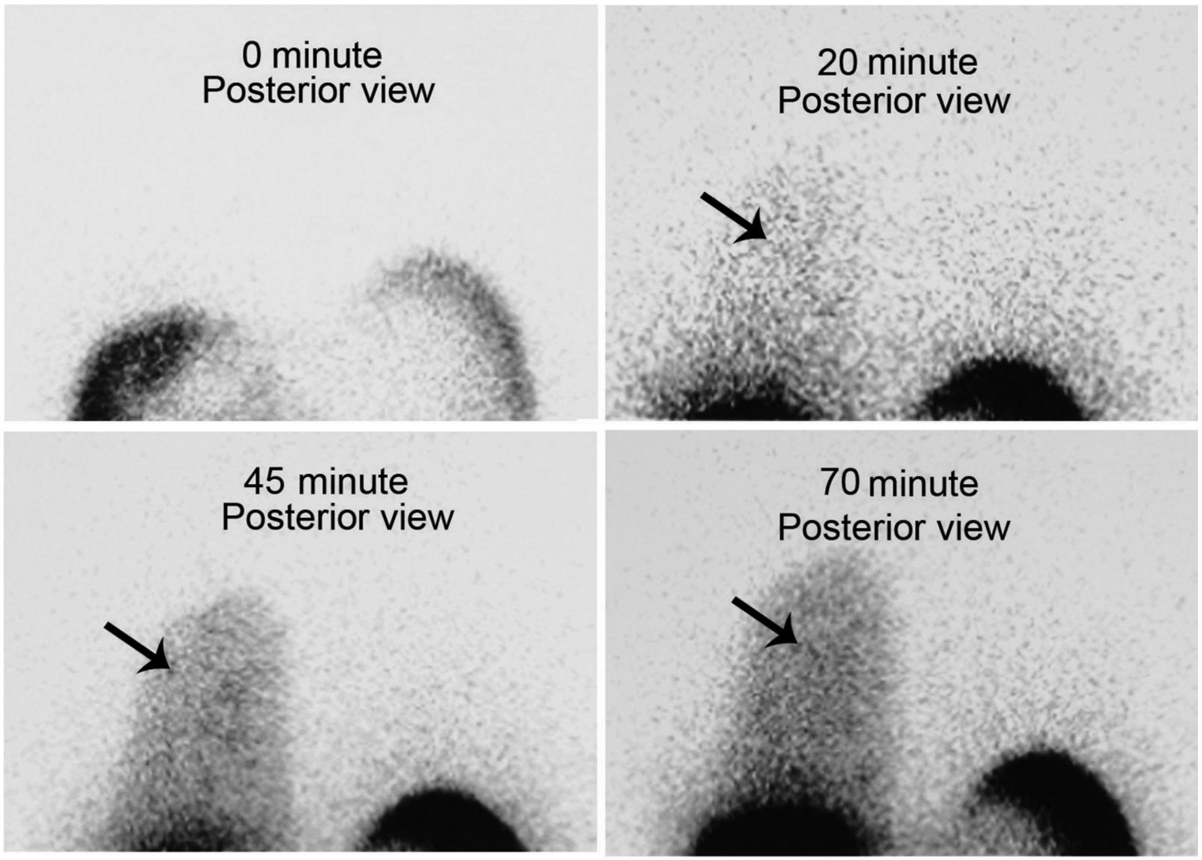
FIGURE 3. Comparison of ascites size and prevalence. The prevalence of ascites and recorded size of ascites is shown in 77 patients in the cohort.

Additional testing for hepatic hydrothorax



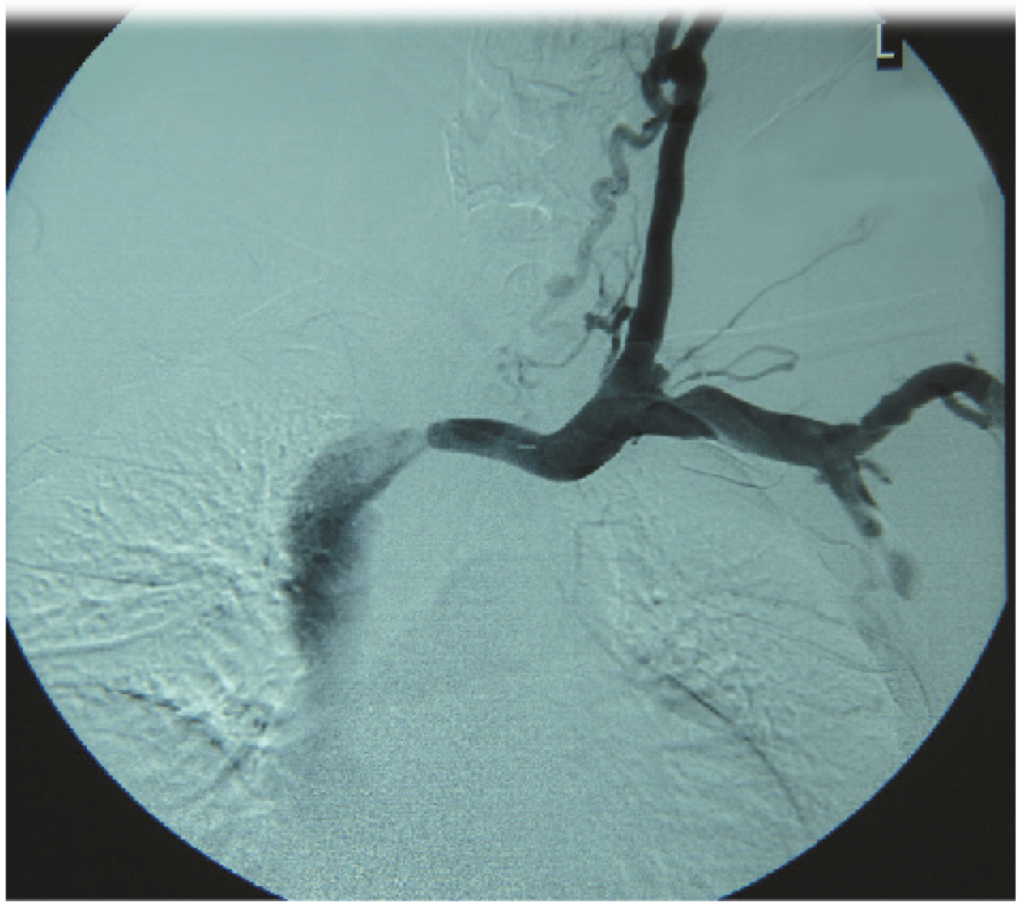
Hepatic venous pressure gradient (HVPG)

Additional testing for hepatic hydrothorax and peritoneal dialysis patients



Peritoneal scintigraphy

Renal disease: other considerations
SVC syndrome, central venous stenosis



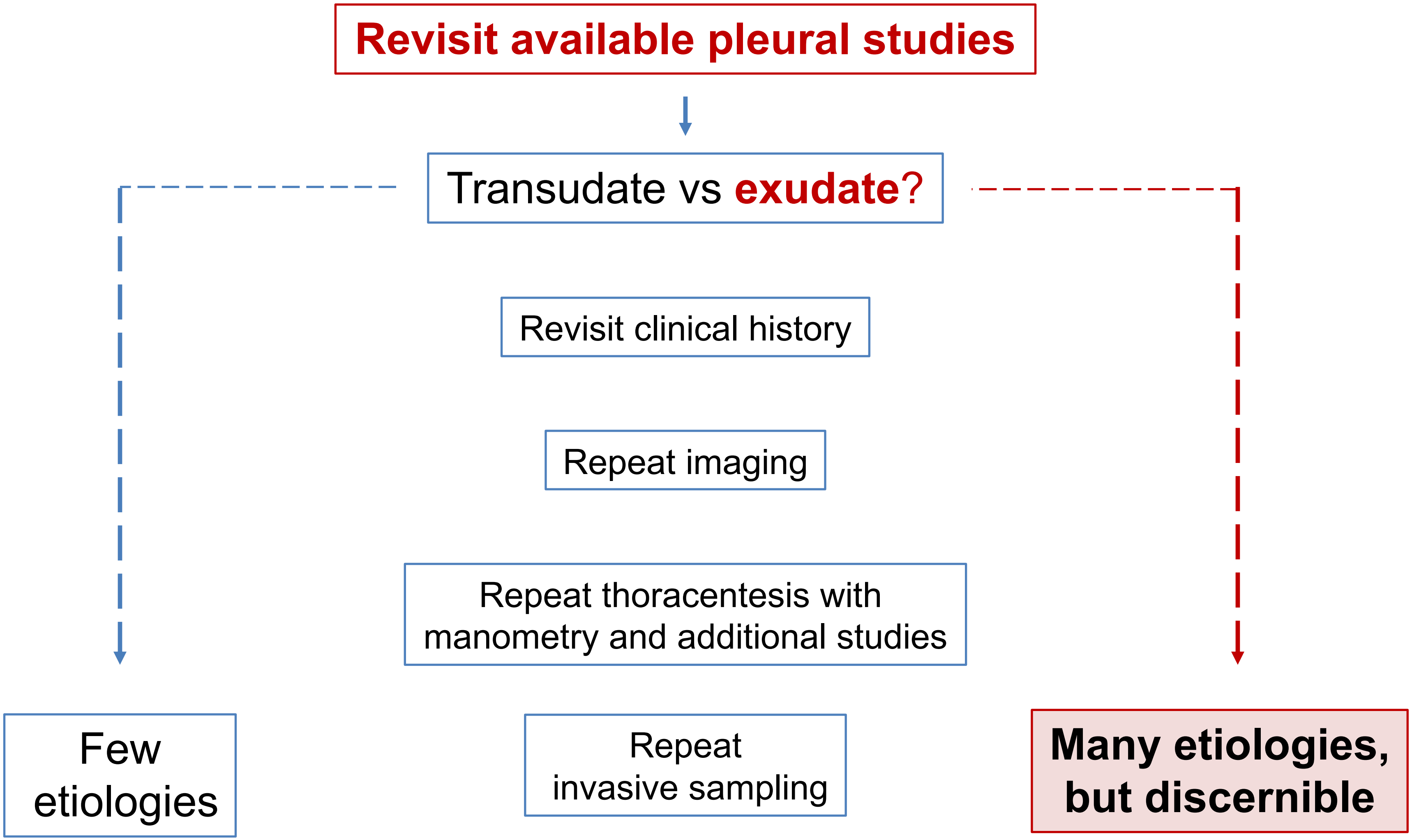
Venogram

Pleural fluid clues to uncommon causes of transudative effusion

Etiology	Effusion feature
Transudates	
Peritoneal dialysis	Glucose > 1.5 serum, protein <0.5
Urinothorax	Creat >1.7 or >1 serum, low Ph, low glucose, urine smell
CSF/duropleural fistula	+B2 transferrin
Usual exudates that can be transudates	PE, chylothorax, sarcoidosis, malignancy

Managing the recurrent pleural effusion

Do you have the right diagnosis?



Most exudates are due to bacterial infection and cancer, and are usually clinically obvious

Congestive heart failure	500,000
Parapneumonic effusion	300,000
Malignant Pleural effusion	200,000
Lung	60,000
Breast	50,000
Lymphoma	40,000
Other	50,000
Pulmonary embolization	150,000
Viral disease	100,000
Cirrhosis with ascites	50,000
Postcoronary artery bypass graft surgery	50,000
Gastrointestinal disease	25,000
Tuberculosis	2,500
Mesothelioma	2,300
Asbestos exposure	2,000

Light, 2007; Kookoolis, 2014

Lots of other causes of exudates

Congestive heart failure	500,000
Parapneumonic effusion	300,000
Malignant Pleural effusion	200,000
Lung	60,000
Breast	50,000
Lymphoma	40,000
Other	50,000
Pulmonary embolization	150,000
Viral disease	100,000
Cirrhosis with ascites	50,000
Postcoronary artery bypass graft surgery	50,000
Gastrointestinal disease	25,000
Tuberculosis	2,500
Mesothelioma	2,300
Asbestos exposure	2,000

Light, 2007; Kookoolis, 2014

Managing the <u>undiagnosed exudate</u>

Step 1: revisit clinical history

Recent thoracic surgery? → PCIS; chylothorax

↓

Abdominal process, recent surgery? → Pancreatitis; sympathetic effusion; abscess

↓

New medications → Amiodarone, tacrolimus nitrofurantoin

↓

Insidious constitutional symptoms → TB, autoimmune disease, undiagnosed cancer

Managing the undiagnosed exudate

Step 2: revisit chest imaging

CT chest with pleural-phase contrast

- Focal thickening → Metastatic cancer
- Diffuse thickening → (Smooth vs irregular) → Pleuritis, remote inflammatory process, trapped lung, mesothelioma
- Other findings → PE, parenchymal disease, lung mass, central venous or pericardial disease

Managing the <u>undiagnosed exudate</u>

Step 3: re-sample fluid

Thoracentesis with manometry

↓

Pleural elastance —high→ Trapped/entrapped lung

↓

Appearance, smell → Chylothorax, abscess

↓

Lymphocyte dominant? → TB, lymphoma, sarcoid, cancer
= Pleural biopsy

Pleural fluid clues to uncommon causes of effusion

Etiology	Effusion feature
Exudates	
Rheumatoid	Glucose < 30 mg/dL
Chylothorax	Non-settling milky fluid, TG >110 mg/dL; + chylomicrons
Tuberculous	Adenosine deaminase >45 U/L
Plasma cell dyscrasia (MM, WM)	Protein > 7.0 g/dL
Pancreatic, esophageal rupture	High amylase

Managing the ***recurrent*** symptomatic non-malignant pleural effusion

CHF | Cirrhosis | ESRD | Uncommon causes

↓

Therapeutic thoracentesis

↓

Optimize medical management

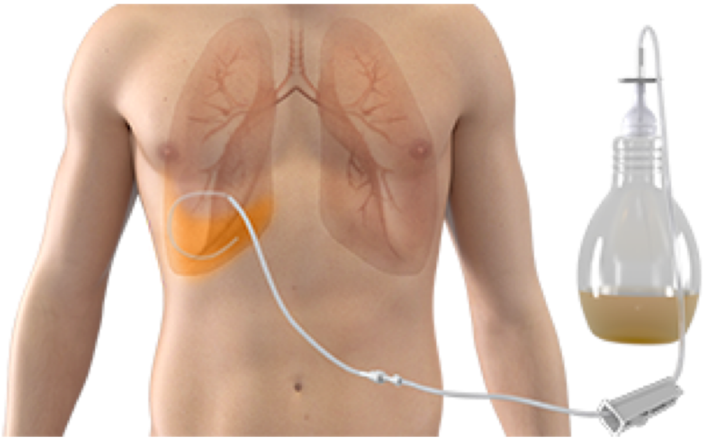
↓

Close subspecialty f/u

Managing the ***refractory*** symptomatic non-malignant pleural effusion

Repeated thoracentesis

Chemical pleurodesis

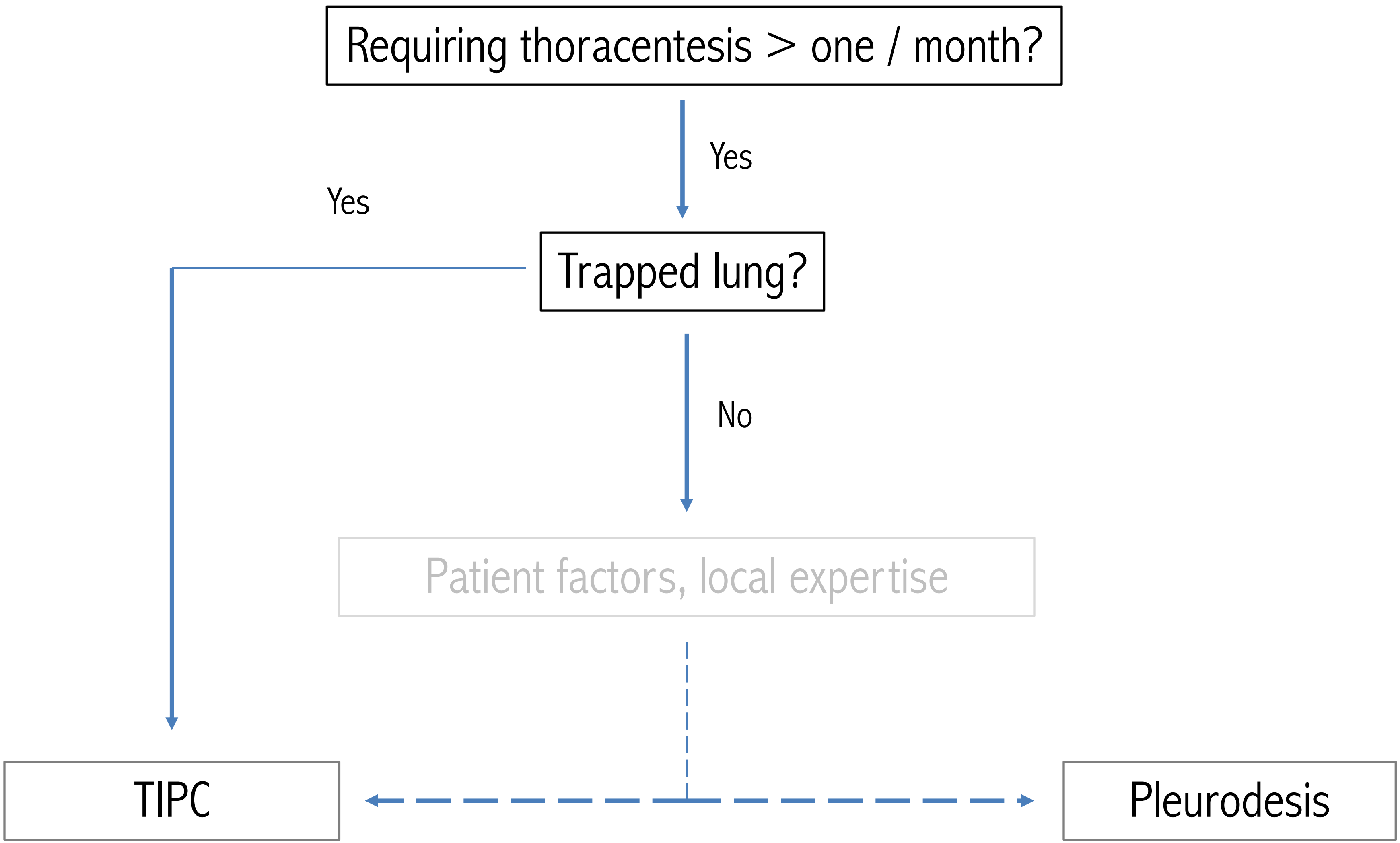


Indwelling pleural catheter

Factors to consider in managing **<u>refractory NMPE</u>** vs MPE

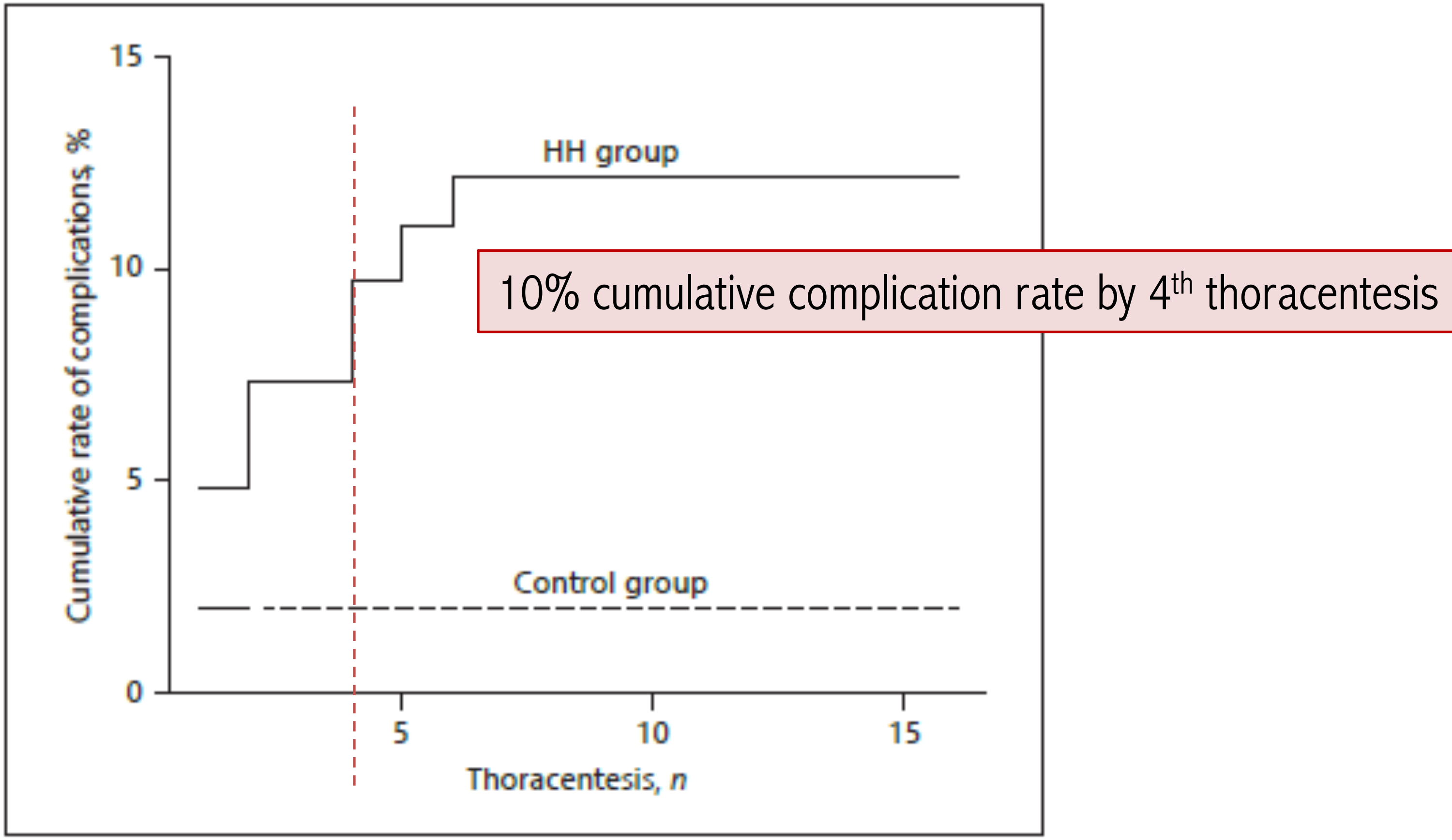
- Paucity of quality data
- NMPE patients have better prognosis
- Chemical pleurodesis rates may be higher
- Certain therapies may be detrimental

Managing **refractory** NMPE



Repeat Thoracentesis in Hepatic Hydrothorax and Non-Hepatic Hydrothorax Effusions: A Case-Control Study

Samira Shojaee[a] Marwah Khalid[a] George Kallingal[a] Le Kang[b] Najib Rahman[c]



Complications within the hepatic hydrothorax group (274 procedures)	
All minor and major complication (95% CI)	6.2% (3.8–9.9)
Pneumothorax (minor and major) (95% CI)	1.5% (0.5–4.0)
Pneumothorax requiring chest tube (95% CI)	0.4% (0.01–2.0)
Hemothorax (95% CI)	1.8% (0.7–4.4)

Respiration 2018;96:330–337

Successful Talc Slurry Pleurodesis in Patients With Nonmalignant Pleural Effusion*

Report of 16 Cases and Review of the Literature

(CHEST 2000; 117:1404–1409)

Table 2—*Literature Review of Pleurodesis in Cases of Benign Effusion*

Diagnosis	Total No. of Patients	Sclerosing Agent, No. of Patients	No. Successful Outcome/Total No.	Reference
CHF	12	Talc, 7	7/7	[15–17] and our series
		Others, 5	3/5	
Liver cirrhosis	28	Talc, 18	16/18	[18–24] and our series
		Others, 11	5/11	
SLE	7	Talc, 4	4/4	[20,25–27,45] and our series
		Others, 5	3/5	
Chylothorax	27	Talc, 20	19/20	[20,28–34] and our series
		Others, 7	4/7	
Empyema	6	Talc, 6	6/6	[30,37]
AIDS	5	Talc, 5	5/5	[15]
Dressler syndrome	1	Talc, 1	1/1	[47]
Postradiotherapy	2	Talc, 2	2/2	[8,47]
Undiagnosed	18	Talc, 18	18/18	[20] and our series
YNS	10	Talc, 4	4/4	[8,18,26,37–41] and our series
		Other, 8	4/8	
Asbestos injury	3	Talc, 3	3/3	[47]
Macroglobulinemia	1	Talc, 1	1/1	[8]
COPD and nephrotic syndrome	6	Talc, 3	3/3	[42–46]
		Others, 3	3/3	
Total	126	Talc, 92 Others, 38	Talc, 89/92 (97%) Others, 23/38 (60%)	

* Mix of slurry and poudrage

Management of Benign Pleural Effusions Using Indwelling Pleural Catheters

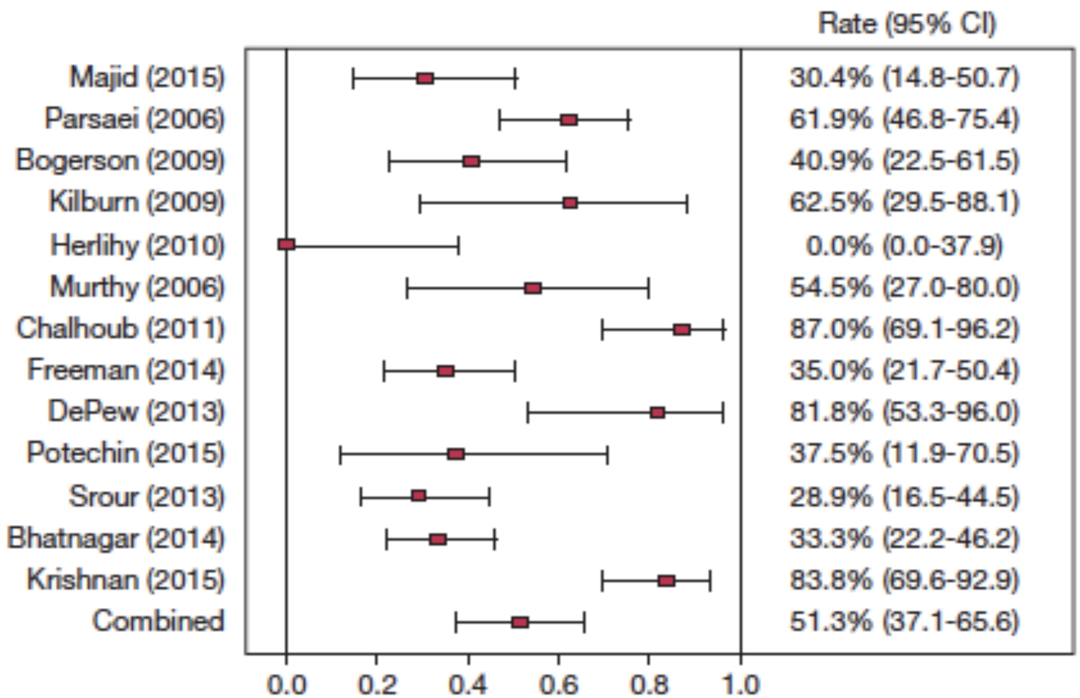
A Systematic Review and Meta-analysis

TABLE 2] Patient Baseline Characteristics

Characteristic	Frequency (% of Patients)
Sex	
Male	175 (53.8)
Female	150 (46.2)
Side of effusion	
Right	135 (41.5)
Left	32 (9.8)
Both	17 (5.2)
Unknown	141 (43.4)
Cause	
Cardiac	162 (49.8)
Hepatic	40 (12.3)
Chylothorax	11 (3.4)
Empyema	9 (2.8)
Inflammatory pleurisy	21 (6.5)
Yellow nail	5 (1.5)
Renal disease	13 (4.0)
Other	64 (19.7)

CHEST 2017; 151(3):626-635

Spontaneous pleurodesis with IPC in NMPE



	Estimated Average Rate (95% CI)	95% Prediction Interval	I^2	Q (*P* value)
Overall	51.3% (37.1-65.6)	(0.1%-100.0%)	87.2%	93.8 (*P* < .001)
Cardiac	42.1% (20.1-64.1)	(0.0%-100.0%)	88.4%	51.8 (*P* < .001)
Non-cardiac	61.4% (45.3-77.4)	(13.2%-100.0%)	50.7%	8.1 (*P* = .087)

CHEST 2017; 151(3):626-635

Clinical Predictors of Successful and Earlier Removal of Indwelling Pleural Catheters in Benign Pleural Effusions

Table 5. Multivariate logistic regression of clinical factors predicting rates of pleurodesis

Variable	OR (95% CI)	*p* value
ECOG score ≤2	4.22 (1.75–10.16)	0.0013
Medical thoracoscopy	5.27 (2.74–10.11)	<0.0001

Higher chance of pleurodesis:

1- Better functional status

2- IPC placed during thoracoscopy

Respiration
DOI: 10.1159/000500428

Clinical Predictors of Successful and Earlier Removal of Indwelling Pleural Catheters in Benign Pleural Effusions

Table 6. Multivariate Cox proportional-hazards regression of clinical factors predicting days to pleurodesis

Variable	HR (95% CI)	*p* value
Pleural effusion above the hilum	0.54 (0.34–0.85)	0.0085
Secondary pleural infection	14.19 (4.11–48.91)	<0.0001
% Eosinophils	1.03 (1.01–1.05)	0.0103
Liver failure	0.31 (0.16–0.60)	0.0004
Heart failure	0.32 (0.20–0.52)	<0.0001
Connective tissue disease	2.59 (1.20–5.57)	0.0153

Longer time to pleurodesis:

1- Large effusion

2- Heart or liver failure

Respiration
DOI: 10.1159/000500428

Complications related to IPC in NMPE are infrequent

TABLE 5] Estimated Rate of All Complications

Complication	Estimated Rate, % (95% CI)
Any complication	17.2 (9.8-24.5)
Skin infection	2.7 (0.6-4.9)
Empyema	2.3 (0.0-4.7)
Loculation	2.0 (0.0-4.7)
Dislodgement	1.3 (0.0-3.7)
Pneumothorax	1.2 (0.0-4.1)
Blockage/drainage failure	1.1 (0.0-3.5)
Leakage	1.3 (0.0-3.5)
Subcutaneous emphysema	1.1 (0.0-4.0)
Other complications	2.5 (0.0-5.2)

CHEST 2017; 151(3):626-635

Hepatic hydrothorax

Survival highly dependent on reversing PoH -TIPS, transplant

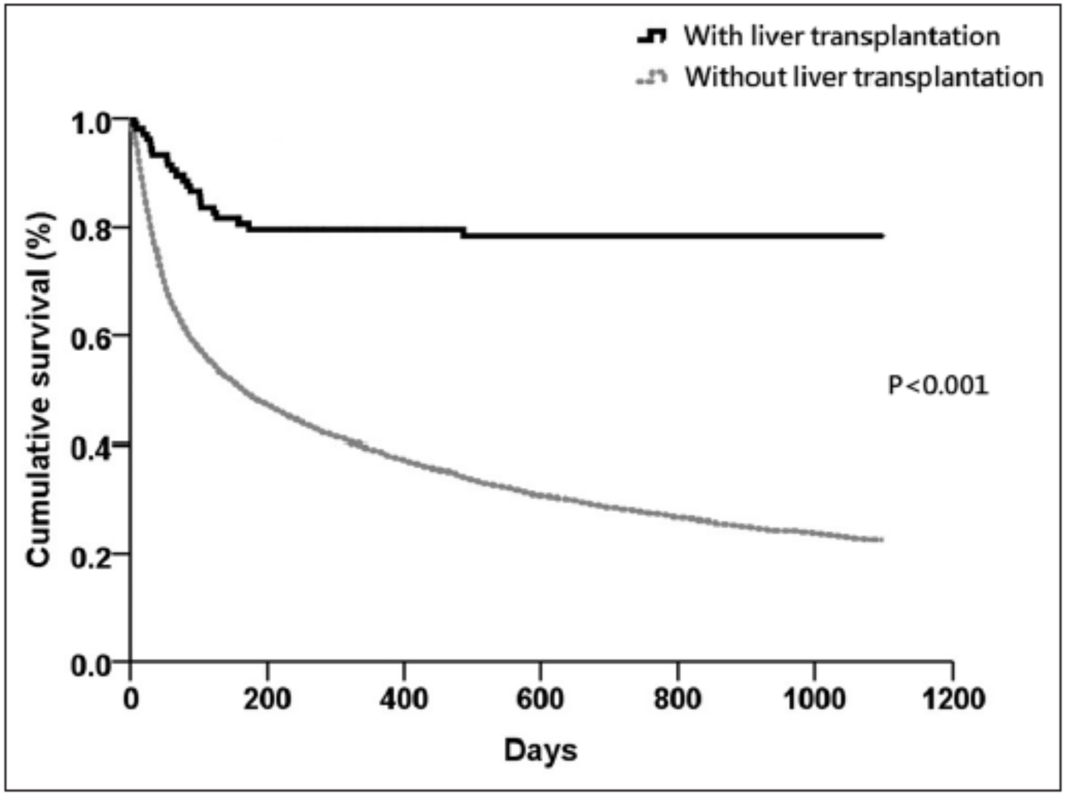
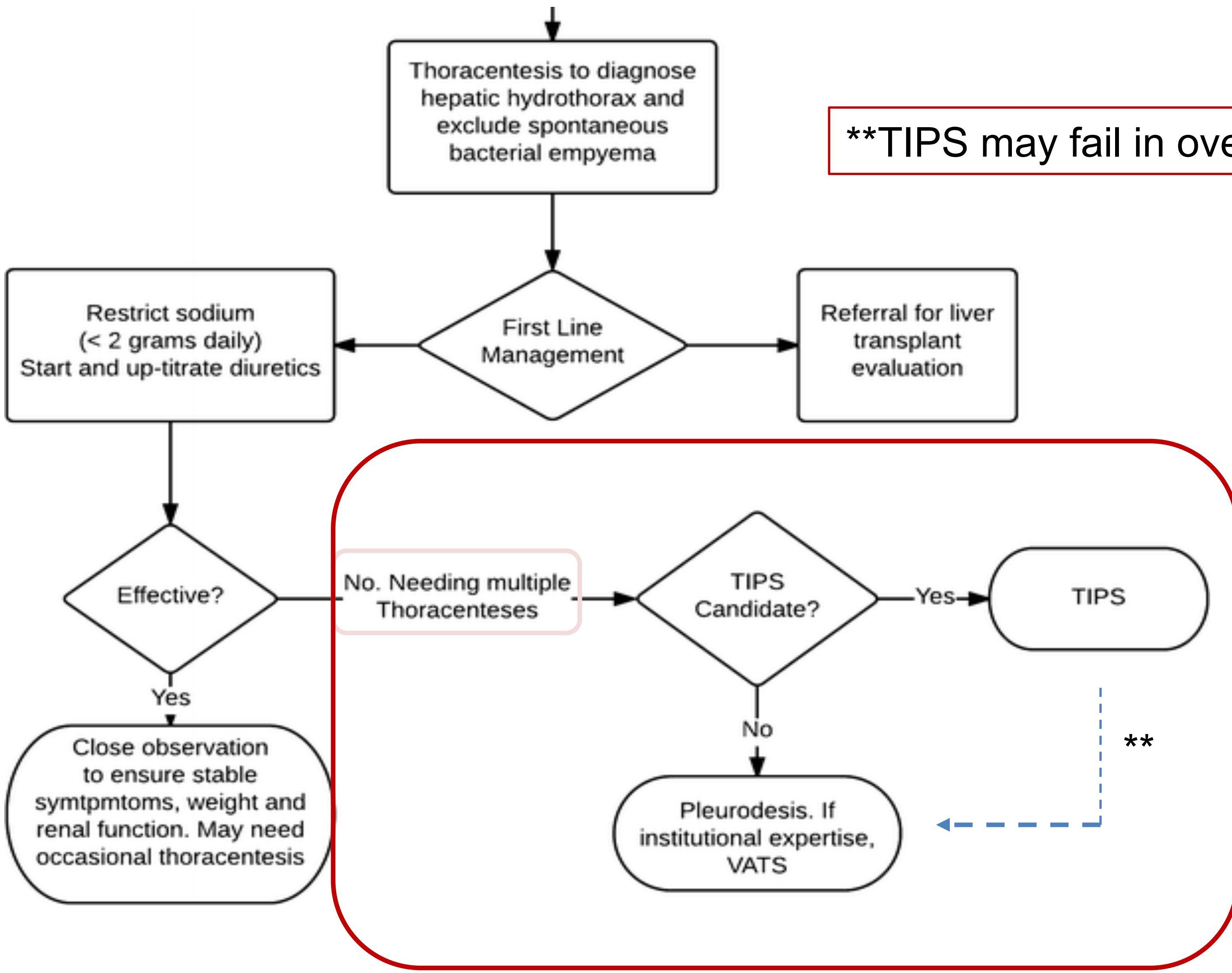


Figure 1: Kaplan–Meier survival analysis for cirrhotic patients with pleural effusion

Management of hepatic hydrothorax



**TIPS may fail in over 25%

Tapper, E.B. & Cárdenas, A. Curr Hepatology Rep (2015) 14: 212

Singh et al. Respiration 2013;86:155–173

Chest tube in Hepatic Hydrothorax:
Avoid if possible!

Table 2—*Outcome of Chest Tube Placement in CTP Class B and CTP Class C Cirrhotic Patients**

Variables	CTP Class B	CTP Class C	Total
Patients	31	25	56
Median days with chest tube in place (range)	5.0 (1–53)	4.0 (1–39)	5.0 (1–53)
Complications in subjects with chest tube in place			
Renal failure	14 (45)	16 (64)	30 (54)
Electrolyte imbalance	15 (48)	17 (68)	32 (57)
Infection	14 (45)	13 (52)	27 (48)
Deaths with chest tube in place	5 (16)	10 (40)	15 (27)
Subjects undergoing TIPS with chest tube in place	1 (3)	0	1 (2)
Subjects undergoing OLT with chest tube in place	3 (10)	1 (4)	4 (7)
Subjects with chest tube removal	22 (71)	14 (56)	36 (64)

*Data are presented as No. or No. (%) unless otherwise indicated.
OLT = open lung transplantation.

*** 80% had at least one complication**
*** 48% had infection**
*** 27% died during chest tube therapy**

Liu et al. Chest. 2004;126(1):142-148.

IPC for Hepatic Hydrothorax

Indwelling Tunneled Pleural Catheters for Refractory Hepatic Hydrothorax in Patients With Cirrhosis

A Multicenter Study

Samira Shojaee, MD, MPH; Najib Rahman, DPhil; Kevin Haas, MD; Ryan Kern, MD; Michael Leise, MD; Mohammed Alnijoumi, MD; Carla Lamb, MD; Adnan Majid, MD; Jason Akulian, MD, MPH; Fabien Maldonado, MD; Hans Lee, MD; Marwah Khalid, MD; Todd Stravitz, MD; Le Kang, PhD; and Alexander Chen, MD

CHEST 2019; 155(3):546-553

IPC for Hepatic Hydrothorax

TABLE 1] Demographic Data

Characteristics	Value
Age, y	60 ± 10.7
Sex	
Male	43 (54)
Female	36 (46)
Relevant medical history	
Prior TIPS	16 (20)
Liver transplant (post-IPC)	15 (19)
Etiology of liver disease	
Hepatitis C cirrhosis	19 (24)
Alcohol-induced cirrhosis	39 (49)
NASH cirrhosis	21 (27)
Indication for IPC placement	
Palliation	58 (73)
Bridge to Transplant	21 (27)

TABLE 2] Laboratory Values Prior to IPC Placement and Thoracentesis Characteristics

Characteristic	Value
Laboratory tests	
ALT	51.49 ± 72.2
Creatinine	1.84 ± 1.7
AST	74.78 ± 73.8
Total bilirubin	5.02 ± 6.8
Albumin	2.96 ± 0.8
WBC count	8.13 ± 8.7
Platelet count	108 ± 97.1
INR	1.62 ± 0.4
MELD score	18.1 ± 5.1

CHEST 2019; 155(3):546-553

IPC for Hepatic Hydrothorax

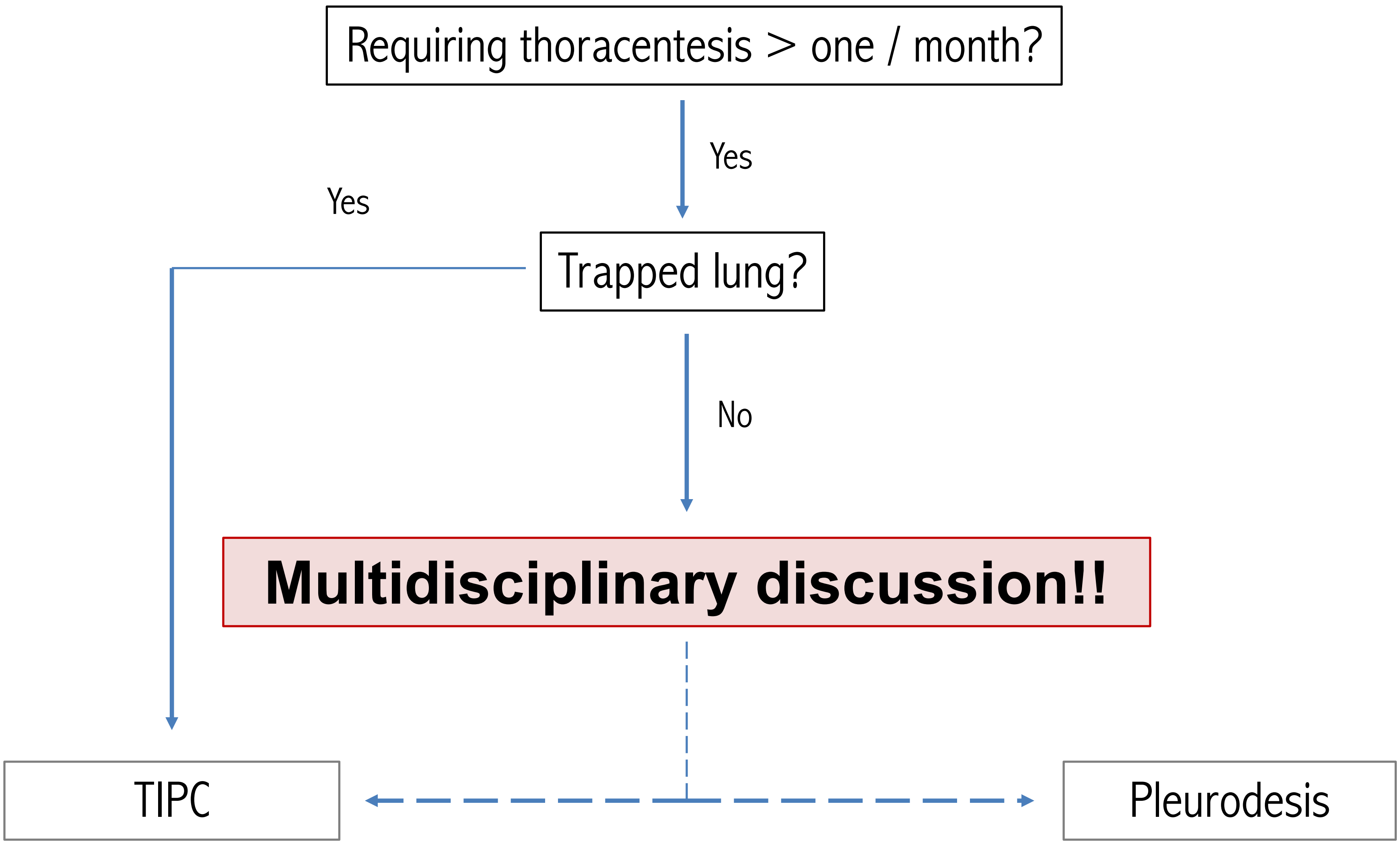
TABLE 3] Indwelling Tunneled Pleural Catheter-Related Complications

Complication	No.
Renal failure	2
Severe electrolyte imbalance	1
Severe malnutrition	0
Subcutaneous fluid collection (seroma)	3
Catheter site fluid leakage	4
Cellulitis	5
Parapneumonic effusion/empyema	8
Catheter-related sepsis leading to death	2

n= 79 patients
Max one liter qod drainage
28% spontaneous pleurodesis
10% pleural infection

CHEST 2019; 155(3):546-553

Managing **refractory** NMPE



Conclusions

- Non-malignant effusions (NMPEs) are a marker of disease severity and often suggest a poor prognosis
- Ensure your diagnosis
- Most NMPEs can be managed by optimizing medical therapy
- Refractory NMPEs may be managed by definitive therapies such as pleurodesis, IPC or surgical approaches, but data is still evolving
- **Multidisciplinary discussion is essential!!**

Thank you, Questions??

Ara A. Chrissian, MD, FCCP, DAABIP

Director, Adult Bronchoscopy and Interventional Pulmonology

Associate Director, Pulmonary and Critical Care Fellowship

Associate Professor of Medicine

Loma Linda University Medical Center

achrissian@llu.edu

Updates on Mesothelioma in 2019

Yaron Gesthalter, MD
University of California
San Francisco

Saturday, October 5, 2019 – 4:10 p.m. – 4:35 p.m.

Dr. Yaron B. Gesthalter is an Assistant Professor in the Division of Pulmonary, Sleep & Critical Care at the University of California San Francisco. He received his medical degree from the Sackler School of Medicine in Israel and completed an Internal Medicine residency at Yale followed by a Pulmonary & Critical Care fellowship at Boston University. He then went on to complete additional training in Interventional Pulmonary Medicine at Harvard. He is a member of The Thoracic Oncology Program where his practice focuses on the management of patients with complex airway and pleural disease.

CALIFORNIA THORACIC SOCIETY
A chapter of the American Thoracic Society

Updates in Pleural Mesothelioma

Yaron B Gesthalter, MD
Director of Pleural Services
Interventional Pulmonary Medicine
Thoracic Oncology Program
Department of Pulmonary, Allergy, Sleep and Critical Care
University of California San Francisco

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Disclosure Slide

- No relevant financial conflicts

2

Talk Outline

- Intro
- Diagnostics
  - Classic need for tissue
  - Biomarkers
- Prognostics
- Therapeutics

3

Pleural Mesothelioma

- A tumor that arises from the mesothelial surfaces of the pleura, peritoneum and pericardium
- 70% involve the pleura
- Stems from asbestos exposure
  - 70% of all mesothelioma cases involving documented asbestos exposure
  - 10% over the lifetime of an asbestos worker
  - Family members at risk as well
- Long latency period delays intervention effect
  - UK still with rising mesothelioma rates 20 years after ban

Mott FE; The Ochsner Journal 12:70–79, 2012
www.asbestos.com

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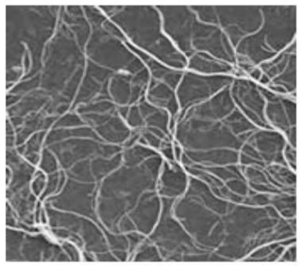
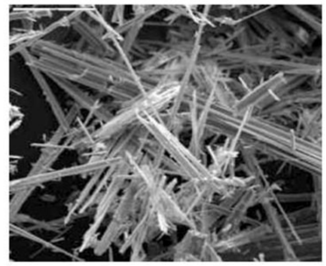
Risk Factors?





SERPENTINE
- **Canadian chrysotile**
- **90% of type found in United States**
- **Less carcinogenic**

AMPHIBOLE

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Prognosis

- **TNM staging:**
  - **Stage I -** T1a-b, N0,M0; ipsilateral parietal pleura without visceral involvement (IA) or with (IB)
  - **Stage II –** T2,N0,M0 : involving each ipsilateral pleural surface with ≥1 of: diaphragm or extending into lung tissue
  - **Stage III -** T1-2, N1-2 ,M0 or T3,N0-3,M0; involvement of thoracic fascia, mediastinal fat, solitary focus into chest wall, pericardium, ipsilateral hilar/mediastinal/sub-carinal lymph nodes
  - **Stage IV –** T4, any N, M0 or T, N3, M0 or M1; chest wall extension without rib destruction, crosses diaphragm, contralateral pleura
- **Histological type** (proportions)
  - Epitheloid – 38.4%
  - Sarcomatoid – 12.3%
  - Biphasic – 11%
  - NOS – 44.7%

Mott FE; The Ochsner Journal 12:70–79, 2012
Katzman D; Curr Opin Pulm Med 2018

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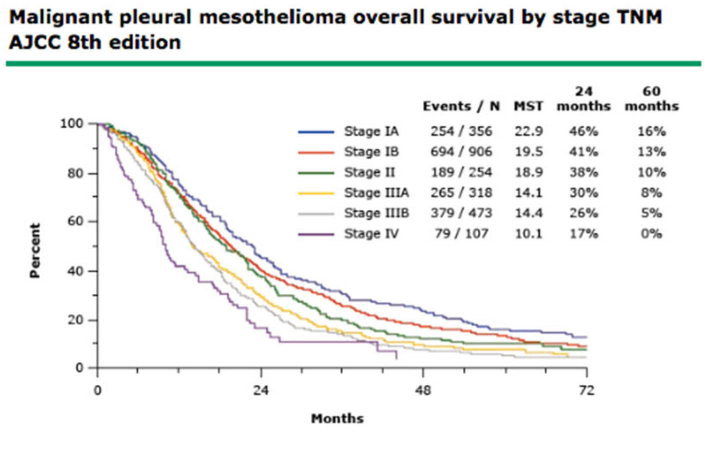
Prognosis



AJCC Cancer Staging Manual, Eighth Edition (2017)

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Treatment Approach Prognosis

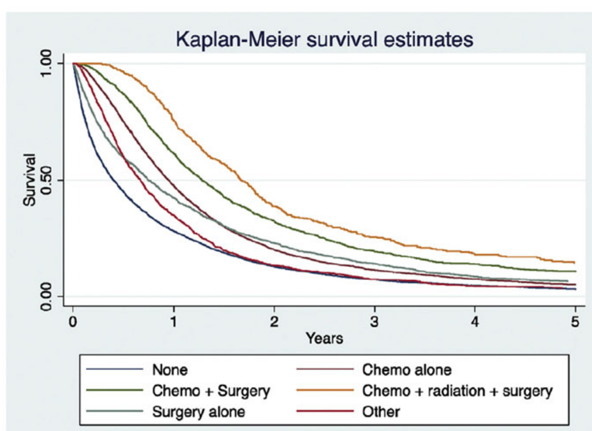

Fig 3. Survival of pleural mesothelioma at 5 years stratified by treatment type. (Chemo = chemotherapy.)

Saddoughi SA ; Ann Thor Surg 2018;105:432–7

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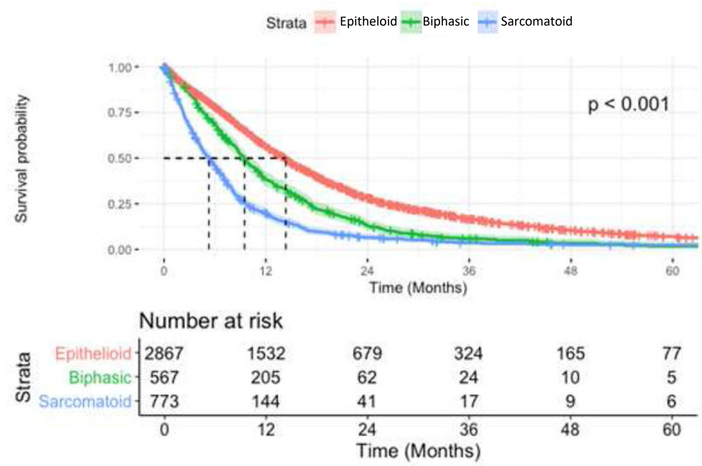
Histologic Prognosis



Verma V; Clinical Lung Cancer 2018

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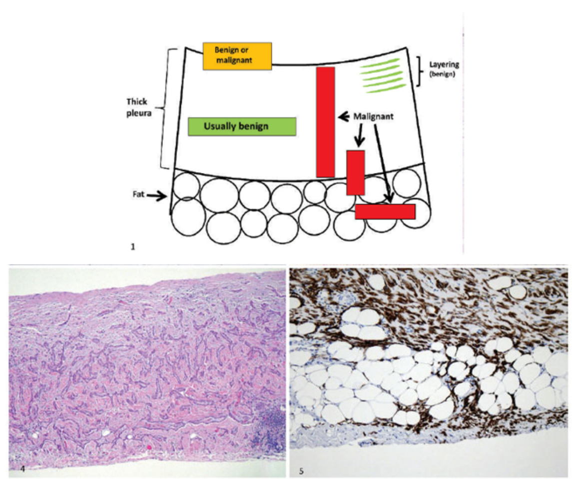
Diagnostics



Churg A ; Arch Pathol Lab Med. 2012;136:1217–1226;

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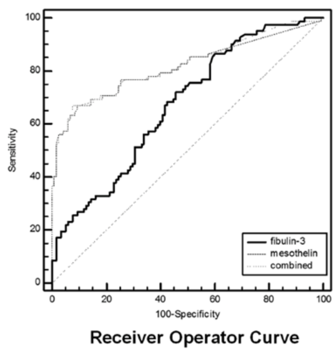
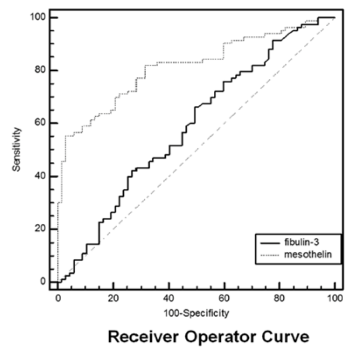
Biomarkers?

Plasma



Pleura



Creaney J; Thorax. 2014; 69:895–902

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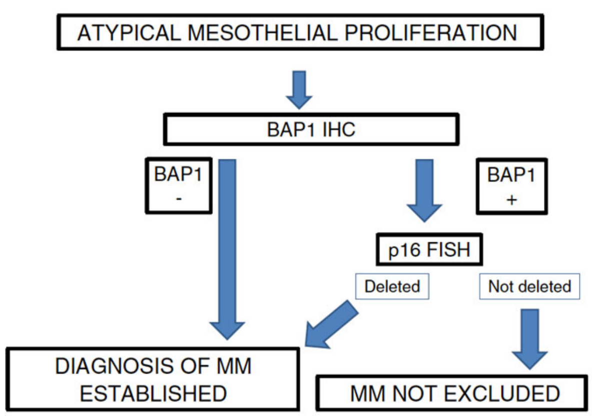
Diagnostics Biomarkers



Monaco S ; Adv Anat Pathol 2018; 25:24–30

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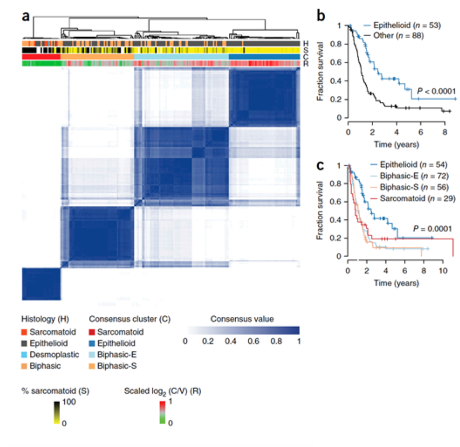
Molecular Profiling?



Bueno R ; Nature Genetics 2016; 48(4):407–419

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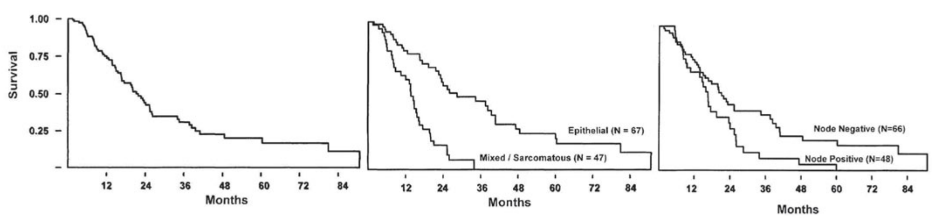
Trimodality Therapy
Where we are now…

- Chemotherapy + Surgery + Radiation

All patients who survived surgery | Epitheloid vs non-epitheloid | Node status



Sugarbaker et al; Chest 1998; 113:61S-65S

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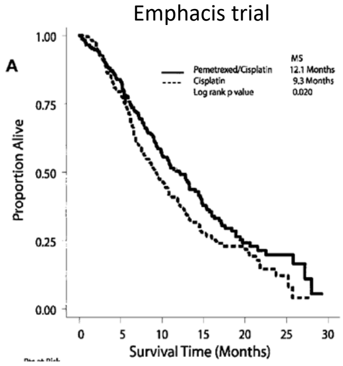
Treatment
Chemotherapy

- First line –
  - Cis/Pem vs Cis alone: mean survival 12.1 vs 9.3 months
  - Bevacizumab/Cis/Pem vs Cis/Pem 18.8 vs 16.1 months
- Second line –
  - None with demonstrated efficacy

Emphacis trial



Vogelzang et al; J Clin Oncol 2003; 21:2636-2644

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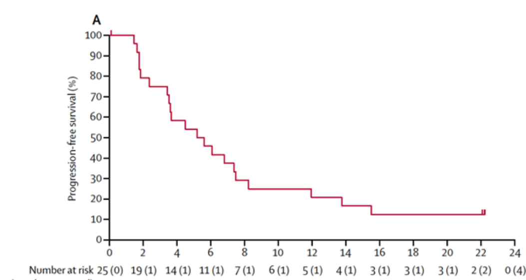
Targeted Therapy?

- No actionable mutations recognized
- Immune therapy –
  - PDL1 – progression free survival?
  - Keynote-028
  - 22 patients, phase II



Alley et al; Lancet Oncol 2017; 18(5):623-630

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Trials

Table 1. Key Malignant Pleural Mesothelioma Clinical Trials

Reference	Study design	Patient population	Treatment arms	Significant findings
Vogelzang *et al.* [6]	Phase III randomized trial	Treatment-naïve, unresectable malignant pleural mesothelioma (MPM), $n=456$	Cisplatin with pemetrexed versus cisplation alone	Improved response rates with combined therapy: 41.3 versus 16.7% ($P<0.0001$) Improved median overall survival (OS) with combined therapy: 12.1 versus 9.3 months ($P=0.020$)
Zalcman *et al.* [7■■]	Phase III randomized trial	Treatment-naïve, unresectable MPM, $n=448$	Cisplatin and pemetrexed with bevacizumab versus cisplatin and pemetrexed	Improved median OS with chemotherapy and bevacizumab: 18.8 versus 16.1 months (P 0.0167)
Clive *et al.* [8■]	Phase III randomized trial	MPM with recent large-bore pleural intervention, $n=203$	Prophylactic radiation therapy versus deferred radiation therapy	No significant difference in incidence of procedure-tract metastasis: 9% in prophylactic radiation therapy arm versus 16% in deferred radiation therapy arm ($P=0.14$)
Rusch *et al.* [9]	Phase II, single arm trial	MPM treated with surgical intervention, $n=54$ with extrapleural pneumonectomy (EPP) and three with extended pleurectomy/decortication (EPD)	Adjuvant high-dose hemithoracic radiation therapy	Overall median OS was 17 months Median OS was 33.8 versus 10 months in early versus late stage disease ($P=0.04$)
Rimner *et al.* [10]	Phase II, single arm trial		Adjuvant intensity-modulated hemithoracic pleural radiation therapy	Overall well tolerated. Complications included six grade II/III pulmonary toxicities and one delayed esophagopleural fistula
de Perrot *et al.* [11■]	Expanded phase I/II single arm trial	MPM treated with EPD and platinum-based chemotherapy with pemetrexed and, $n=27$	Neoadjuvant hypofractioned hemithoracic radiation therapy	Median progression-free survival (PFS) and OS were 12.4 and 23.7 months, respectively Overall well tolerated. Complications included eight grade II/III radiation pneumonitis
		MPM treated with EPP with or without chemotherapy, $n=62$		Overall median OS 36 months. Median OS 51 vs. 10 months in epithelioid vs. biphasic MPM ($P=0.001$) 30-day mortality: 0%. Three treatment-related deaths (two because of infections and one unwitnessed arrest)
Maio *et al.* [12■]	Phase IIb randomized trial	Unresectable malignant pleural or peritoneal mesothelioma with progression after one to two systemic treatments, $n=571$	Second-line or third-line tremelimumab versus placebo	Median OS 7.7 months in treatment arm and 7.3 months in placebo arm ($P=0.041$)
Alley *et al.* [13■]	Phase Ib single arm trial	Previously treated MPM with tumor PD-L1 expression $\geq$ 1%, $n=25$	Pembrolizumab	Overall response rate 20%, disease control rate 72%, and median response duration 12 months Overall well tolerated
Zalcman *et al.* [14]	Phase II randomized trial	Relapsed MPM after first line chemotherapy with or without second-line treatment, $n=125$	Nivolumab versus nivolumab with ipilimumab	No significant differences in response rates: 18.5 vs. 27.8% or 12-month OS: 51 vs. 58% (Nivo vs. Nivo with Ipi) More grade 3/4 toxicities with Nivo with Ipi: 26.2 vs. 12.7%
Cornelissen *et al.* [15■]	Pilot and feasibility study	Non-sarcomatoid MPM with disease control after chemotherapy with or without surgery, $n=10$	Adjuvant cycolophosphamide and systemic dendritic cell immunotherapy	7/10 survived at least 24 months 2/10 alive after 50 and 66 months Overall well tolerated
Sterman *et al.* 2016 [16■]	Pilot and feasibility study	Unresectable MPM, $n=40$	Intrapleural adenovirus-IFN-α2b with celecoxib then chemotherapy	Overall response rate was 25%. Epithelioid and non-epithelioid MPM median OS were 21 and 7 months, respectively Overall well tolerated
Zauderer *et al.* 2017 [17■]	Phase II randomized trial	MPM after surgery and a second treatment modality, $n=41$	Galinpepimut-S (WT1 vaccine) with GM-CSF and Montanide vs. GM-CSF and Montanide alone	Trend towards longer median PFS: 10.1 versus 7.4 months. Trend towards longer OS: 22.8 versus 18.3 months Combination therapy overall well tolerated
Szlosarek *et al.* 2017 [18■]	Phase II randomized trial	Argininosuccinate synthetase 1 (ASS1) deficient MPM, $n=68$	Standard treatment with and without pegylated arginine deaminase	Improved PFS: 3.2 vs. 2.0 months ($P=0.03$), Four-month disease stability: 52 vs. 22% ($P=0.23$) and OS 15.7 vs 12.1 months ($P=0.13$) with trend towards improvement Overall well tolerated

Katzman D; Curr Opin Pulm Med 2018

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Summary

- Pleural mesothelioma diagnosis remains a clinical challenge
- Biomarkers such as BAP1 may limit the need for tissue confirmation in the diagnostic work up of pleural mesothelioma
- Pleural mesothelioma prognosis is poor and mainly depends on clinical staging, histology

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CLOSING, POST TEST AND BREAK

Shazia Jamil, MD
Scripps Clinic
University of California San Diego

Saturday, October 5, 2019 – 4:35 p.m. – 4:50 p.m.

Pleural Procedures and Hands on Session

Moderators: Laren Tan, MD, Shazia Jamil, MD, Jason Lee, MD, Ara Chrissian, MD, Steve Escobar, MD, and Yaron Gesthalter, MD

Saturday, October 5, 2019 – 4:50 p.m. – 6:45 p.m.

SESSIONS:

1. **Ultrasound-Guided Thoracentesis – Hands on, audience participation**

2. **Pleural Manometry – Hands on, audience participation**

3. **Tunneled Indwelling Pleural Catheter Placement – Hands on, audience participation**

4. **Small Bore and Standard Thoracostomy Tube Placement – Hands on, audience participation**