

Complex Pleural Cases

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Disclosures

None

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Outline

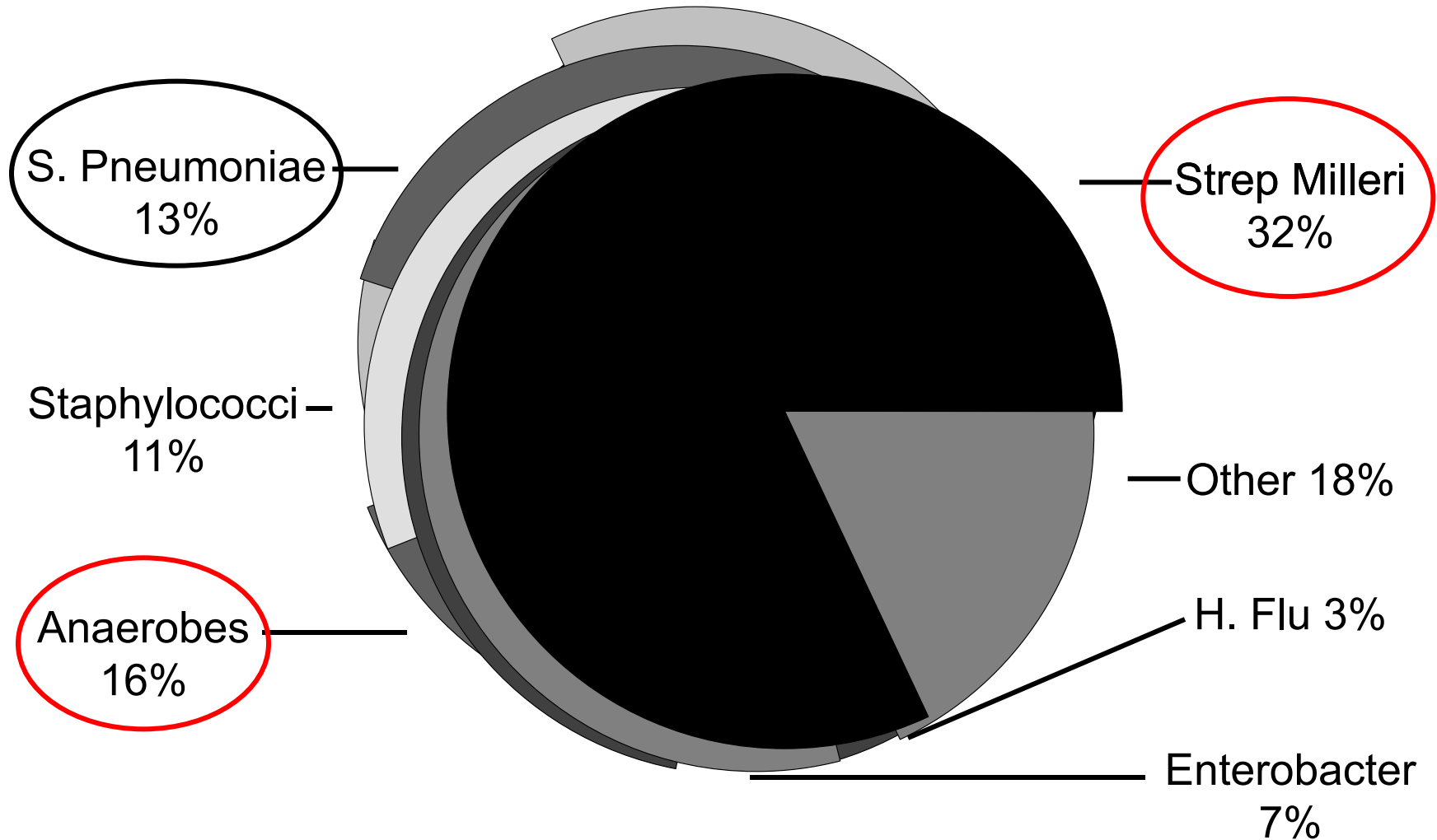
- Review evidence-based management of more common pleural diseases
 - Empyema
 - Hemothorax
 - Malignant pleural effusions
- Review more rare and “advanced” pleural diseases
 - Chylous and pseudo-chylous effusions
 - Thoracic endometriosis syndrome
 - Hepatic Hydrothorax
- And, helpful pleural tips along the way!

Empyema and Parapneumonic Effusions

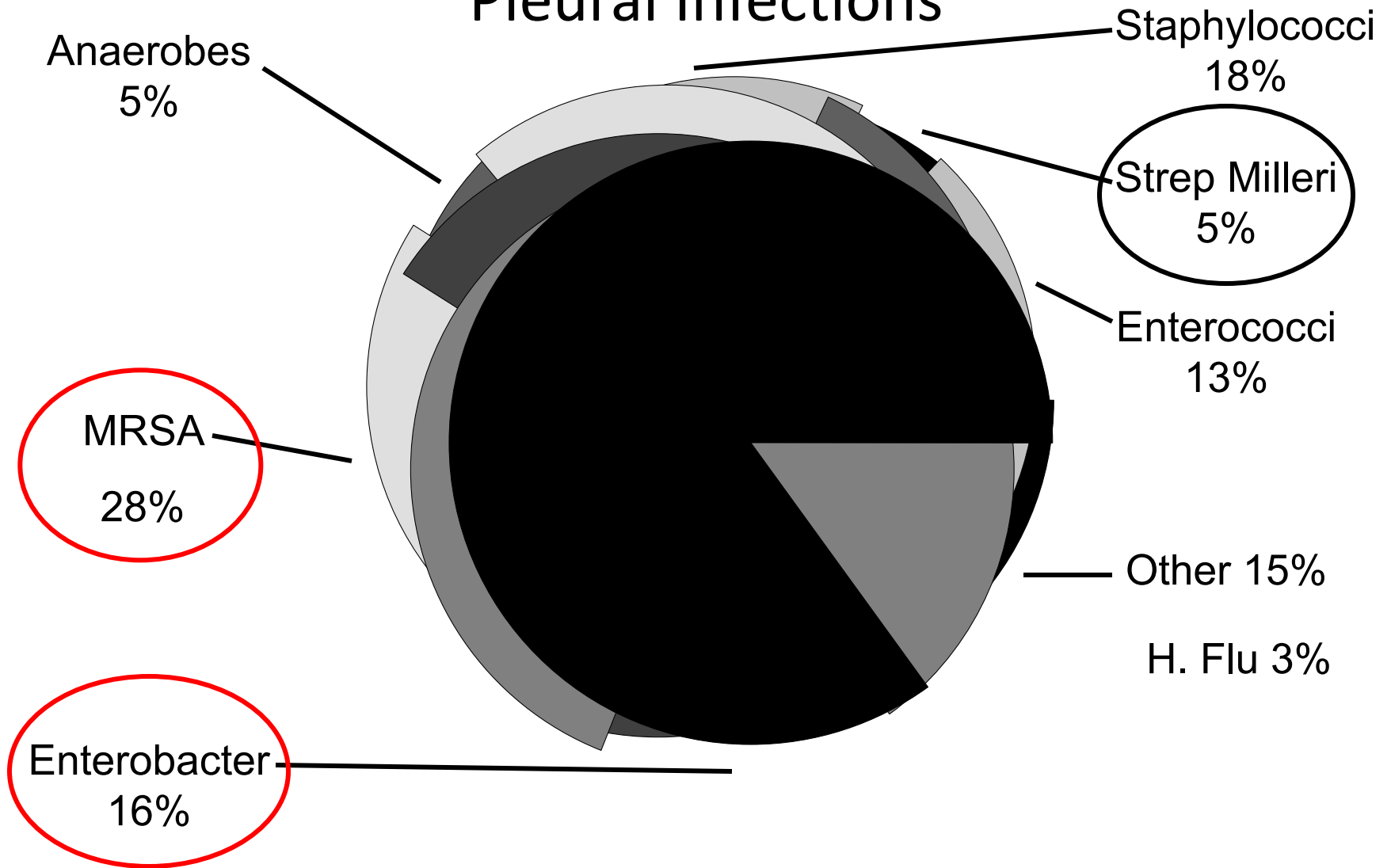


- 72 year old man with 3 days of
 - Cough, Sputum, Fever, and dyspnea
- Exam
 - T 100.9, Decreased BS right base
- Labs
 - Serum WBC 15K (80 poly's, 10% bands)
- Lateral Decubitus CXR revealed a free-flowing moderate-sized effusion
- Blood cultures were obtained and Antibiotics started

Microbiology of COMMUNITY-Acquired Pleural Infections



Microbiology of HOSPITAL-Acquired Pleural Infections



Optimize Pleural Cultures: bedside blood culture-bottle inoculation

- *Thorax 2011* **66**: p658
 - Pleural fluid cultures + in only ~35% of empyema patients
 - 62 patients with clinical empyema
 - Standard pleural fluid cultures and...
 - 2,5, and 10 mL of fluid immediately cultured in standard aerobic and anaerobic blood-culture bottles
 - Blood culture bottles increased pathogen yield from **37% to 59%**
 - 2 mL of pleural fluid = 10 mL
 - *Consider Blood culture-bottle inoculation of pleural fluid when empyema suspected*

Quick Quiz

- Thoracentesis ->
- Pleural Fluid Analysis
 - Sero-sanguinous
 - PF protein 3 (serum 4)
 - PF LDH 800 (serum 300)
 - PF pH 7.18
 - Gram stain and cultures NEG

The next step in managing this effusion is:

- A. Antibiotics and close observation, including daily CXRs
- B. Thoracentesis to drain the pleural space
- C. VATS decortication
- D. Chest tube drainage +/- fibrinolytics to the pleural space**
- E. A or D

COMPLICATIONS of Parapneumonic

Effusions: *why drain?*

- Chronic Pleural Infection
- Secondary Lung Abscess
- Bronchopleural Fistula
- Empyema Necessitans
 - Pleuro-cutaneous fistula

- Pleural Fibrosis
 - Lung entrapment →
 - Impaired lung function →
 - Surgical decortication

Who to Drain ?

Pleural Anatomy	Fluid Micro	Fluid pH	Risk of Poor outcome	Drain?
<10 mm on Lat decub CXR	N/A	N/A	LOW	No

Who to Drain ?

Pleural Anatomy	Fluid Micro	Fluid pH	Risk of Poor outcome	Drain?
<10 mm on Lat decub CXR	N/A	N/A	LOW	No
< ½ hemithorax <i>AND -></i>	GS and Cx NEG <i>AND -></i>	pH > 7.20	LOW	No, BUT need to follow
> ½ hemithorax, loculated, thick pleura <i>Or -></i>	GS or Cx + <i>Or -></i>	pH < 7.20	Moderate / High	YES

Who to Drain: patient / clinical risk factors?

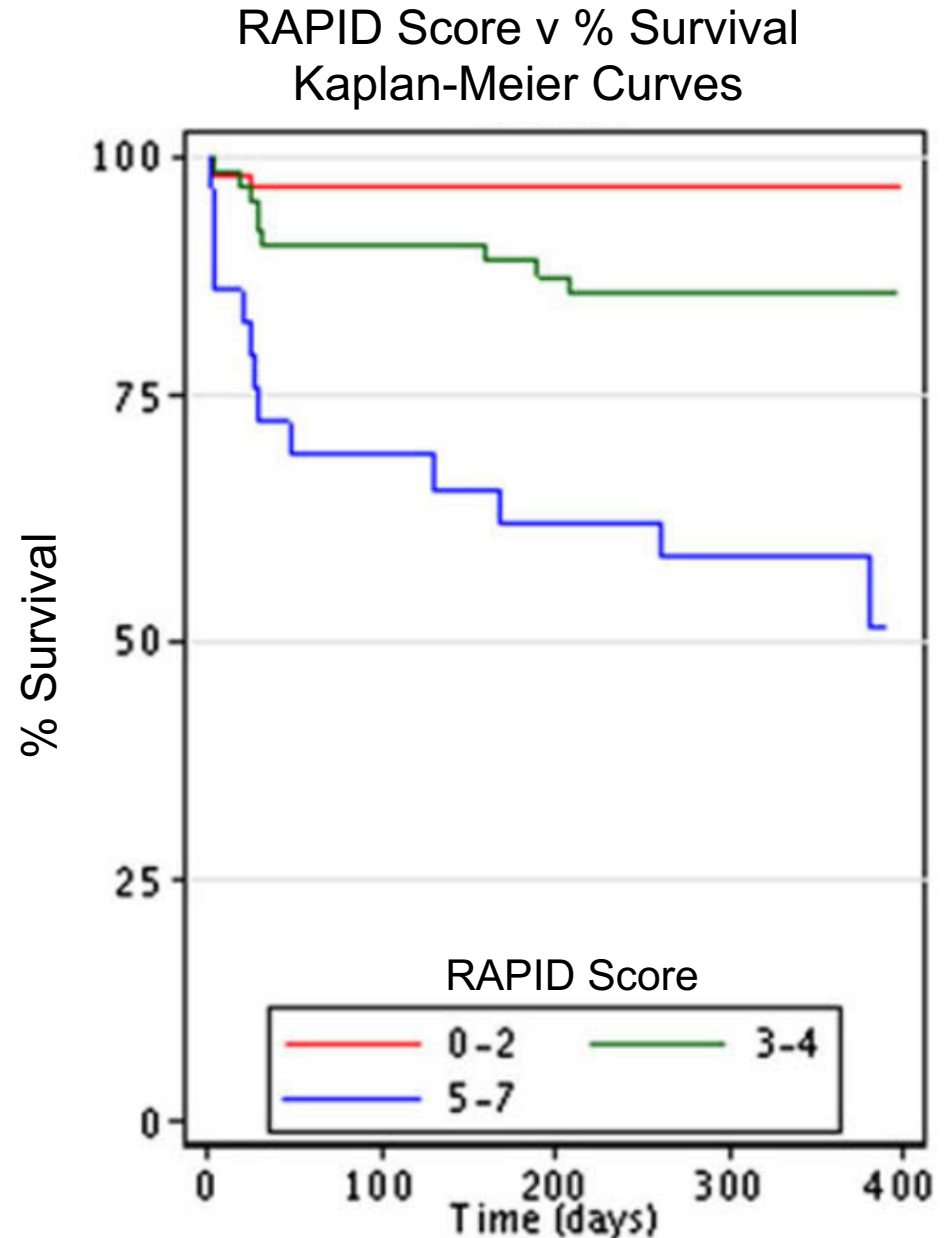
- **Chest 2014 145 (4): p848**
 - 22 variables studied in 411 “MIST1” trial patients
 - 5 variables = UREA, AGE, pleural fluid purulence, infection source (hospital v community), serum albumin → “RAPID” score
 - Associated with poor outcome = 3 month mortality, need for surgery, hospital length of stay
 - Validated in “MIST2” cohort
 - RAPID scores...

RAPID scores from 0 - 7

Parameter	Measure	Score	
Renal			
Urea, mM	<5	14 mg/dL	0
	5-8		1
	>8	22 mg/dL	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

Who to Drain: patient / clinical risk factors?

- *Chest* 2014 **145 (4)**: p848
 - RAPID score v poor outcome in pleural space infection
 - Score ≥ 5 associated with increased 30 D mortality
 - High RAPID score may factor into decision to drain the pleural space early
 - Interestingly, RAPID variables similar to “CURB-65” factors for pneumonia severity



Treating Complex Parapneumonic Effusions / Empyema

- Definitive Pleural Drainage
 - Commonly via chest tube
 - Serial thoracenteses an alternative, but not well-studied
- Pleural Catheter + Fibrinolytics
 - Variably used and STILL requires individual assessment
 - Multicenter Intrapleural Sepsis Trial (MIST-1)
 - Pleural saline v. streptokinase
 - Streptokinase did NOT improve survival, need for surgical intervention, Chest CT appearance, or lung function
 - *N Engl J Med* 2011 **365: 516**
 - Additional fibrinolytic trial (s)....

Small Drainage Catheters + Fibrinolytic + DNA'se Treatment of Empyema

- *N Engl J Med* 2011 **365: 516**
 - Pleural saline v. tPA v. DNase v. tPA + DNase x 3 days
 - tPA + DNase group had decreased need for:

Important considerations with intra – pleural tPA

- ~1.8% risk of pleural hemorrhage
- Markedly stimulates pleural fluid production (up to 6-fold)
- Contraindicated in presence of broncho-pleural fistula
- tPA 5mg (versus 10mg) likely an acceptable alternative
(Ann Am Thorac Soc **14** (6), p929, Jun 2017)

Treating Complex Parapneumonic Effusions / Empyema

- Surgical Decortication
 - Consider *EARLY* in complex effusions with good surgical candidates
 - Indicated if little clinical or radiographic improvement after 1 week of antibiotics and chest tube drainage +/- pleural lytics
 - Required in ~30% of cases
 - VATS adequate in 60% of these cases
- Appropriate Antibiotics
 - Duration uncertain: 2 weeks minimum, but as long as necessary for drains to be removed
 - Sometimes longer courses required for atypical pathogens (e.g. actinomyces) or in cases of prolonged pleural drainage

Spontaneous Hemothorax

- 37 year old woman with 2 months of dry cough and dyspnea on exertion with mild R anterior pleuritic chest pain
- Past Medical History
 - Migraines
 - HTN
 - Anemia
 - Metromenorrhagia
 - Ectopic thyroid, hypothyroidism

Chest X-ray



Pleural Fluid Analysis

Pleural Fluid:

LDH: 459

pH: 7.37

glucose: 72

WBC: 900 Diff: 27N 28M 40L 5 mesothelial cells

RBC: too numerous to count

Fluid hematocrit: 22%

Grossly Bloody Pleural Fluid

Fluid Hematocrit	Cause
<1%	Not significant
1-20% (hemorrhagic process)	Cancer>> PE>Trauma>empyema
20 – 50%	Hemorrhagic process v. Hemothorax
>50% circulating HCT	Hemothorax

Spontaneous Bloody Effusions and Hemothorax

BLOODY Pleural effusion

No Trauma
No Procedures

Pleural Fluid HCT < 50%
of peripheral blood HCT

Etiologies

Lung Ca

PE - pulmonary infarction

Tuberculosis

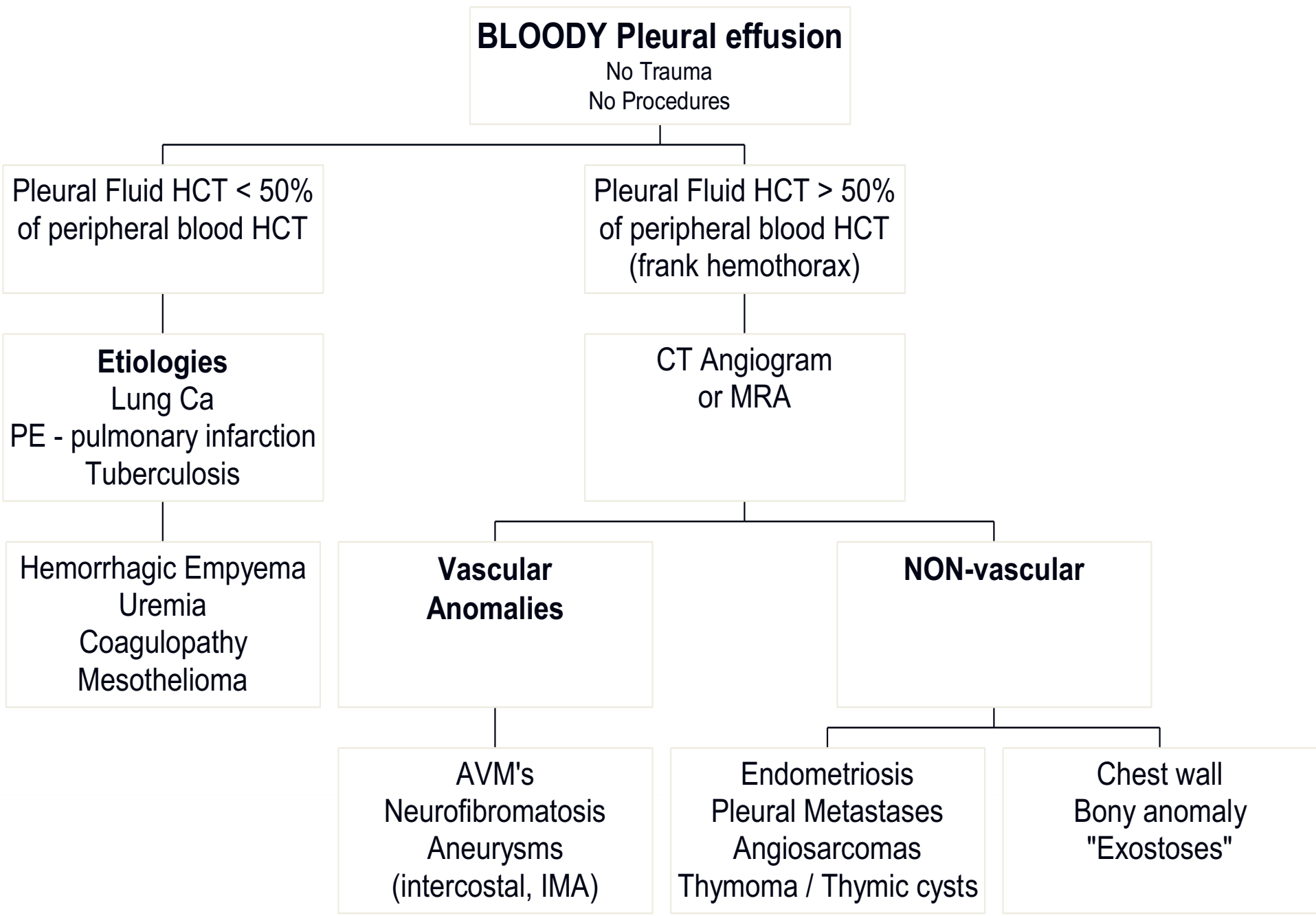
Hemorrhagic Empyema

Uremia

Coagulopathy

Mesothelioma

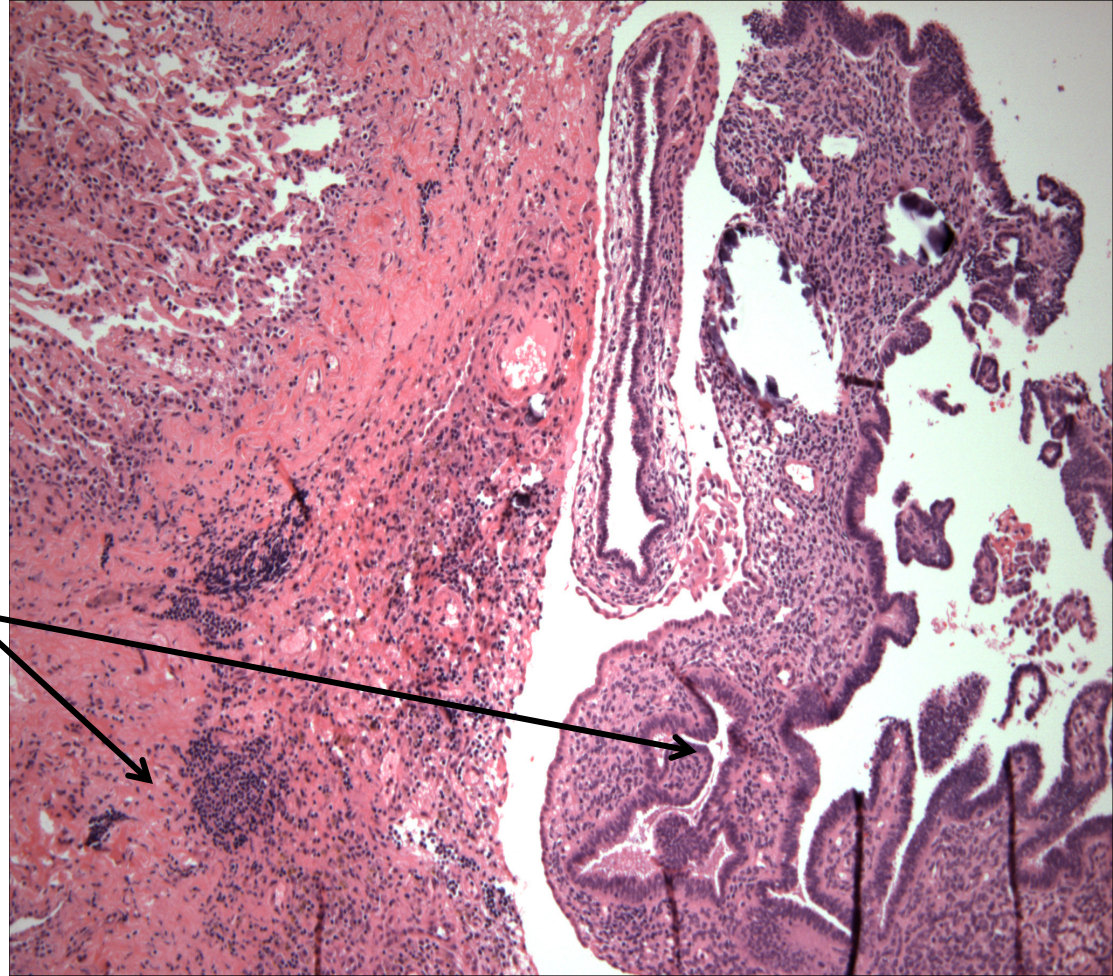
Spontaneous Bloody Effusions and Hemothorax



Back to the case...

- R VATS with pleural biopsy and wedge resection

- hemothorax > 1 L
- Endometrial tissue
- lung



Thoracic Endometriosis Syndrome (TES): Clinical Manifestations

- Relatively RARE
 - ~ 5 - 7% of pts with endometriosis will develop TES
- Most common manifestation of TES is catamenial pneumothorax
 - 80 – 90% of TES cases
- *A side thought* – how many spontaneous pneumothoraces in women are due to TES ?
 - Nakamura et al. Chest 1986. 89: 378. Retrospective study of 664 cases; pt characterization minimal: **TES incidence ~ 1%**
 - Shearin et al. Mayo Clin Proc 1974. 49: 98. Retrospective study of 196 cases: **TES incidence ~ 6%**
 - Alifano et al. Chest 2003. 124: 1004. Prospective study of 38 cases; aggressive pt characterization: **TES incidence ~ 20%**

Thoracic Endometriosis Syndrome (TES): Clinical Manifestations

- Major manifestations of TES -
 - Pneumothorax ~ 80%
 - Hemothorax / hemopneumothorax ~ 14%
 - Hemoptysis ~ 7%
 - Lung nodules ~ 6%
- Other rare manifestations of TES
 - Isolated, catamenial chest pain
 - Catamenial pneumomediastinum
 - Pulmonary vascular invasion
 - Pleural-based mass
- Interesting aside –
 - Pelvic endometriosis is NOT found in up to 15 – 30% (depending on case series) of TES patients

TES: treatment and outcome

- Medical therapy – goals are to suppress growth and maintenance of the endometrium
 - Oral contraceptives
 - Danazol
 - Progestational agents
 - GnRH analogs
 - Most successful for long-term suppression of catamenial pneumothorax and hemoptysis
 - Medical therapy ALONE often leads to recurrent thoracic disease

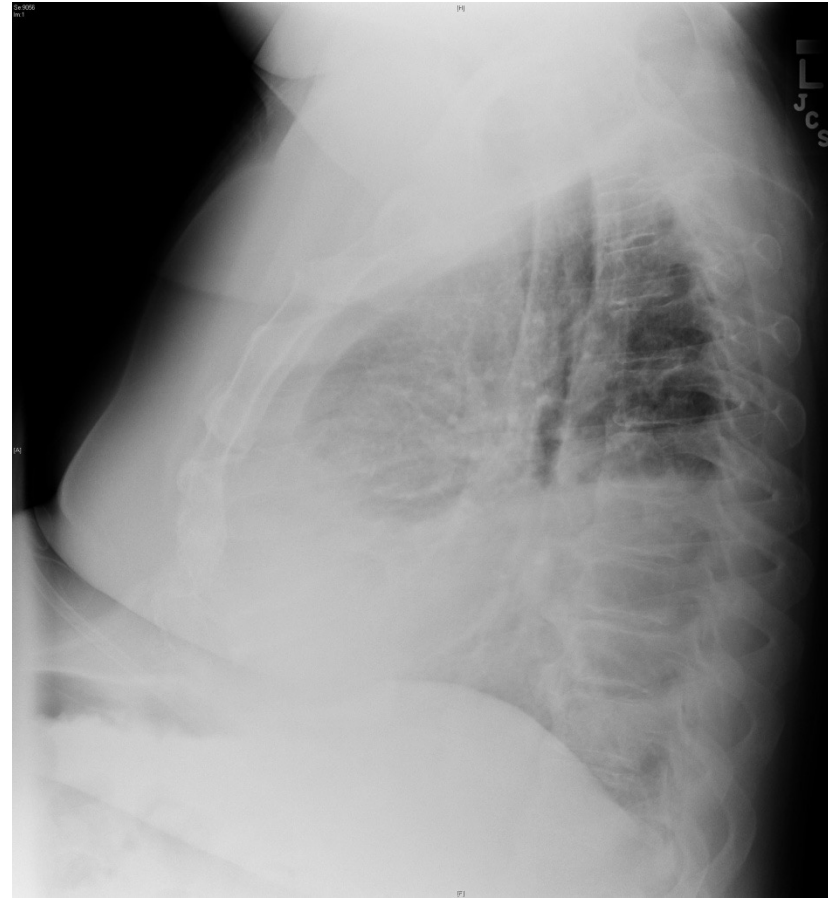
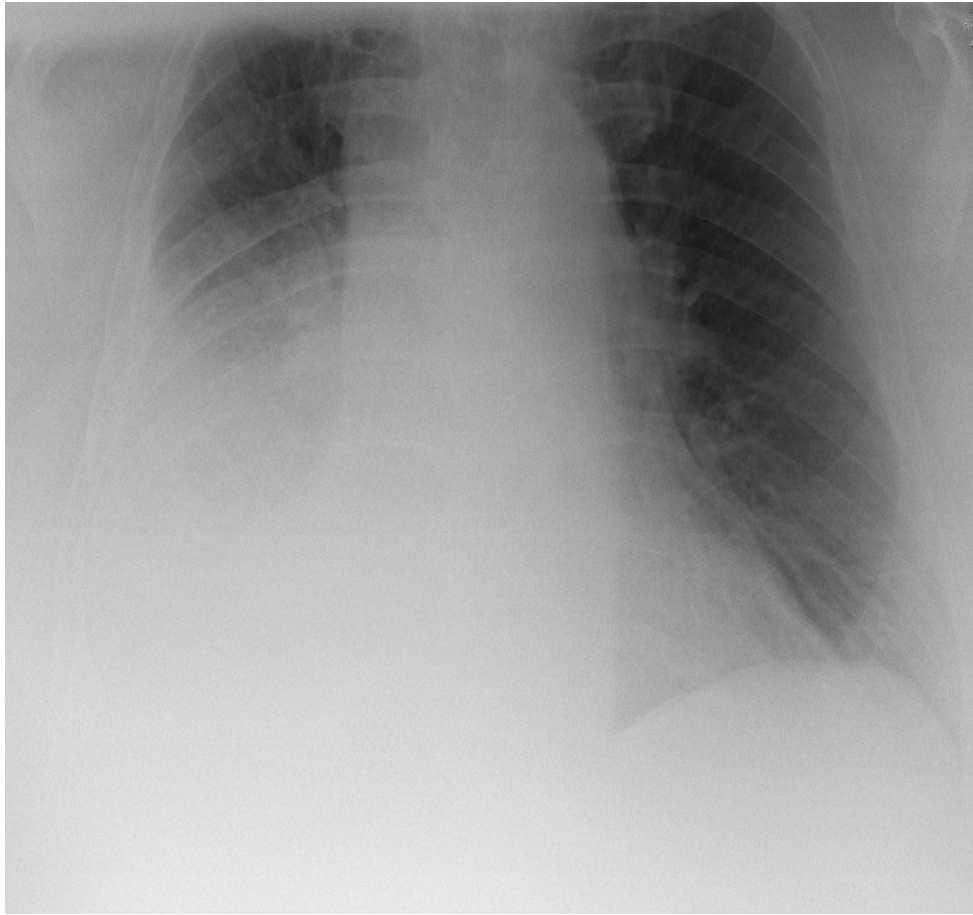
TES: treatment and outcome

- Surgical therapy – goals are to treat the pulmonary mechanical complications of TES
 - Chest tube for pneumothorax
 - Pleuroscopy for hemo or hemo-pneumothorax
 - VATS for resection of pleural / parenchymal nodules
 - Repair of diaphragmatic defects – important intervention
 - Surgical intervention with medical therapy can reduce recurrence of thoracic disease
 - Catamenial pneumothorax recurs in **60%** of patients on hormonal therapy at 12 months and in only **20%** of patients with both surgical and medical Rx.

A Surprise Case...

- 53 year old man with 2 months of acute on chronic exertional dyspnea
- 3+ ankle edema
- Orthopnea & paroxysmal nocturnal dyspnea, worse than baseline
- PMH:
 - HFpEF: LV EF 55%
 - Atrial Fibrillation
 - HTN
 - Dyslipidemia

Case CXR



Thoracentesis

Removed: 1200 cc

WBC 1650 (P₁₄ L₈₃ M₂)

pH 7.57

Glucose 262

Total Protein 3.9

Albumin 2.3

LDH 159

Gram stain/culture negative

Cytology negative

Cholesterol 77

Triglycerides 1,276



Chylothorax?

Pleural Fluid Triglyceride level (mg/dl)

>110
Chylothorax

50-110
Lipoprotein
analysis

<50
PSEUDO-
Chylothorax
(likely chronic exudate)

+ Chylomicrons ->
CHYLOTHORAX



Traumatic

Chest trauma
Thoracic surgery

Non Traumatic

Lymphoma, solid tumors, chest XRT
Histoplasmosis, MTB, Sarcoid
Chylous ascites
LAM, yellow nail syndrome, Amyloid
L subclavian DVT
Filariasis

Pseudo - Chylothorax

- **Pseudo - Chylothorax:** **Cholesterol**, phospholipid Complexes = from:
Cell degradation, chronic exudate, empyema

Cholesterol > 250 mg/dL

+ cholesterol crystals (rhomboid)

TG_{fluid} LOW

- **Chylothorax:**

TG_{fluid} > 110mg/dL

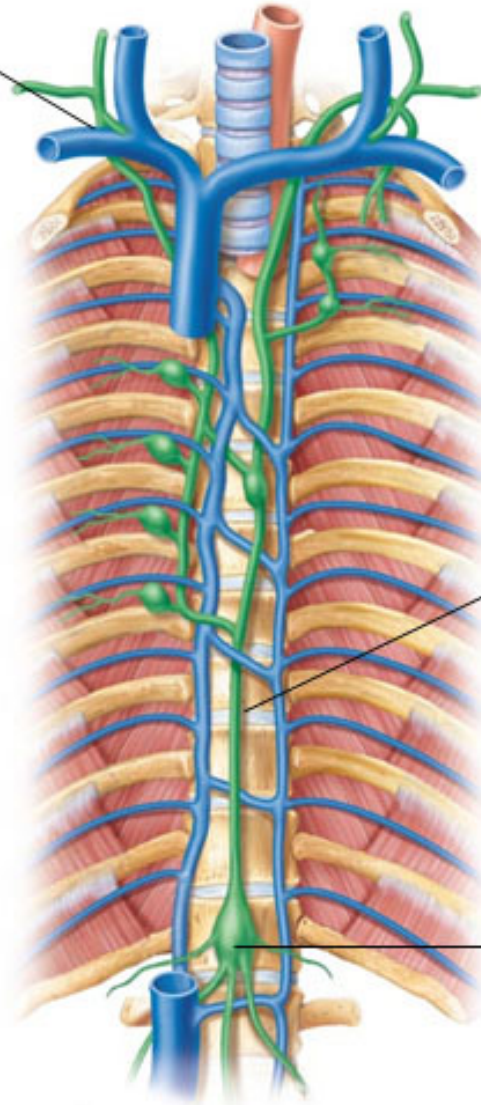
TG_{fluid} > TG_{serum}

Cholesterol_{fluid} < 200 mg/dL

+ chylomicrons

Location of Duct Disruption Determines Side of Chylothorax

Right Lymphatic Duct



Thoracic Duct

Cisterna Chyli

Chyle Loss Increases Mortality



Fat

Vitamins
A, D, E, K

Proteins
Immunoglobulins

Lymphocytes

Malnutrition

Immunosuppression

17-35% mortality
(limited data)

4.5-fold ↑ risk
of death in
surgical patients

Paul et al. *J Thorac Cardiovasc Surg.* 1985 Feb;89(2):221-7.
Shah et al. *Ann Thorac Surg.* 2012 Mar;93(3):897-903.

Management

↓ Chyle Flow

No short- or long-chain TG intake
Octreotide or Somatostatin

Remove Chyle

Thoracentesis
Tube Thoracostomy
Pleuroperitoneal Shunt
Pleurovenous Shunt

Maintain Nutrition

Medium-chain TGs →
enter portal circulation directly
Total parental nutrition (TPN)

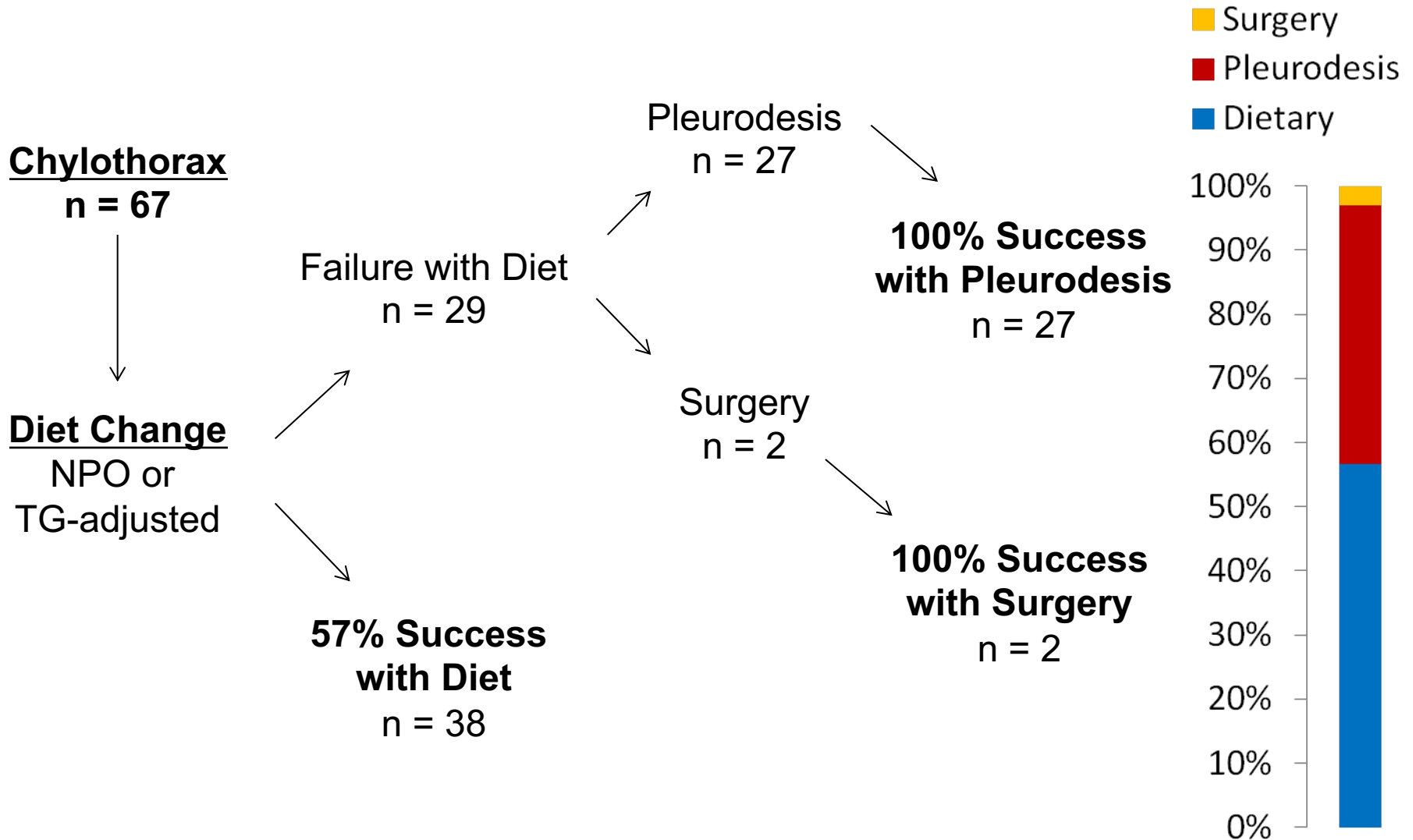
Close Chyle Leak

Pleurodesis
Duct Embolization
Surgical Duct Ligation

Surgical Interventions for Chylothorax

- Recommended if pleural fluid > 1 L/day
- Thoracic Duct Ligation
 - In select patients, up to 90% success rate
- Pleurectomy
- Surgical Pleurodesis
- Pleuroperitoneal Shunt
 - Contraindicated if chylous ascites
- Pleurovenous Shunt
 - Extremely technically difficult
- Complications
 - Respiratory Failure / Prolonged Ventilation, Air Leak, Surgical Anastomotic Leak

Diet & Pleurodesis for *Traumatic* Chylothorax



Cho et al. *Ann Thorac Surg* 2014; 97:408-13.

Medical Therapy for Chylothorax

- Case report level, but impressive anecdotal responses
- Octreotide / Somatostatin
 - Decrease splanchnic blood flow → decrease intestinal fat absorption → decrease lymphatic flow
- Midodrine
 - α 1-adrenergic agonist → lymphatic smooth muscle constriction
- Orlistat
 - Pancrealipase inhibitor → prevents triglyceride absorption

Evans et al. *Hematol Oncol*. 2003 Jun;21(2):77-81.

Kelly RF, Shumway SJ. Conservative management of postoperative chylothorax using somatostatin. *Ann Thorac Surg*. 2000; 69 (6): 1944 - 1945.

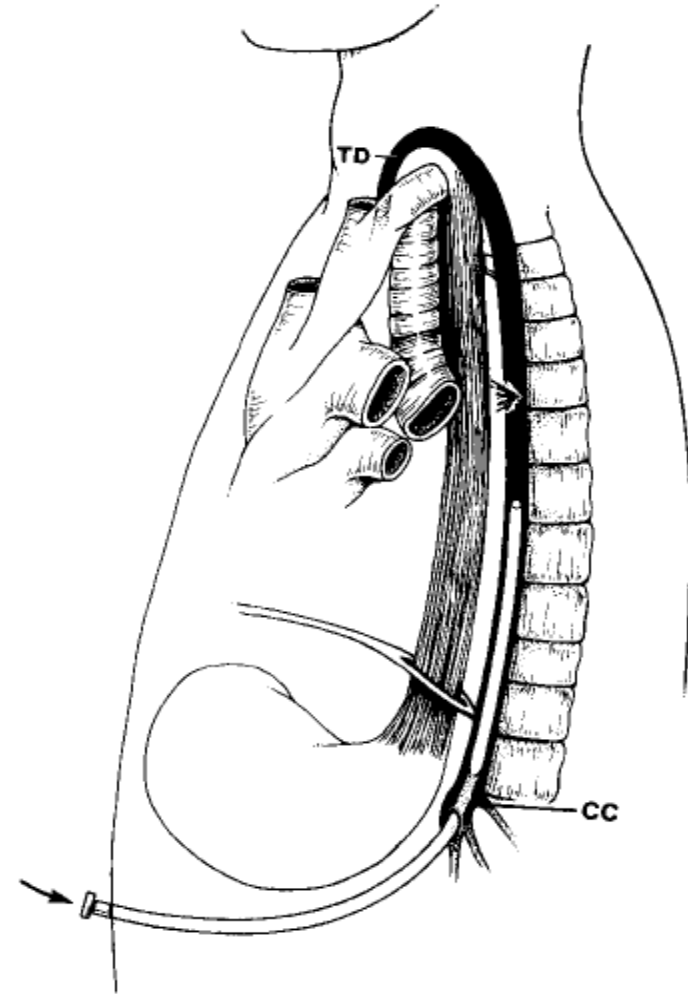
Guillem et al. Etilefrine use in the management of post-operative chyle leaks in thoracic surgery. *Interact Cardiovasc Thorac Surg*. 2004 Mar;3(1):156-60.

Liou et al. Midodrine: a novel therapeutic for refractory chylothorax. *Chest*. 2013 Sep;144(3):1055-7.

Chen et al. Use of orlistat (xenical) to treat chylous ascites. *J Clin Gastroenterol*. 2005 Oct;39(9):831-3.

Occlusion of Thoracic Duct via Interventional Radiology

- Limited by ability to visualize a & cannulate thoracic duct
- Lipiodol dye = iodinated oil
 - Radio-opaque
 - Sclerosing effect
 - Risk of Pulmonary Emboli
- Embolization
 - Microcoils, Particles



Our case...

Lymphangiogram

Example: well visualized thoracic duct



Our patient: no visible thoracic duct



Malignant Pleural Effusions



- 73 yo man with stage IIIB non-small cell lung Ca (*ECOG 2*)
- Presents with 3 weeks of progressive DOE
- CXR reveals a new large R pleural effusion
- A large volume thoracentesis is performed removing 1.8L of sero-sanguinous fluid
- Pleural fluid analysis reveals malignant cells
 - *PF LDH 1,780*
 - *PF Poly 60, Lymph 5, Eos 5, Mono 30*
- The patient reports marked improvement in his dyspnea

Prognosis for Patients with Malignant Effusions

- ECOG performance status useful, but falls short...
- **LENT score** combines several prognostic indicators and,
- Can inform treatment / management decisions
- Clive A, et al. *Thorax* 2014, **69**: p1098
 - Longitudinal / observational study from 3 large European cohorts of patients with malignant pleural effusions, n = 789

	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

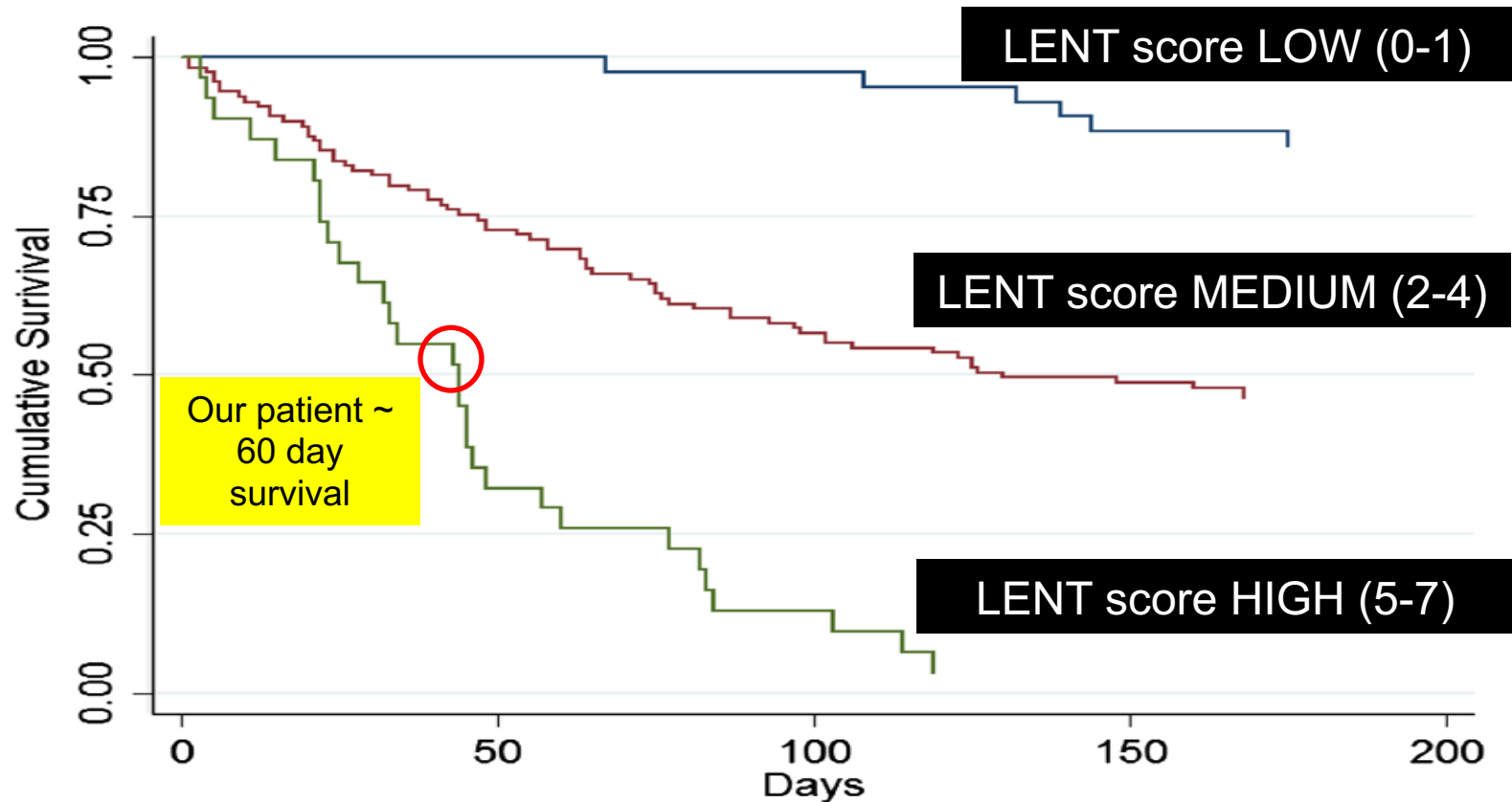
Our patient's LENT score = 6 (high risk)

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

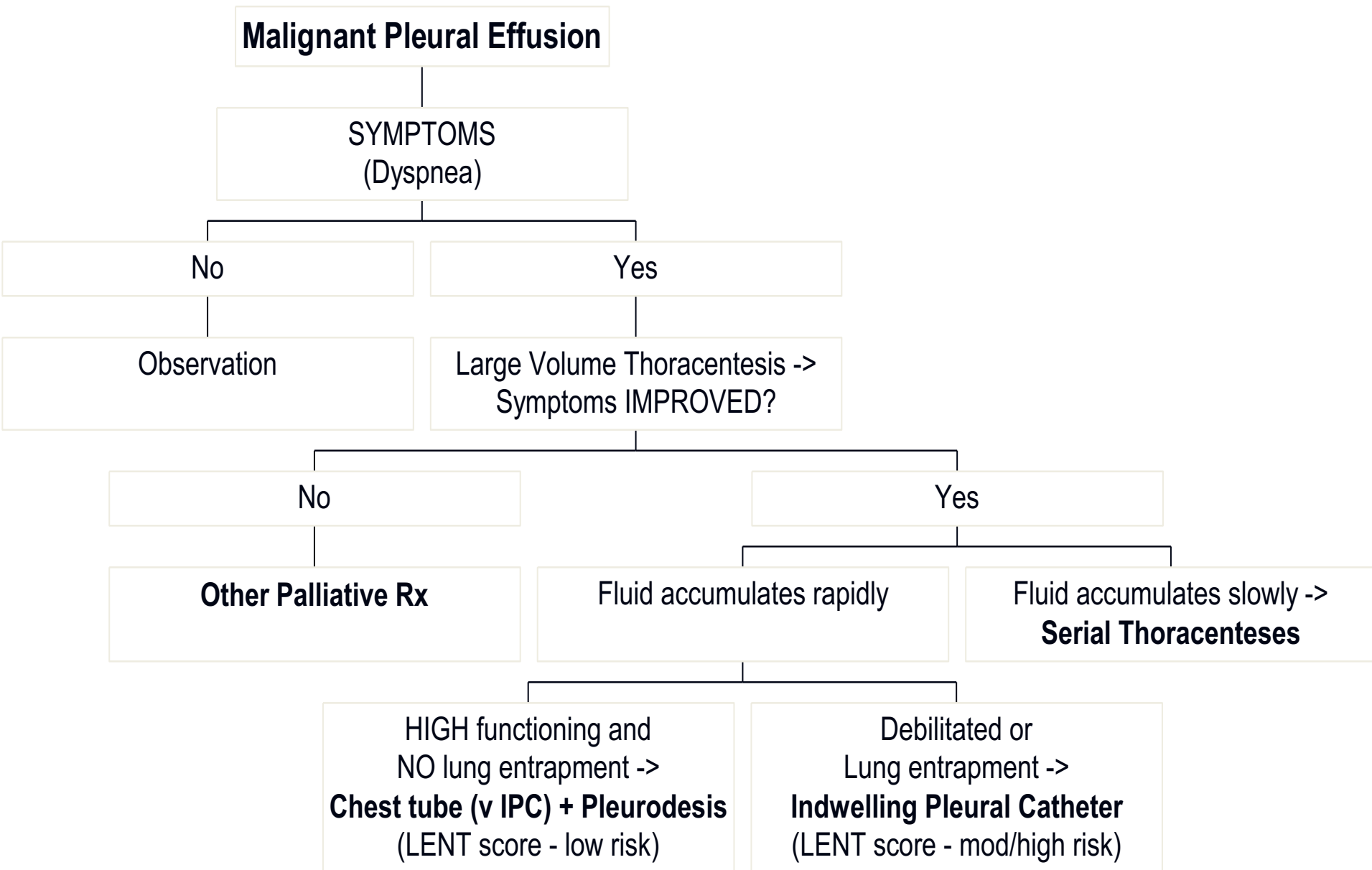
LENT Score for Malignant Effusions

- Clive A, et al. *Thorax* 2014, **69**: p1098
 - Longitudinal / observational study from 3 large European cohorts of patients with malignant pleural effusions, n = 789

Survival versus LENT Score / Risk

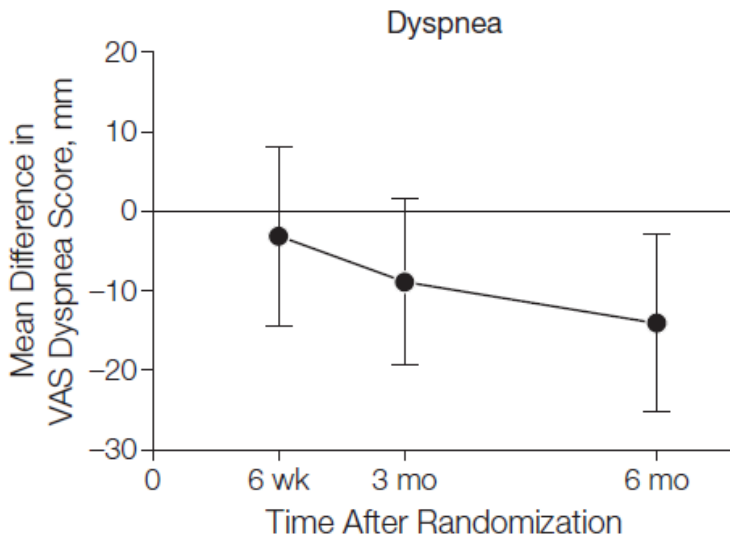


Therapeutic Approach to Malignant Effusions



Pleural IC v. Pleurodesis for Malignant Effusions

- **JAMA 2012 307 (22): 2383**
 - 106 patients randomized to IC v talc pleurodesis as 1st intervention
 - The IC group had:
 - Improved dyspnea at 6 mo
 - 0 initial hospital days v 4 for pleurodesis
 - BUT...had:
 - More complications = local site infections and clogged catheters



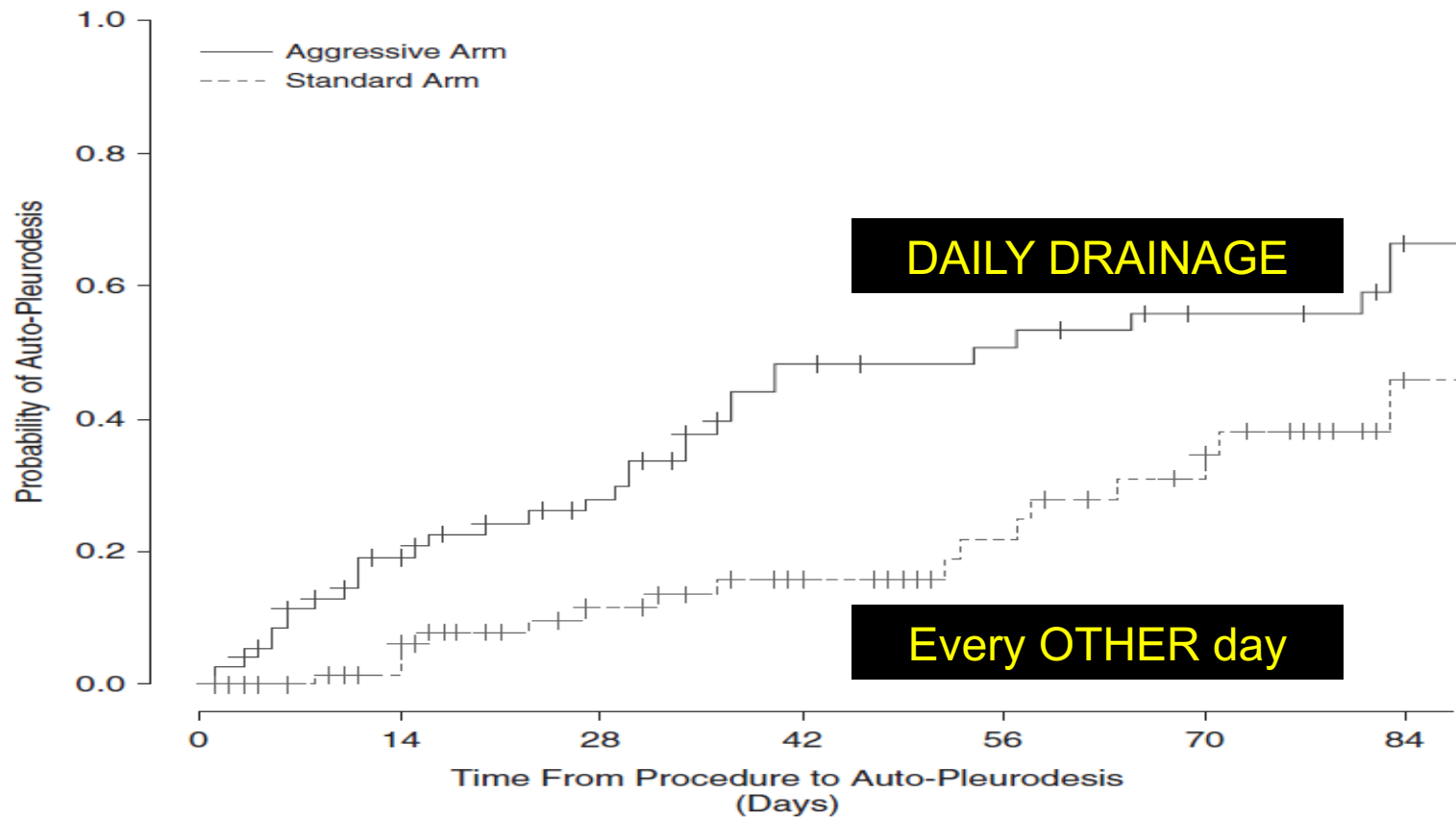
No. of patients
Talc
IPC

32	26	21
30	31	22

Type of Adverse Event	IPC		Talc	
	Serious	Nonserious	Serious	Nonserious
Pleural infection	5	2	1	0
Cellulitis	1	5	0	1
Symptomatic fluid loculation requiring fibrinolytics	1	2	1	0
Catheter site metastases	0	1	0	0
Catheter blockage	1	9	1	0

Daily Drainage: faster pleurodesis with pleural IC

- *Am J Resp Crit Care Med* 2017 **195** (8): 1050
 - 149 patients with an IPC randomized to 1L daily versus every other day drainage
 - The DAILY DRAINAGE group had:
 - Faster “auto-pleurodesis”: 50 days versus 90 days
 - Higher pleurodesis rates at 85 days: 62% versus 42%

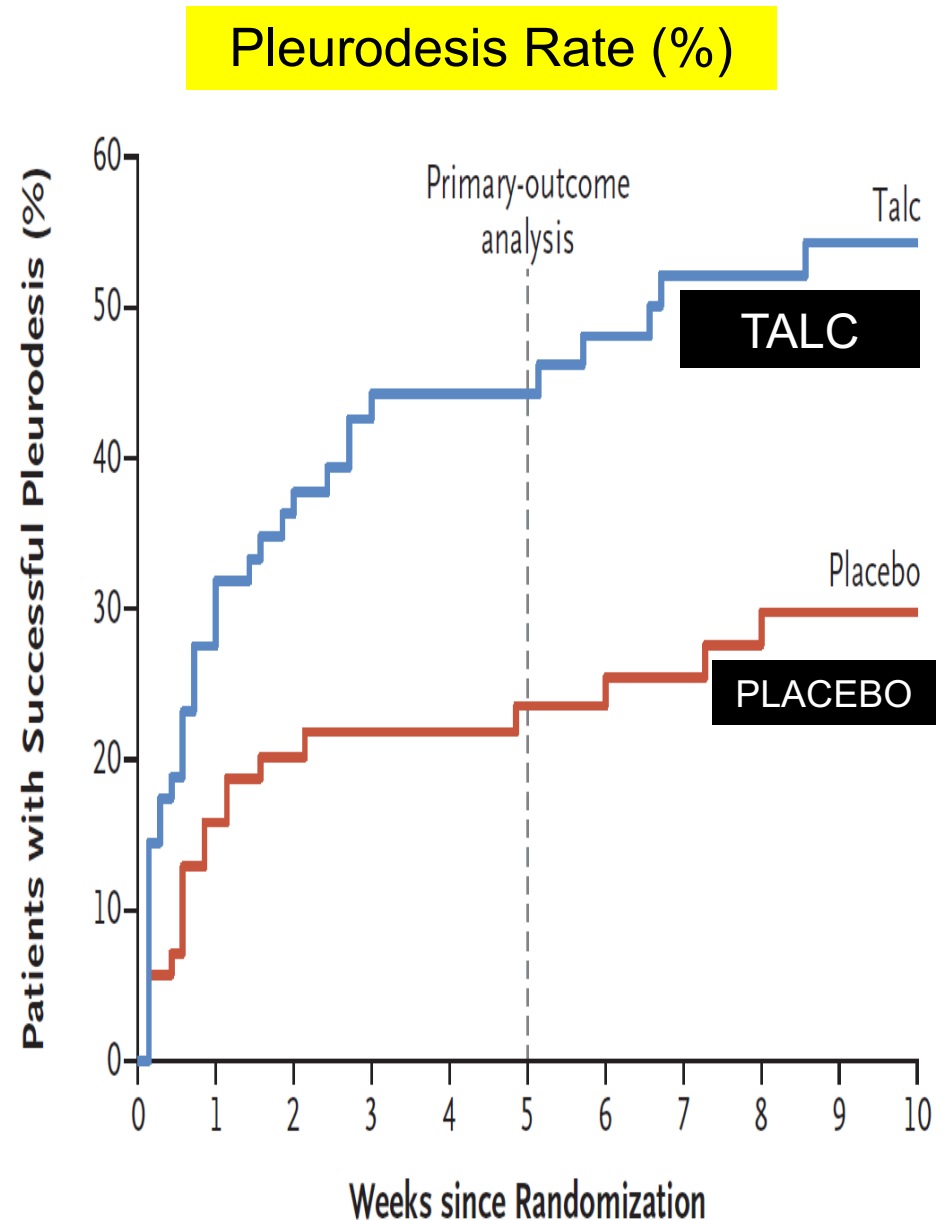


Indwelling Catheter (IC) v. Pleurodesis (PD)

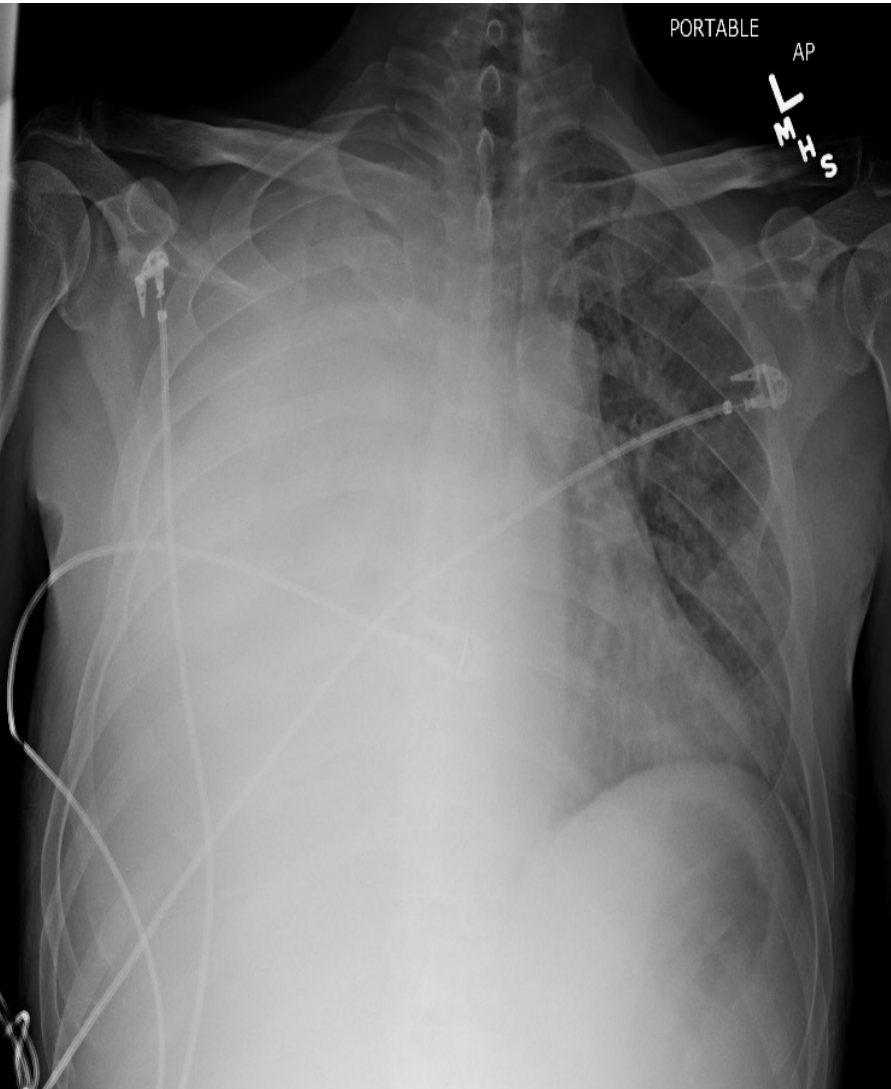
<u>“Costs”</u>	<u>IC</u>	<u>PD</u>
Invasive	+	+++
Peri-procedure Pain	+	+++
Hospital Stay (days)	1	6
<u>Benefits</u>	<u>IC</u>	<u>PD</u>
Dyspnea resolved/improved	~89%	90%
Effusion Recurrence	13%	21%
Spontaneous Pleurodesis	~60%	90+%

IPC versus Talc Pleurodesis: do we need to choose?

- Bhatnagar R et al. *N Engl J Med* 2018, **378**: p1313
- 154 patients with malignant effusions and IPC placement:
- randomized to single 4G TALC infusion versus placebo, 10 days after IPC placement:
 - Not eligible if lung entrapment present
 - ***Talc instilled at an OUT patient visit and sent home after ~ 2 hours!***
- The TALC group had:
 - Faster pleurodesis at day 35: **43% versus 23%**
 - NO increase in adverse events: catheter obstruction, inpatient days, mortality



A Tension, RIGHT Hydrothorax...



- 55 yo man with subacute dyspnea
 - History: EtOH
 - Exam: Decreased BS R chest, + Ascites
 - Pleural fluid analysis:
 - PF protein 1.0 (serum 3.0)
 - PF LDH 100 (serum 300)
- What is the etiology of the patient's R-sided pleural effusion?

Answer: Hepatic Hydrothorax

- Occurs in ~7% of pts with ascites
- Usually large R effusion (80% on R)
- Forms due to rifts in the diaphragm
- Can accumulate rapidly
- 20% of HH can form withOUT ascites
 - “one way valve” effect through diaphragm
- Tap pleural + peritoneal fluid (to r/o infection – “SBP” - and alleviate symptoms)

- Treat underlying ascites and cirrhosis -> often difficult... (see next slide)
- *TIPS can be affective for refractory HH*

Hepatic Hydrothorax: follow-up



- Spironolactone, furosemide, IV Albumin, and octreotide minimally effective –
- TIPS performed and discharged on diuretic regimen
- CXR 3 months later!

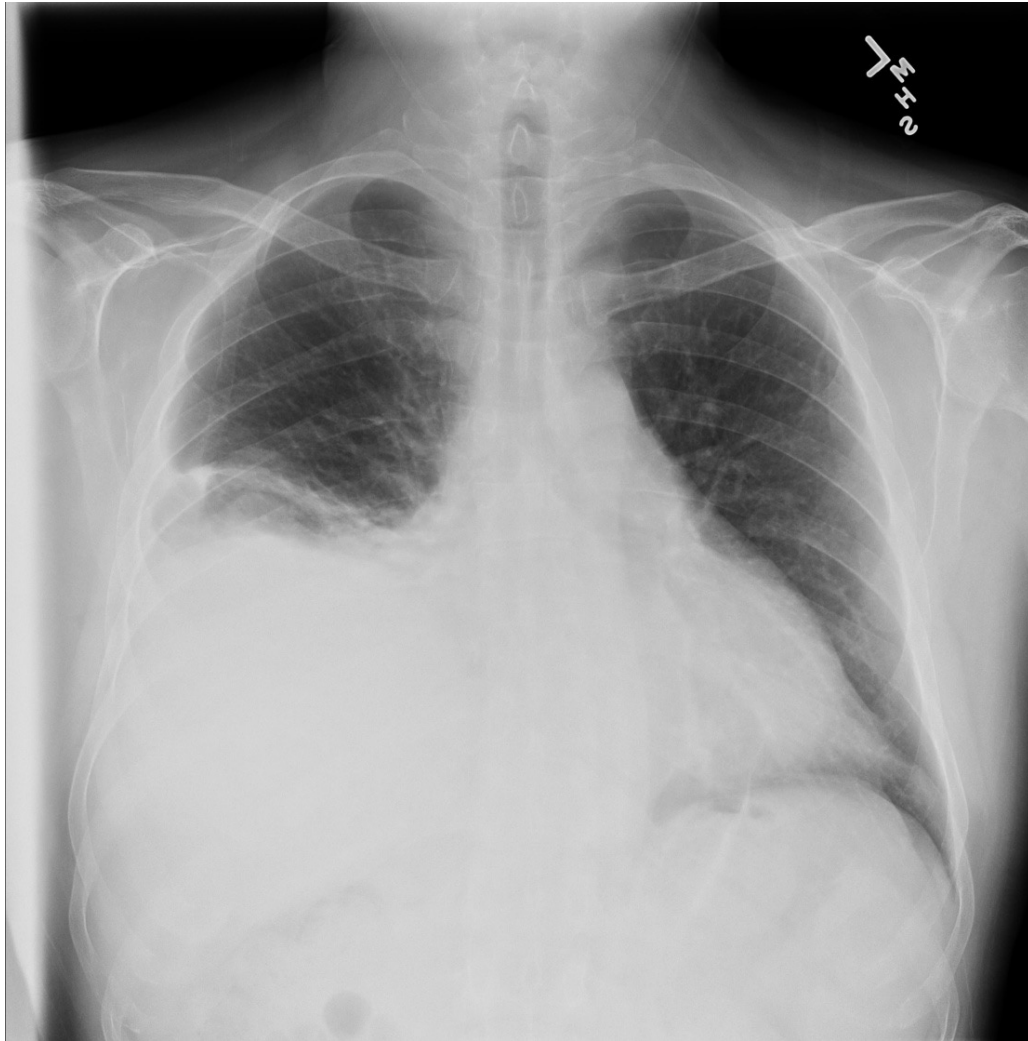
Hepatic Hydrothorax: “never place a chest tube...”

- ...because no clear end point:
 - Excessive pleural drainage -> hypoalbuminemia, vascular volume loss, potential for hepato-renal syndrome, and pleural infection...
- However, a pilot study of tunneled pleural catheters challenges this concept
- *Ann Am Thor Soc* 2016 **13**(6): p862
 - 24 HH patients requiring > 1 thoracentesis, tunneled pleural catheters placed and drained “intermittently”
 - 8/24 (33%) had spontaneous pleurodesis after IPC placement, mean days to pleurodesis = 131
- ***IPC related infections = 16%, no infection related deaths***
- ***IPC placement a possible salvage option for HH, but high risk for infection***

Exudative Effusion of Unclear Etiology

- 46 year old man with a h/o myelodysplastic syndrome, s/p an unrelated allo-stem cell transplant: complicated by cutaneous and GI graft-versus host disease
- NOW with dyspnea and progressive right-sided pleuritic chest pain x 2-3 weeks
- No fevers/chills, known sick contacts, or recent travel
- Medications: prednisone 20 mg daily, tacrolimus, atovaquone, valganciclovir

Chest X ray



Thoracentesis

- Labs:
 - Serum: LDH 229, Total Protein 6.5, Albumin 3.7
 - Fluid: LDH 226, Total Protein 4.1, Albumin 2.7
 - Fluid: pH 7.6, Glucose 208, Amylase 12
 - Fluid: ADA 3.1 (usually > 40 U/L in tuberculous pleural effusions)
- Cultures: AFB, Fungal, Aerobic/Anaerobic, Actinomyces, Nocardia, PCP all negative
- Cytology + flow cytometry negative for malignancy

Exudative Effusion of Unclear Etiology

- Up to 20% of exudative pleural effusions have no clear etiology, even after:
 - Pleural fluid analysis from thoracentesis and
 - Thoracoscopy and pleural biopsy
- Most undiagnosed exudates are from:
 - Malignancy (including mesothelioma)
 - Chronic empyema (including atypical organisms)
 - Tuberculosis
 - Rheumatoid Arthritis / inflammatory
 - Pulmonary Embolus
 - “Diuresed” CHF

Exudative Pleural Effusion

"Borderline" Exudate

Serum:PF Albumin > 1.2 g/dL
Pleural Fluid NT-proBNP > 2000 pg/mL
Consider CHF, nephrosis, cirrhosis

All Other Exudates

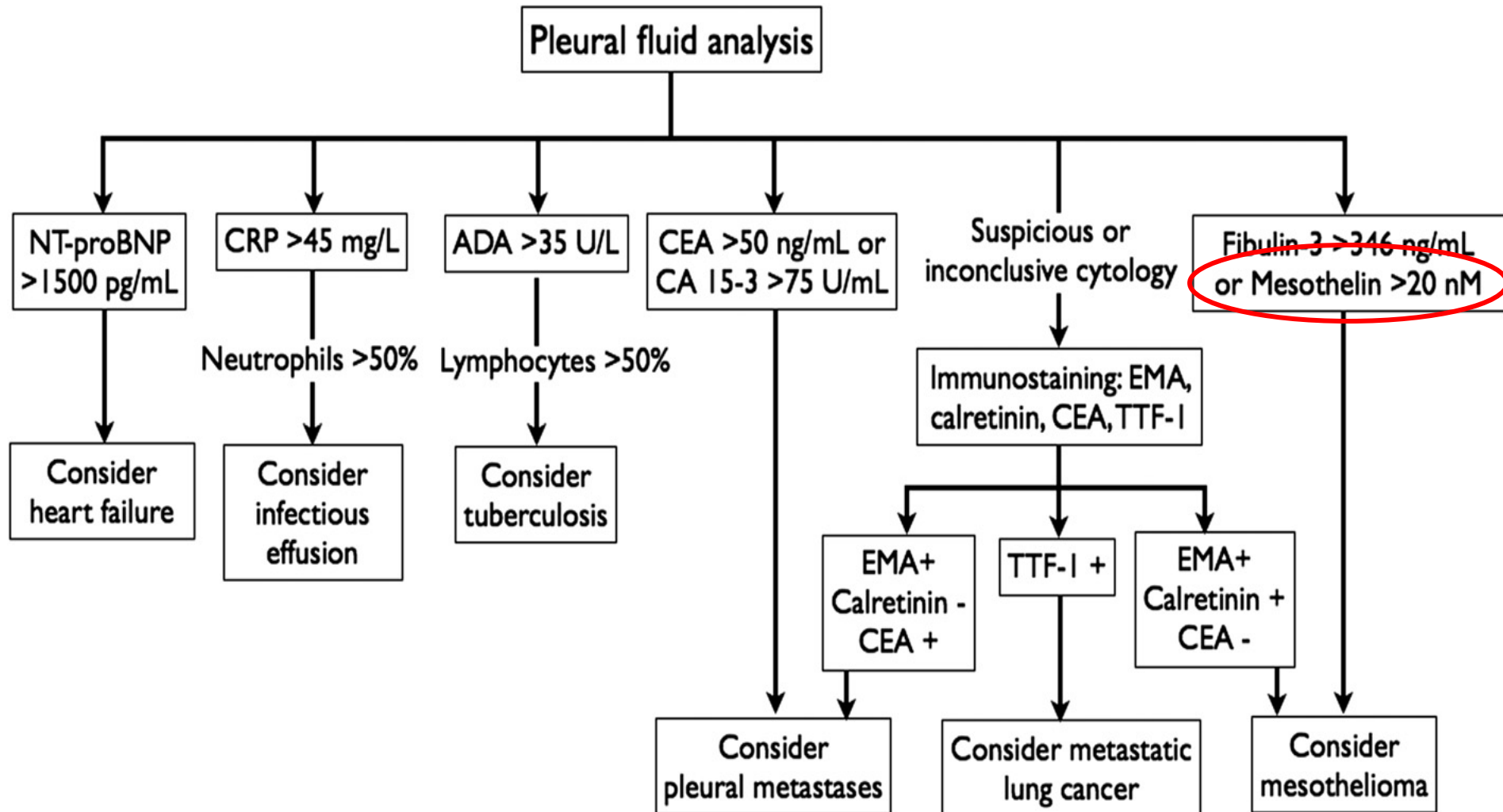
NEGATIVE
History
Microbiology
Cytology

Consider PE (DDIMER, PE-CT)
Consider TB
ADA > 40 U/L or
IFN-gamma > 140 pg/mL

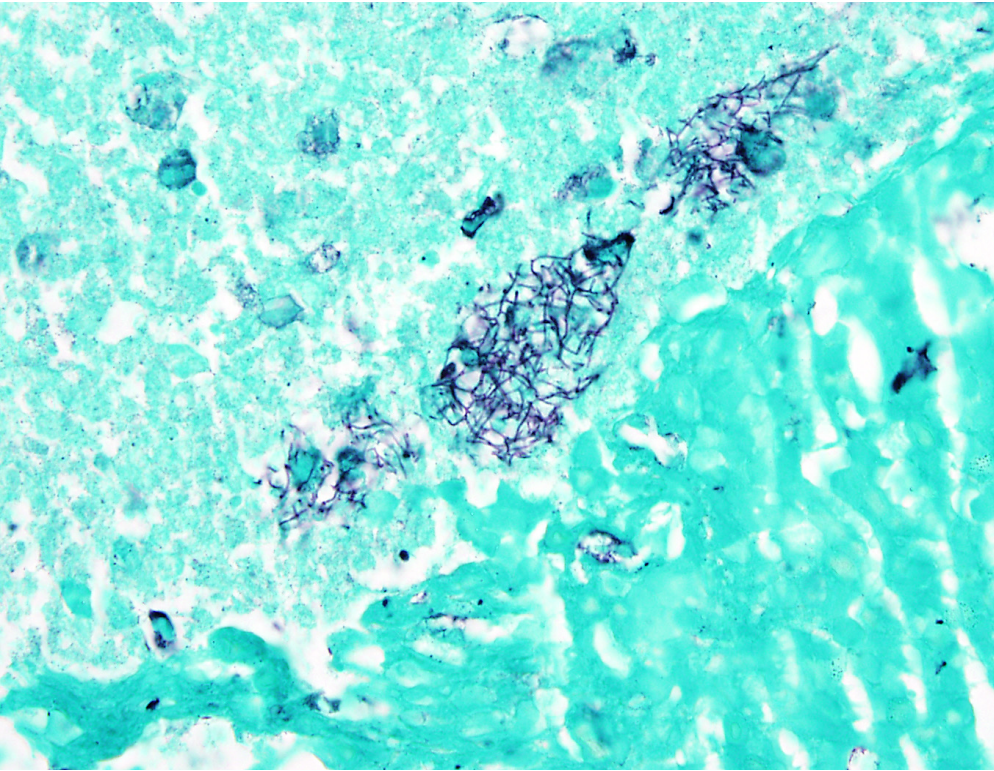
NEGATIVE

**Thoracoscopy and
Pleural Biopsy**

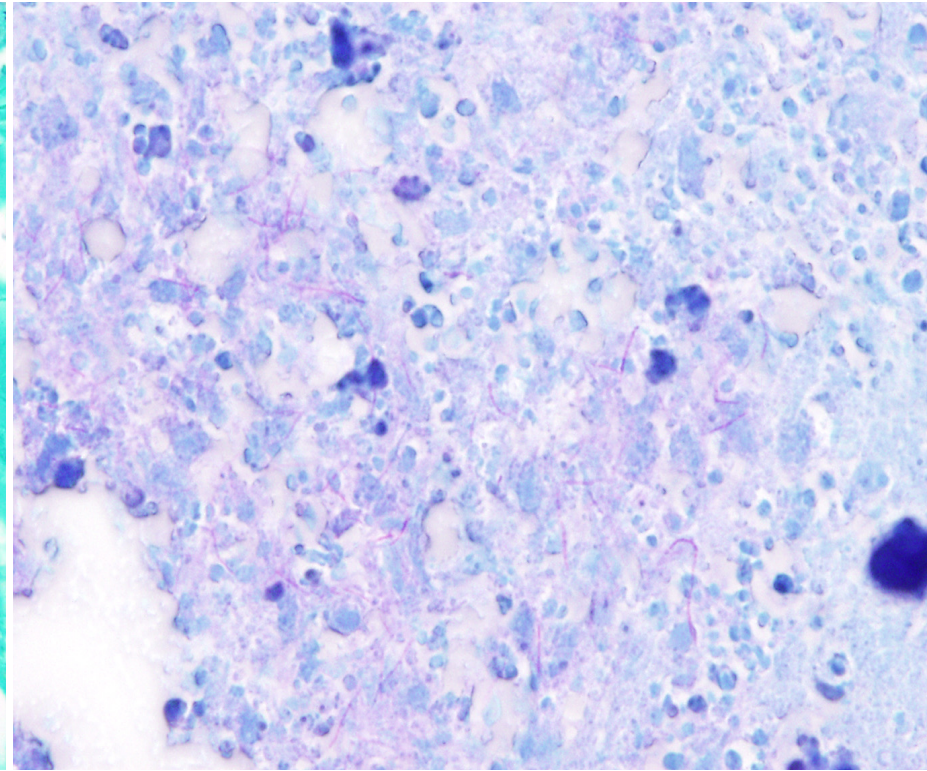
Pleural Fluid Biomarkers: new diagnostic tools for idiopathic exudates



Back to the case: bronchoscopy, pleuroscopy and pleural biopsy



Methenamine Silver Stain (MSS) 100x



Modified AFB Stain 100x

***Nocardia sp.* empyema**

Key Summary Points

- Empyema
 - Definitive pleural drainage for high risk *fluid* AND high risk *patients* (i.e. RAPID score)
 - Chest tube + fibrinolytic therapy a good treatment option, but initial VATS reasonable for low-risk surgical patients with complex empyema
- Malignant Pleural Effusions
 - Evidence supports the prevalent use of tunneled pleural catheters for symptom management, but a risk – benefit, patient-centered discussion should occur regarding chemical pleurodesis
 - Daily drainage via a tunneled pleural catheter likely superior to intermittent drainage
- Hepatic Hydrothorax
 - Salvage therapy with TIPS or indwelling pleural catheter reasonable in select cases
- Chylothorax
 - Malnutrition and lymphopenia lead to significant morbidity and mortality