بسم الله الرحمن الرحيم

MANAGEMENT AND PROGNOSIS OF PARAPNEUMONIC PLEURAL EFFUSION AND EMPYEMA

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- A parapneumonic effusion is a pleural effusion that forms in the pleural space adjacent to a pneumonia.
- When micro-organisms infect the pleural space, a complicated parapneumonic effusion or empyema may result.

DEFINITIONS

- An uncomplicated or simple parapneumonic effusion refers to a free-flowing effusion that is sterile.
- A complicated parapneumonic effusion refers to an effusion that has been infected with bacteria or other micro-organisms (eg, positive gram stain or biochemical evidence of marked inflammation)
- An empyema refers to a collection of pus within the pleural space, which can develop when pyogenic bacteria invade the pleural space, from an adjacent pneumonia, direct inoculation (eg, from blunt trauma) or other source. Empyema that develops from an adjacent pneumonia is a subclass of a complicated parapneumonic effusion. While a complicated parapneumonic effusion and empyema represent a spectrum of infection within the pleural space, no pus is directly visualized in patients with a complicated parapneumonic effusion.
- A complex effusion refers to an effusion with internal loculations (septae).
- A uniloculated effusion is one where the effusion is without internal septae (it is not necessarily free-flowing).

GENERAL APPROACH TO MANAGEMENT

- The management of parapneumonic effusions and empyema generally includes prompt antibiotic initiation and drainage of infected pleural fluid.
- For most patients with known or suspected parapneumonic effusions or empyema, we start empiric antibiotics immediately.
- Antibiotic selection varies based on the site of acquisition (ie, community versus hospital-acquired), severity of illness, local epidemiology, and patient risk factors for drug-resistant pathogens or infection with other specific organisms.
- In general, empiric regimens should include antibiotics that target anaerobes and other likely pathogens (eg, streptococci if community-acquired; methicillin-resistant *Staphylococcus aureus* [MRSA] and *Pseudomonas* if hospital-acquired) when a complicated parapneumonic effusion or empyema is suspected.
- Patients with known or suspected uncomplicated effusions can generally be treated similarly to other patients with CAP.

- Because of the high morbidity and mortality associated with acute pneumonia and infected pleural effusions, antibiotics should not be delayed pending diagnostic testing or drainage of the effusion.
- However, an exception includes selected stable patients with indolent illness onset who lack signs or symptoms of systemic infection, it is reasonable to drain the effusion and send for microbiologic testing before starting antibiotic treatment.
- The spectrum of pathogens that cause subacute and chronic pleural effusions and empyema differs from acute empyema (eg, includes mycobacteria, fungi). Deferring antibiotic therapy until microbiologic testing has been obtained may enhance diagnostic yield and allow for targeted therapy.

- The approach to drainage depends on the type, size, and complexity of the effusion.
- For patients with small uncomplicated parapneumonic effusions (ie, sterile effusions), drainage is generally not necessary unless the effusion is sizeable enough to impair respiratory function. Close clinical and radiographic monitoring should be performed to ensure that the effusion is resolving. Larger effusions have increased risk of complications

- For patients with complicated parapneumonic effusions (ie, with clinical or laboratory evidence of infection) or empyema, drainage should be performed as soon as possible for source control.

➢ This is particularly true for empyema, which carries a worse prognosis.

➢ Loculated effusions, large free-flowing effusions (eg, ≥0.5 hemithorax), and effusions with a thickened pleural membrane should also be drained.

➢ When the collection is free-flowing, a single tube or catheter thoracostomy is the procedure of choice.

➢ When the collection is loculated, the approach to drainage is individualized depending on the complexity of the effusion and the patient's severity of illness.

➢ A common approach is to place a single tube or catheter in the largest locule, and reassess the need for placement of additional drains and/or surgical intervention based on clinical and radiographic response.

ANTIBIOTIC THERAPY

- In general, antibiotic therapy mirrors that selected for the underlying pneumonia. However, attention should also be paid to the appropriate coverage of anaerobic bacteria and to choosing antibiotics that have good penetration in to the pleural space.

Empiric therapy (agent choice)

- For most patients, empiric antibiotic therapy should be started as soon as the diagnosis of a parapneumonic effusion or empyema is known or suspected.
- While drainage of infected fluid within the pleural space is critical to care, antibiotic initiation should not be delayed while awaiting diagnostic procedures (eg, thoracentesis) or drainage.
- Exceptions can be made for selected stable patients with long-standing effusions since the pathogens that cause subacute and chronic empyema differ from those associated with acute pneumonia (eg, mycobacteria and fungi); in such situations, deferring antibiotic therapy until microbiologic testing has been obtained may enhance diagnostic yield and allow for targeted therapy.

- Generally, empiric antibiotic regimens should include an antibiotic that targets anaerobic bacteria, which are common causes of complicated parapneumonic effusions and empyema.
- Additional antibiotics should be selected based on the site of acquisition (eg, community- versus hospital-acquired), mode of acquisition (eg, aspiration, trauma), and local epidemiology.

- Nearly all antibiotics adequately penetrate the pleural space. Aminoglycosides (eg, gentamicin, amikacin, tobramycin) are exceptions. Because their pleural penetration is poor and because they may be inactivated in acidic environments (eg, empyemas), we generally avoid them when alternatives are available.
- Initial antibiotic therapy should be given intravenously.
- Transition to oral therapy can be considered once the patient has demonstrated clear clinical improvement and adequate drainage has been achieved.
- There is no role for routine use of intrapleural antibiotics.

Community-acquired

- For most community-acquired complicated parapneumonic effusions or empyema, we select an empiric IV antibiotic regimen that targets *Streptococcus pneumoniae* and the pathogens that colonize the oropharynx, including microaerophilic streptococci (eg, *S. anginosus, S. intermedius*) and anaerobic bacteria
- Reasonable options include:

➢ A third-generation cephalosporin (eg, ceftriaxone or cefotaxime) **plus** metronidazole

➢ A beta-lactam/beta-lactamase inhibitor combination (eg, ampicillin-sulbactam)

- For patients with penicillin hypersensitivity who cannot tolerate cephalosporins, alternate options include monotherapy with a carbapenem (eg, imipenem, meropenem), combination therapy with a respiratory fluoroquinolone (eg, levofloxacin, moxifloxacin) plus metronidazole or a monobactam (eg, aztreonam) plus metronidazole.
- Although clindamycin has been used historically for the treatment of anaerobic lung infections, resistance rates to clindamycin among anaerobes now consistently exceed 20 percent across treatment settings. For this reason, we no longer routinely use clindamycin for empiric treatment of anaerobic infections

- Modifications to these regimens may be needed for severely-ill patients or for those with risk factors for specific pathogens.

➢ As examples, we may expand coverage to include methicillin-resistant *Staphylococcus aureus* (MRSA) in patients with antecedent influenza infection or other MRSA risk factors.

➢ For patients with concurrent necrotizing community-acquired pneumonia (CAP), we may include coverage for both MRSA and *Pseudomonas*.

Risk factors for CAP caused by MRSA and *Pseudomonas*

	MRSA	***Pseudomonas***
Strong risk factors	Known MRSA colonization	Known *Pseudomonas* colonization
	Prior MRSA infection	Prior *Pseudomonas* infection
	Detection of gram-positive cocci in clusters on a good-quality sputum Gram stain	Detection of gram-negative rods on a good-quality sputum Gram stain
		Hospitalization with receipt of IV antibiotics in the prior 3 months
Other factors that should raise suspicion for infection	Recent hospitalization or antibiotic use, particularly hospitalization with receipt of IV antibiotics in the prior 3 months	Recent hospitalization or stay in a long-term care facility
	Recent influenza-like illness	Recent antibiotic use of any kind
	Necrotizing or cavitary pneumonia	Frequent COPD exacerbations requiring glucocorticoid and/or antibiotic use
	Empyema	Other structural lung diseases (eg, bronchiectasis, cystic fibrosis)
	Immunosuppression	Immunosuppression
	•Risk factors for MRSA colonization, including: End-stage kidney disease •Crowded living conditions (eg, incarceration)[Δ] •Injection drug use •Contact sports participation •Men who have sex with men	

- Local epidemiology should also be taken into account when selecting empiric antibiotics because the prevalence of pathogens that cause parapneumonic effusions vary with geography. Prominent examples include *Burkholderia pseudomallei* (cause of melioidosis) in Southeast Asia and tuberculosis in developing regions of the world.
- In general, we do not include an agent that targets atypical pathogens (eg, *Legionella, Chlamydia, Mycoplasma* spp) in our empiric treatment regimens, as these pathogens rarely cause complicated parapneumonic effusions and empyema.
- Generally, patients with uncomplicated parapneumonic effusions can be treated similarly to other patients with CAP.

Hospital-acquired

- For most hospital-acquired infections (eg, empyema secondary tohealthcare-associated pneumonia or postprocedural empyema), we select an empiric IV antibioticregimen that targets MRSA, gram-negative bacteria (including *Pseudomonas* spp), and anaerobicbacteria

- For example, combining **vancomycin** with **metronidazole** and **anantipseudomonal cephalosporin** (eg, cefepime, ceftazidime) is appropriate.
- Combining **vancomycin** with an **anti-beta-lactam/beta-lactamase inhibitor** (eg, piperacillin-tazobactam, ticarcillin-clavulanate) is an alternative.
- However, there is growing concern that the **combination of vancomycin plus piperacillin-tazobactam is nephrotoxic.** Thus, some clinicians **use linezolid in place of vancomycin** when piperacillin-tazobactam is used.
- For those who are **penicillin-allergic**, we suggest combining **vancomycin with metronidazole** and an **antipseudomonal fluoroquinolone** (eg, ciprofloxacin); alternatively, combining **vancomycin** with an **antipseudomonal carbapenem** (eg, imipenem or meropenem) is appropriate.

Directed therapy

- Definitive therapy should be based on culture results and clinical suspicion for a monomicrobial or a polymicrobial infection.
- When suspicion for a monomicrobial infection is high (ie, isolation of S. pneumoniae or S.aureus as sole pathogens from pleural fluid), it is reasonable to direct therapy at the isolated pathogen.

- In most other circumstances (eg, **aspiration pneumonia**, **negative cultures**, or **isolation of a constituent of the oral/gastrointestinal [GI] flora** such as *S. milleri)*, we consider the infection to be polymicrobial and inclusive of multiple anaerobic bacteria.
- In these circumstances, we select a regimen based on the likely source of infection (eg, healthcare associated pneumonia, community acquired pneumonia, or aspiration) that also targets the isolated pathogen as well as any other anaerobic bacteria.
- Because anaerobic bacteria can be difficult to culture and are common causes of parapneumonic effusions and empyema, **most experts include an antibiotic that targets anaerobes for the duration of therapy regardless of culture results.**

Duration of therapy

- The optimal duration of therapy is not known.
- We generally individualize the duration of therapy based upon the **type of effusion**, **the adequacy of drainage**, **clinical and radiographic response to treatment**, and the **patient's immune status**.
- In general, for self-resolving uncomplicated bacterial parapneumonic effusions, therapy may last **one to two weeks**, while therapy for complicated parapneumonic effusions and empyema are often longer (eg, **two to three weeks for a complicated parapneumonic effusion** and **four to six weeks for empyema**).
- While we take radiographic response into account when determining the duration of therapy, complete radiographic resolution may take many weeks or months and residual pleural thickening can persist for longer periods. Thus, **treating with the goal of complete radiographic resolution is not necessary.**

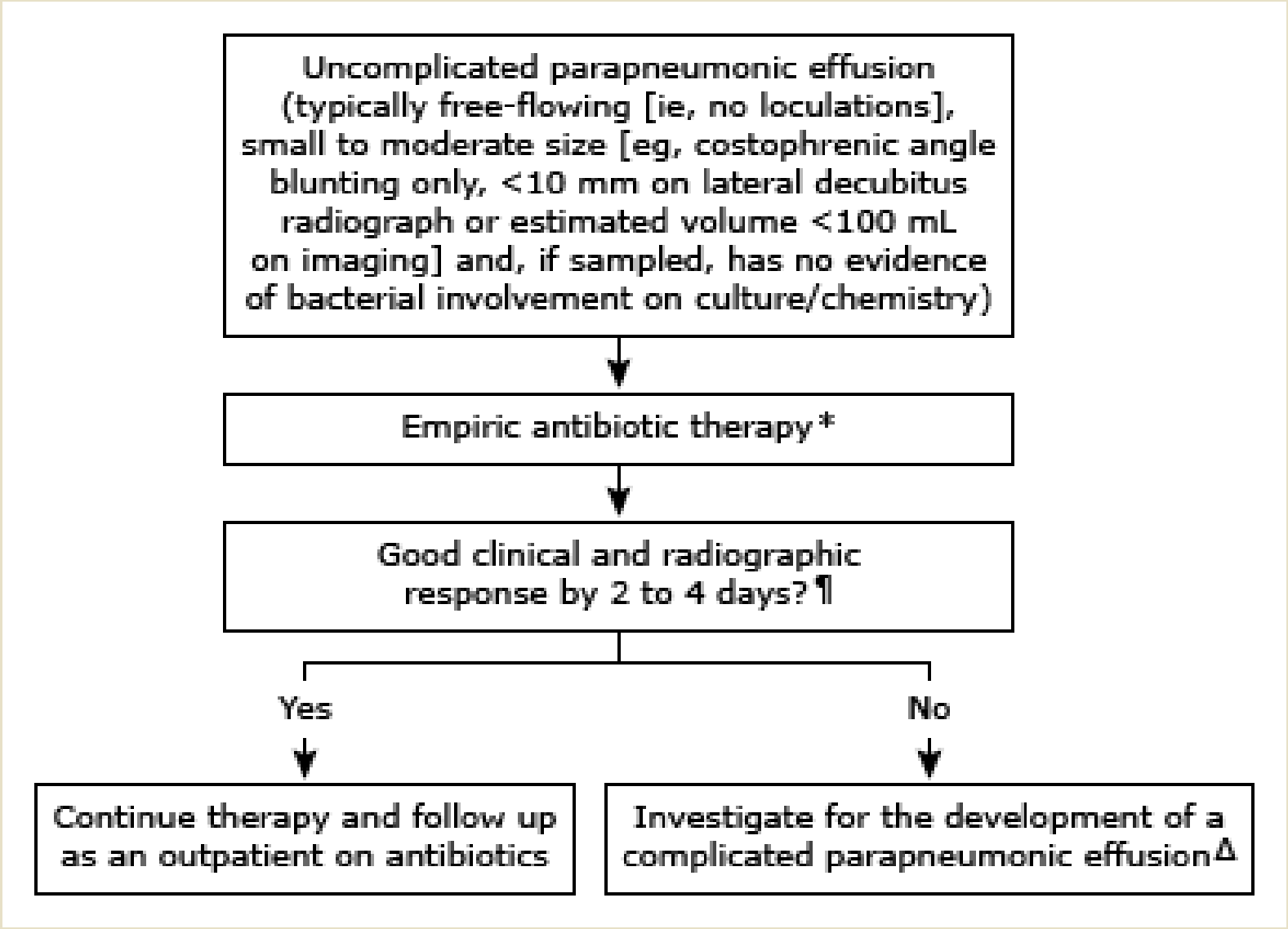
- The initial IV antibiotic regimen can be switched to an **oral regimen** with a similar treatment spectrum when **clinical response is clear** (eg, patient is **afebrile**, **hemodynamically stable**, **clinically improving**), **no further drainage procedures are needed**, and the **patient is able to tolerate oral medications.**

APPROACH TO DRAINAGE

Uncomplicated parapneumonic effusion (antibiotics alone)

- Uncomplicated parapneumonic effusions are small to moderate-sized (ie, less than half the hemithorax) free-flowing effusions with no evidence of infection by culture or chemistry that generally resolve with antibiotics alone and generally do **not** need drainage. In such cases, the diagnosis and therapy with antibiotics alone are empiric
- In some cases, thoracentesis may be performed. For example, if the **effusion is sizeable enough to impair respiratory function** (eg, typically in patients with underlying lung disease), drainage can be performed for symptomatic relief.
- Other indications may include patients with a **severe clinical presentation**, or **patients in whom the pleural space is the suspected source of infection**.
- If after thoracentesis, suspicion remains for infection in the pleural space despite a negative Gram stain, culture, or pleural fluid chemistries (eg, patient with septic shock), we generally proceed with drainage and treat the patient as if they have a complicated (ie, infected) parapneumonic effusion.

- All patients with uncomplicated parapneumonic effusion should be followed clinically and with serial chest radiographs or ultrasound examinations to assess for improvement or deterioration.
- The optimal frequency of radiographic follow-up is unknown but it is appropriate that the **first follow-up imaging be obtained within 48 hours if thoracentesis was not performed**.
- If thoracentesis was performed and confirms an uncomplicated parapneumonic effusion, **serial radiographs can be repeated within one week of the diagnosis and followed every one to two weeks until resolution since progression to empyema** while appropriate antibiotics are being administered is rare.
- Should patients fail to improve, the effusion enlarges, or new fever develops, repeat imaging with chest computed tomography should be performed to evaluate for the development of a complicated parapneumonic effusion that may need to undergo sampling and drainage

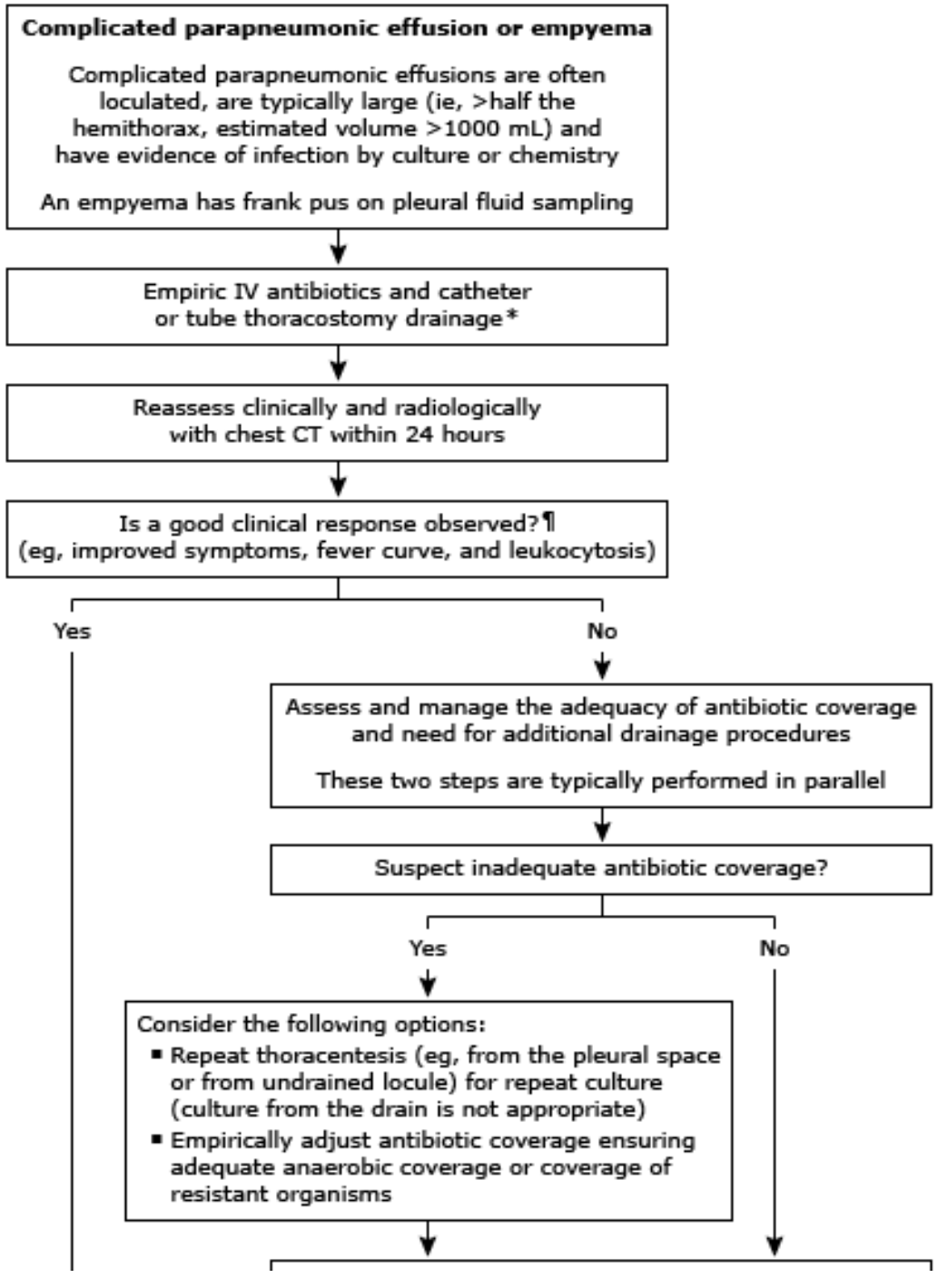

Uncomplicated parapneumonic effusion (typically free-flowing [ie, no loculations], small to moderate size [eg, costophrenic angle blunting only, <10 mm on lateral decubitus radiograph or estimated volume <100 mL on imaging] and, if sampled, has no evidence of bacterial involvement on culture/chemistry)
Empiric antibiotic therapy*
Good clinical and radiographic response by 2 to 4 days?¶
Yes
No
Continue therapy and follow up as an outpatient on antibiotics
Investigate for the development of a complicated parapneumonic effusionΔ

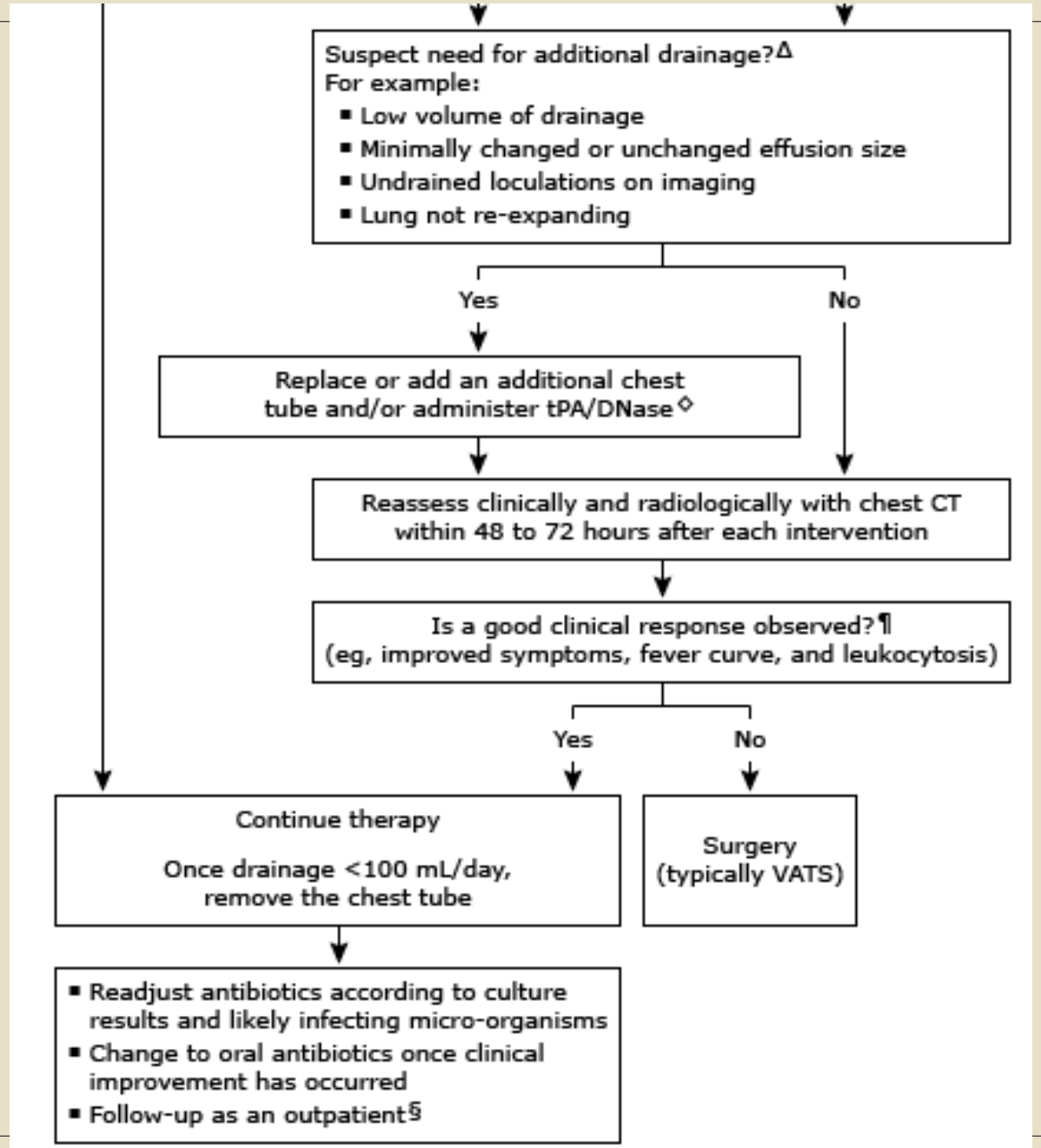
- In addition to appropriate antibiotic therapy, PROMPT drainage is indicated in patients when there is clinical concern for or evidence of infection in the pleural space, based upon the following features

- Empyema (ie, overtly purulent pleural fluid)
- Positive pleural fluid Gram stain or culture
- Loculated pleural effusion
- Large free-flowing effusions (ie, ≥0.5 hemithorax)
- Effusions associated with thickened parietal pleura
- Sepsis from a pleural source

- This approach is based upon the rationale that without drainage (ie, source control), patients have poor outcomes including an increased requirement for more than one procedure, eventual need for surgery, and longer hospitalization. This is particularly important for empyema, which carries the poorest prognosis and highest mortality.
- A pleural fluid pH of <7.2 is also an indicator of infection in the pleural space. However, other pleural diseases can have a low pleural fluid pH (eg, malignant effusions, rheumatoid and lupus pleurisy, urinothorax, and saline from a misplaced central venous catheter)
- Therefore, the decision to drain fluid from the pleural space based on a low pleural fluid pH alone should be made after pleural fluid analysis is complete.

- The initial procedure of choice is a single tube or catheter thoracostomy.
- Importantly, this recommendation applies to those in whom residual effusion remains following diagnostic thoracentesis.
- However, when an effusion is loculated, choosing to drain the largest locule (usually guided by ultrasound or chest computed tomography [CT]) is appropriate; in such situations, consideration should be given to the prompt insertion of a second or third drain during follow-up.
- Early thoracic surgical consultation is appropriate because some of these patients will require thoracoscopic or open surgery.


Complicated parapneumonic effusion or empyema
Complicated parapneumonic effusions are often loculated, are typically large (ie, >half the hemithorax, estimated volume >1000 mL) and have evidence of infection by culture or chemistry
An empyema has frank pus on pleural fluid sampling
Empiric IV antibiotics and catheter or tube thoracostomy drainage*
Reassess clinically and radiologically with chest CT within 24 hours
Is a good clinical response observed?¶ (eg, improved symptoms, fever curve, and leukocytosis)
Yes
No
Assess and manage the adequacy of antibiotic coverage and need for additional drainage procedures
These two steps are typically performed in parallel
Suspect inadequate antibiotic coverage?
Yes
No
Consider the following options:
Repeat thoracentesis (eg, from the pleural space or from undrained locule) for repeat culture (culture from the drain is not appropriate)
Empirically adjust antibiotic coverage ensuring adequate anaerobic coverage or coverage of resistant organisms


Suspect need for additional drainage?Δ
For example:
Low volume of drainage
Minimally changed or unchanged effusion size
Undrained loculations on imaging
Lung not re-expanding
Yes
No
Replace or add an additional chest tube and/or administer tPA/DNase◇
Reassess clinically and radiologically with chest CT within 48 to 72 hours after each intervention
Is a good clinical response observed?¶
(eg, improved symptoms, fever curve, and leukocytosis)
Yes
No
Continue therapy
Once drainage <100 mL/day, remove the chest tube
Surgery (typically VATS)
Readjust antibiotics according to culture results and likely infecting micro-organisms
Change to oral antibiotics once clinical improvement has occurred
Follow-up as an outpatient§

Initial drainage (tube or catheter thoracostomy)

- Chest tube or catheter thoracostomy drainage is the least invasive option for drainage of infected pleural fluid in patients with a complicated parapneumonic effusion or empyema.
- It is best suited for patients with free-flowing or uniloculated effusions (ie, effusion without internal septae), but is also frequently used to drain complex effusions (ie, effusions with internal septations or locules).

Image guidance

- thoracostomy tubes are typically placed using either ultrasound or CT guidance. However, many experts place chest tubes blindly at the bedside, especially when the effusion is large or free-flowing.

Size

- In general, we prefer small-bores tubes (10 to 14 French [Fr]) based upon data that suggest similar efficacy and less pain when compared with large-bore thoracostomy tubes.
- However, in practice the choice may be dependent upon factors including physician and patient preference, institutional policy, and available expertise. Some experts prefer larger bore tubes in patients with effusions that have multiple locules since larger tubes may penetrate locules more readily than smaller tubes.
- Traditionally, larger bore tubes (>28 Fr) were preferred for drainage of more viscous empyema fluid and smaller bore tubes were reserved for less viscous fluid.

➢ no significant difference was found in mortality or need for thoracic surgery between large (15 to 20 Fr), medium (10 to 14 Fr), or small (<10 Fr) bore tubes

Suction

- The application of suction is typical to assure maximal and consistent pleural fluid removal since pleural fluid output is the major determinant that suggests that any tube can be removed. However, suction is not necessary unless the pleural space fails to drain or an air leak is present.
- Once an air leak is excluded, the chest tube or catheter can be placed to water seal.

Efficacy

- Although some patients with complicated parapneumonic effusions may improve with antibiotics alone, the response is variable and drainage is not always successful.
- pleural pH <7.2 was the most useful predictor of a complicated clinical course.
- If pleural pH is not measured, a pleural fluid glucose value <40 mg/dL (2.2 mmol/L) and/or pleural fluid lactate dehydrogenase (LDH) value >1000 international units/L, or significant loculations also appear predictive of the need for tube thoracostomy.
- Thoracic empyema (ie, pus in the pleural space) invariably requires drainage (akin to draining a pyogenic abscess for source control) because among those with an infected pleural space, patients with empyema have the highest mortality.

با تشکر!