New trends in the diagnosis and treatment in parapneumonic effusion and empyema

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ÖZET

Parapnömonik efüzyon ve ampiyemin tanı ve tedavisinde yeni eğilimler

Antibiyotik tedavisine rağmen parapnömonik efüzyon (PPE) ve ampiyem morbidite ve mortalitesinde kısmende olsa yönetim hataları nedeniyle artış olmaktadır. PPE antibiyotik tedavisi başlanan tüm pnömoni olgularında akla getirilmelidir. Eğer göğüs röntgenogramında diyaframlar boylu boyunca görülemiyorlarsa yan dekübit grafisi, ultrasonografi ya da bilgisayarlı tomografi çekilmelidir. Eğer efüzyon 10 mm'den daha kalınsa tedavi edici torasentez yapılmalıdır. Eğer sıvı tamamen boşaltılamaz ve sıvı özellikleri kötü prognozu işaret ediyorsa göğüs tüpü takılmalıdır. Eğer PPE'nin loküle olmasına bağlı tam drenaj olmuyorsa intraplevral fibrinolitikler ya da torakoskopi uygulanmalıdır. Eğer torakoskopi ile akciğer tam açılmazsa gecikmeden dekortikasyon yapılmalıdır.

Anahtar Kelimeler: *Parapnömonik efüzyon, ampiyem.*

SUMMARY

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Despite treatment with antibiotics, patients with complicated parapneumonic effusion (PPE) and empyema have an increased morbidity and mortality due at least in part to inappropriate management of the pleural effusion. PPE should be considered in all patients with pneumonia as antibiotic therapy is being initiated. If the diaphragms cannot be seen throughout their length on the chest radiographs, a lateral decubitus radiograph, ultrasonography or computerized tomography scan should be obtained. If the effusion is more than 10 mm in thickness, a therapeutic thoracentesis should be performed. If the fluid cannot all be removed and the characteristics of the pleural fluid indicate a poor prognosis, a chest tube should be inserted. If the drainage is incomplete due to loculation of the PPE intrapleural fibrinolytics or thoracoscopy should be performed. If the lung does not reexpand completely with thoracoscopy, then decortication should be performed without delay.

Key Words: *Parapneumonic effusion, empyema.*

INTRODUCTION

This review will discuss the diagnosis and treatment of complicated parapneumonic effusion (PPE) and empyema, with particular emphasis on recent advances articles. It will end with recommendation of treatment and simple management algorithm. The objectives of this review are to provide the practicing physician with practical guidelines.

Definitions

A complicated PPE is a pleural effusion that is commonly accompanied by loculations or septations of the pleural fluid on computed tomography (CT) or ultrasonography (USG) examination, and needs invasive therapy such as chest tubes or thoracoscopy for its resolution or on which the Gram stain or cultures are positive. Pleural fluid markers of a complicated PPE are shown in Table 1 (1,2). An empyema is by definition pus in the pleural space (3). A staging system for PPE and empyema is shown in Table 2 (1).

Table 1. Poor prognostic factors and indications of chest tube drainage in parapneumonic effusions and empyema.*

Pus present in pleural space
Gram stain of pleural fluid positive
Pleural fluid glucose below 40 mg/dL
Pleural fluid culture positive
Pleural fluid pH < 7.0
Pleural fluid LDH > 3 x upper limit for serum
Pleural fluid loculated
Large non-purulent effusions

* Listed in order of decreasing importance.
LDH: Lactic dehydrogenase.

Incidence

The annual incidence of bacterial pneumonia is estimated to be 4 million, with approximately 20% of patients requiring hospitalization (4). PPE develops in approximately 40% of patients admitted to the hospital with community-acquired pneumonia and about 10% of these require surgical drainage (5,6).

Markers of a Poor Prognosis

The early recognition of features that predict the need for invasive management is key to the successful management of PPE. If invasive management is delayed, then the fluid is likely to become more loculated and difficult to drain. In addition to biochemical parameters such as low pleural fluid pH and glucose, and high pleural fluid LDH, several reports have identified other risk factors for a poor outcome (3). These include the purulence of pleural fluid, the presence of co-morbid diseases such as diabetes or alcoholism, delayed time to pleural drainage, the presence of pleural fluid loculation or a low white cell count of pleural fluid, older age, low serum albumin, and gram-negative bacilli or multiple pathogens (7-11).

DIAGNOSIS

The presence of PPE should be suspected in all patients with pneumonia who have progressive, gravity-dependent, pleural-based opacities that obscure the diaphragm; or fail to respond to appropriate antibiotic treatment within 72 hours (12).

Table 2. A classification and treatment scheme for PPE and empyema.

Class		pH, Glucose and LDH level	Gram stain and culture or frank pus	Loculation	Treatment in addition to antibiotics
1	Nonsignificant pleural effusion				Antibiotics only
2	Typical parapneumonic pleural effusion	pH > 7.2, Glucose > 40 mg/dL, LDH < 3 x upper limit normal for serum	Negative	No	Antibiotics only
3	Borderline complicated pleural effusion	7.0 < pH < 7.2 and/or Glucose > 40 mg/dL and LDH > 3 x upper limit normal for serum	Negative	No	Serial thoracentesis
4	Simple complicated pleural effusion	pH < 7.0 or Glucose < 40 mg/dL	Positive	No	Thoracostomy
5	Complex complicated pleural effusion	pH < 7.0 and/or Glucose < 40 mg/dL	Positive	Multiple	Thoracostomy plus fibrinolytics or Thoracoscopy
6	Simple empyema	pH < 7.0	Frank pus	Single or free flowing	Thoracostomy ± decortication
7	Complex empyema	pH < 7.0	Frank pus	Multiple	Thoracostomy ± fibrinolytics Often require thoracoscopy or decortication

Nonsignificant pleural effusion, small effusions less than 10 mm thickness on decubitus chest radiography is not necessary for the thoracentesis.

Clinical Manifestations

The clinical manifestations of PPE and empyema depend to a large part on whether the patient has an aerobic or an anaerobic infection. The clinical presentation of patients with aerobic bacterial pneumonia and PPE is no different from that of patients with bacterial pneumonia without PPE. The patients first manifest an acute febrile illness with chest pain, sputum production, and leukocytosis. Infections with anaerobes are more likely to have an insidious clinical onset, with less fever, greater weight loss, and are more common in patients who are alcoholics, have had an episode of unconsciousness or who have poor dental hygiene (13).

Radiological Examination

Chest radiography: The presence of a significant amount of pleural fluid is usually suggested on the lateral view where the posterior costophrenic angle is blunted or one of the diaphragms is not visible throughout its length (14). All patients with pneumonia should have a lateral view. However, the sensitivity of posteroanterior and/or lateral view for detecting pleural fluid was 80% in parapneumonic effusions diagnosed with lateral decubitus view (15). The amount of free pleural fluid can be semiquantitated by measuring the distance between the inside of the chest wall and the outside of the lung on a lateral decubitus view. The positive predictive value of lateral decubitus view for pleural effusion was 92% in patients diagnosed with USG (16). If this distance measures less than 10 mm, the pleural effusion is not clinically significant and a thoracentesis is not indicated as the pleural effusion will resolve with antibiotics alone (1) (Table 2).

Ultrasonography (USG): The amount of pleural fluid can be semiquantitated with USG. Ultrasound can also demonstrate whether septations are present within loculations (17).

Chest computed tomography (CT): Contrast-enhanced thoracic CT provides detailed information about how much of the increased density on a chest radiograph is due to pleural fluid and how much is due to parenchymal infiltrate. It also demonstrates fluid loculation (but not septations), pinpoints the position of existing chest tubes, help to differentiate pleural empyema from a lung abscess and can identify any airway obstruction caused by tumor or foreign body (2). High resolution CT scan is not indicated as it adds nothing to the regular CT scan in this situation.

Thoracentesis

If the thickness of the fluid is greater than 10 mm on the decubitus radiograph or on the USG examination, a therapeutic thoracentesis rather than a diagnostic thoracentesis with a needle-catheter system should be performed immediately because it is impossible to separate complicated from uncomplicated effusions without a thoracentesis (1). If the fluid does not reaccumulate, one need not worry about the PPE. USG is particularly well suited for guiding pleural interventions. It increases the success rate and reduces complications of thoracentesis (18).

Analysis of Pleural Fluid

The pleural fluid should be sent for Gram stain and bacterial culture, white blood cell count and differential, and for determination of its level of glucose, LDH, and pH. In the diagnosis of complicated PPE, the demonstration of a threshold of a pH < 7.2 is most important. Other pleural fluid parameters such as reduced glucose (< 40 mg/dL) or elevated LDH (> 3 times the upper limit of normal) may support the diagnosis of complicated PPE, although these are less useful diagnostically than the pleural fluid pH (19). The pH should be measured with a blood gas analyzer, not a pH meter or an indicator tape (3). In a given patient with loculated pleural fluid, there can be variations in pH, glucose and LDH between different locules (20). The diagnostic yield from the bacterial cultures will be increased if the pleural fluid is inoculated into blood culture bottles at the bedside (21).

Recent studies have reported that pleural fluid TNF-α levels, myeoloperoxidase levels and polymorphonuclear elastase levels are higher in complicated PPE and empyema than in uncomplicated PPE, but additional studies are necessary to determine the rightful place of these tests in the management of PPE (22-24).

TREATMENT

Despite of effective antibiotics and drainage of the infected pleural fluid, the overall mortality rates of empyema is as high as 20% (11). The management of PPE and empyemas involves two separate areas-selection of an appropriate antibiotic and management of the pleural fluid (1).

I. Antibiotics Treatment

All patients with PPE or empyema should be empirically treated with intravenous antibiotics as initial therapy for hospitalized patients. If the Gram stain of the pleural fluid is positive, it should guide the selection of an antibiotic. The recent common microorganisms of complicated PPE and empyema are *Streptococcus milleri* group, *Streptococcus pneumoniae*, other streptococci, Enterobacteriaceae, anaerobic bacteria, *Staphylococcus aureus* including methicillin-resistant, and enterococci (25). The initial antibiotic selection is not influenced by the presence or absence of pleural effusion, and usually based on whether the pneumonia is a community-acquired or a hospital-acquired and how sick the patient is (1). Because anaerobes are difficult to culture and often coexist with aerobes, additional empirical treatment of anaerobes should be considered. Beta-lactam show good penetration of the pleural space (26). However, aminoglycosides appear to penetrate poorly into purulent pleural fluid and are less active at an acid pH and are not usually recommended exept infection with *Pseudomonas aeruginosa*. Because atypical pathogens like as *Legionella pneumonphila* or *Mycoplasma pneumoniae* rarely lead to empyema, macrolide should only be ad-

ded in suspected case (2). New antibacterials used in treatment of community-acquired pneumonia like the respiratory fluoroquinolones or telithromycin have not been not adequately studied in PPE or empyema.

In patients with community-acquired PPE or empyema, a beta-lactam (cefotaxime, ceftriaxone) plus metronidazole or beta-lactamase inhibitor (amoxicillin-clavulanate, ampicillin-sulbactam) are recommended (28). For patients allergic to both penicillin and cephalosporins, combinations such as ciprofloxacin and clindamycin may be effective (2). In patients with hospital acquired and severe community-acquired PPE or empyema, the antibiotics should be chosen to treat both gram-positive and gram-negative aerobes and also anaerobes. Recommended antibiotics include anti-pseudomonal beta-lactam (cefepime) plus metronidazole or beta-lactamase inhibitor (piperacillin-tazobactam), or anti-pseudomonal carbapenem (imipenem, meropenem) with anti-pseudomonal fluoroquinolone (ciprofloxacin, levofloxacin) or aminoglycoside (26,28,29). Anti-staphylococcal coverage including methicillin resistant *Staphylococcus aureus* (vancomycin or linzolid) is often required (28).

The optimal duration of antibiotic treatment is unclear, although it is likely to be at least 3 weeks. Measurement of inflammatory markers such as serum C-reactive protein, in addition to clinical assessment, may provide a useful guide to treatment response (1).

II. Management of Pleural Fluid

There are several treatment options available for the management of the pleural fluid in patients with complicated PPE and these include repeated therapeutic thoracentesis, tube thoracostomy, intrapleural instillation of fibrinolytics, video-assisted thoracoscopic surgery (VATS) with the breakdown of adhesions, thoracotomy with decortication and the breakdown of adhesions, and open drainage (1). Patients with class 5, 6, and 7 effusions will often require thoracoscopy or thoracotomy for complete drainage and adequate lung re-expansion (Table 2) (19).

Chest Tube Thoracostomy

Findings that indicate that tube thoracostomy will be necessary for resolution of a PPE are listed in Table 1 (1,2). Patients with characteristics higher in Table 1 are more likely to need tube thoracostomy or some other invasive procedure. Successful closed-tube drainage of complicated PPE is evidenced by improvement in the clinical and radiological status within 24 hours (3). In general, chest tubes should be left in place until the volume of the pleural drainage is under 50 mL for 24 hours and until the draining fluid becomes clear yellow.

What sized tube should be used?

In the past, relatively large (28 to 36F) tubes have been recommended owing to the belief that smaller tubes would become obstructed with the thick viscous fluid. Small catheters (6 to 14F) pigtail or Malecot served as the definitive treatment in 78% of patients and had the advantages that they were easier to insert and less painful (30). In cases where small sized catheters are used, the use of suction (20 cmH_2O) and regularly flushes (eg, 30 mL normal saline every 6 hours) may help to prevent their occlusion (2).

What next if tube fails?

The failure rate associated with primary intervention using tube thoracostomy is at least 40% (31). If the patient is not improving with chest tube drainage, either the patient is receiving the wrong antibiotics agent or the drainage is inadequate that can be caused by poor positioning of the chest tube, obstruction or kinking of the chest tube, loculated or inaccessible pleural fluid, or the presence of highly viscous fluid (3). If the chest tube is occluded attempts should be made to restore its patency with saline flushes or the intratubal injection of tissue plasminogen activator (tPA), or the tube should be removed to prevent pleural superinfection (2).

Fibrinolytic Treatment

The intrapleural administration of fibrinolytic agents has been used to aid the drainage of infected pleural fluids with the hope that this will reduce the need of surgery for over 50 years.

The use of fibrinolytics is recommended by management guidelines (2,31). The theory behind their use is that loculations in the pleural space are produced by fibrin membranes; intrapleural fibrinolytics may dissolve the fibrin membranes and facilitate drainage of the pleural space (3). The intrapleural fibrinolytic agents that used mostly, are streptokinase (SK) 250.000 IU and urokinase (UK) 100.000 U for 3 days.

Is the streptokinase effective management?

In three earlier randomized controlled trials, patients treated with intrapleural SK appeared to have benefit by having a higher total volume of pleural fluid drained, greater chest radiograph improvement, higher clinical success rate, fewer referrals for surgical interventions (VATS or open decortication), and decreased length of hospital stay (32-34). These three studies had low statistical power because of the small number of patients included. In a recent randomized multicenter trial of 427 patients by Maskell et al., the intrapleural administration of SK did not improve mortality, the rate of surgery, or the length of the hospital stay (25). In view of this latter study, SK should only be considered if the patient refuses surgery or is too sick for surgery. At the present time, SK is unavailable in the United States.

How about urokinase?

In one randomized trial of intrapleural UK, there was a statistically significant benefit in mean time to defervescence, duration of hospitalization, duration of pleural fluid drainage, total fluid drained, and improvement in chest radiographs with no significant side effects (35). More randomized studies in large number may be needed.

Are there any new agents?

The patients that received alteplase, recombinant tPA, had more pleural fluid drainage than UK with similar overall success rates (36). When tPA was administered within 24 hours of diagnosis, the amount of pleural fluid drainage was higher and there was a shorter duration of chest tube drainage than after 24 hours of diagnosis (37). It will be an effective treatment for loculated PPE.

In a single case report, use of intrapleural human recombinant DNase (Pulmozyme) was successful in the treatment of empyema following failure of SK (38). At the present time, there is a multicenter study in the United Kingdom where patients with multiloculated PPE are randomized to saline, tPA, DNase or tPA plus DNase.

Surgery

When medical treatment fails, surgical intervention should be considered without further delay. Failure of medical treatment is indicated by clinical evidence that the sepsis syndrome has progressed or persisted (i.e., there is fever, leukocytosis, and/or elevated C-reactive protein) and by the presence of significant residual pleural fluid. Lim et al. reported that an empirical treatment strategy which combines adjunctive intrapleural fibrinolysis with early surgical intervention results in shorter hospital stays and may reduce mortality in patients with pleural sepsis (39). Kalfa et al. reported that thoracoscopy within four days of diagnosis was associated with a shorter operative time and postoperative hospital stay, fewer technical difficulties, fewer complications, and no need for other surgical procedures (40).

Video assisted thoracoscopic surgery (VATS): VATS is less invasive than open thoracotomy and is associated with less patient discomfort and less severe pain compared with thoracotomy. In a randomized controlled study of 20 patients with pleural infection, Wait et al. reported that early immediate treatment with VATS compared with intrapleural SK resulted in higher primary treatment success, shorter drainage time, shorter hospital stay, and similar costs (41). Luh et al. reported recently that 202 of 234 patients (86.3%) achieved satisfactory results with VATS treatment (42). Multiloculated empyema can also be treated with medical thoracoscopy. Brutsche et al. recently reported in a retrospective study that 119 of 127 patients (91%) were healed by medical thoracoscopy, and the median duration of chest tube drainage post medical thoracoscopy was seven days (43).

Thoracotomy with decortication: With this procedure, which involves a full thoracotomy, all the fibrous tissue is removed from the visceral pleura and all pus is evacuated from the pleural

space. Decortication eliminates the pleural sepsis and allows the underlying lung to expand (3).

Open drainage by rib resection: Chronic drainage of the pleural space can be achieved with open drainage procedures. In general open drainage procedures are recommended only for patients who are debilitated and not candidates for thoracoscopy or thoracotomy.

RECOMMENDED MANAGEMENT of PARAPNEUMONIC EFFUSIONS

It is recommended that a stepwise approach be taken for patients with PPE (Figure 1). When a patient with pneumonia is initially evaluated, the possibility of a PPE should be assessed. If pleural fluid is present and its thickness is more than 10 mm, a thoracentesis (a therapeutic rather than a diagnostic thoracentesis) should be performed without delay. If the fluid reaccumulates after initial thoracentesis, a second therapeutic thoracentesis should be performed if poor prognostic factors were present, and if the fluid reaccumulates after second thoracentesis, a tube thoracostomy should be performed if poor prognostic factors are present. If the pleural fluid is loculated, then more aggressive therapy is indicated. If the therapeutic response with thoracostomy is inadequate, a CT scan of the chest should be obtained and fibrinolytics may be used. However, if complete drainage is not obtained with one or two administrations of the fibrinolytics, one should move to thoracoscopy. If with thoracoscopy, the lung does not reexpand completely, then decortication should be performed without delay. Open drainage procedures are reserved for those patients who are too ill to undergo thoracoscopy or thoracotomy. The definitive treatment should be performed within the first 10 days of hospitalization.

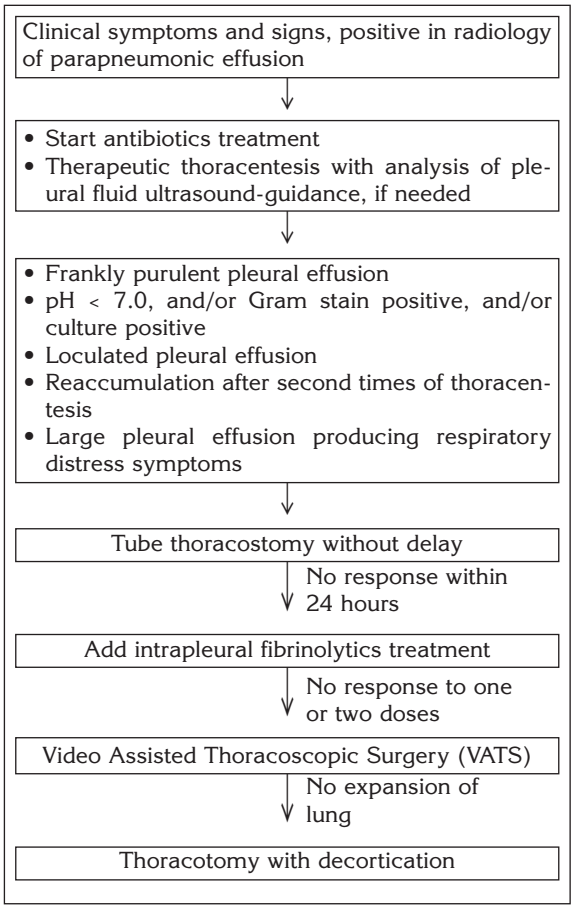

Figure 1. Management algorithm in paients not responsive to each treatment.

REFERENCES

1. *Light RW. Parapneumonic effusions and empyema. In: Light RW (eds). Pleural Disease. 4th ed. Philadelphia: Lippincott Williams & Wilkins, 2001: 151-81.*
2. *Davies CW, Gleeson FV, Davies RJ. BTS guidelines for the management of pleural infection. Thorax 2003; 58 (Suppl 2): 18-28.*
3. *Light RW, Rodriguez RM. Management of parapneumonic effusions. Clin Chest Med 1998; 19: 373-82.*
4. *Niederman MS, Bass JB Jr, Campbell GD, et al. Guidelines for the initial management of adults with community-acquired pneumonia: Diagnosis, assessment of severity, and initial antimicrobial therapy. Am Rev Respir Dis 1993; 148: 1418-26.*
5. *Light RW, Girard WM, Jenkinson SG, George RB. Parapneumonic effusions. Am J Med 1980; 69: 507-11.*
6. *Davies CW, Kearney SE, Gleeson FV, Davies RJ. Predictors of outcome and long-term survival in patients with pleural infection. Am J Respir Crit Care Med 1999; 160: 1682-7.*
7. *Chen KY, Hsueh PR, Liaw YS, et al. A 10-year experience with bacteriology of acute thoracic empyema: Emphasis on Klebsiella pneumoniae in patients with diabetes mellitus. Chest 2000; 117: 1685-9.*
8. *Ashbaugh DG. Empyema thoracis. Factors influencing morbidity and mortality. Chest 1991; 99: 1162-5.*
9. *Huang HC, Chang HY, Chen CW, et al. Predicting factors for outcome of tube thoracostomy in complicated parapneumonic effusion for empyema. Chest 1999; 115: 751-6.*

10. *Heffner JE, McDonald J, Barbieri C, Klein J. Management of parapneumonic effusions. An analysis of physician practice patterns. Arch Surg 1995; 130: 433-8.*
11. *Ferguson AD, Prescott RJ, Selkon JB, et al. The clinical course and management of thoracic empyema. QJM 1996; 89: 285-9.*
12. *Lim TK. Management of parapneumonic pleural effusion. Curr Opin Pulm Med 2001; 7: 193-7.*
13. *Bartlett JG, Gorbach SL, Thadepalli H, Finegold SM. Bacteriology of empyema. Lancet 1974; 303: 338-40.*
14. *Evans AL, Gleeson FV. Radiology in pleural disease: State of the art. Respirology 2004; 9: 300-12.*
15. *Taryle DA, Potts DE, Sahn SA. The incidence and clinical correlates of parapneumonic effusions in pneumococcal pneumonia. Chest 1978; 74: 170-3.*
16. *Kocijancic I, Vidmar K, Ivanovi-Herceg Z. Chest sonography versus lateral decubitus radiography in the diagnosis of small pleural effusions. J Clin Ultrasound 2003; 31: 69-74.*
17. *Wu RG, Yuan A, Liaw YS, et al. Image comparison of real-time gray-scale ultrasound and color Doppler ultrasound for use in diagnosis of minimal pleural effusion. Am J Respir Crit Care Med 1994; 150: 510-4.*
18. *Jones PW, Moyers JP, Rogers JT, et al. Ultrasound-guided thoracentesis: Is it a safer method? Chest 2003; 123: 418-23.*
19. *Maskell NA, Davies RJO. Effusions from parapneumonic infection and empyema. In: Light RW, Lee YCG (eds). Textbook of Pleural Disease. 1st ed. London: Arnold, 2003: 310-28.*
20. *Maskell NA, Gleeson FV, Darby M, Davies RJ. Diagnostically significant variations in pleural fluid pH in loculated parapneumonic effusions. Chest 2004; 126: 2022-4.*
21. *Ferrer A, Osset J, Alegre J, et al. Prospective clinical and microbiological study of pleural effusions. Eur J Clin Microbiol Infect Dis 1999; 18: 237-41.*
22. *Porcel JM, Vives M, Esquerda A. Tumor necrosis factor-alpha in pleural fluid: A marker of complicated parapneumonic effusions. Chest 2004; 125: 160-4.*
23. *Alegre J, Jufresa J, Segura R, et al. Pleural-fluid myeloperoxidase in complicated and noncomplicated parapneumonic pleural effusions. Eur Respir J 2002; 19: 320-5.*
24. *Aleman C, Alegre J, Segura RM, et al. Polymorphonuclear elastase in the early diagnosis of complicated pyogenic pleural effusions. Respiration 2003; 70: 462-7.*
25. *Maskell NA, Davies CW, Nunn AJ, et al. Controlled trial of intrapleural streptokinase for pleural infection. N Engl J Med 2005; 352: 865-74.*
26. *Hughes CE, Van Scoy RE. Antibiotic therapy of pleural empyema. Semin Respir Infect 1991; 6: 94-102.*
27. *Thys JP, Vanderhoeft P, Herchuelz A, et al. Penetration of aminoglycosides in uninfected pleural exudates and in pleural empyemas. Chest 1988; 93: 530-2.*
28. *Mandell LA, Bartlett JG, Dowell SF, et al. Update of practice guidelines for the management of community-acquired pneumonia in immunocompetent adults. Clin Infect Dis 2003; 37: 1405-33.*
29. *American Thoracic Society; Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am J Respir Crit Care Med 2005; 171: 388-416.*
30. *Shankar S, Gulati M, Kang M, et al. Image-guided percutaneous drainage of thoracic empyema: Can sonography predict the outcome? Eur Radiol 2000; 10: 495-9.*
31. *Colice GL, Curtis A, Deslauriers J, et al. Medical and surgical treatment of parapneumonic effusions: An evidence-based guideline. Chest 2000; 118: 1158-71.*
32. *Davies RJ, Traill ZC, Gleeson FV. Randomised controlled trial of intrapleural streptokinase in community acquired pleural infection. Thorax 1997; 52: 416-21.*
33. *Diacon AH, Theron J, Schuurmans MM, et al. Intrapleural streptokinase for empyema and complicated parapneumonic effusions. Am J Respir Crit Care Med 2004; 170: 49-53.*
34. *Misthos P, Sepsas E, Konstantinou M, et al. Early use of intrapleural fibrinolytics in the management of postpneumonic empyema. A prospective study. Eur J Cardiothorac Surg 2005; 28: 599-603.*
35. *Bouros D, Schiza S, Tzanakis N, et al. Intrapleural urokinase versus normal saline in the treatment of complicated parapneumonic effusions and empyema. A randomized, double-blind study. Am J Respir Crit Care Med 1999; 159: 37-42.*
36. *Wells RG, Havens PL. Intrapleural fibrinolysis for parapneumonic effusion and empyema in children. Radiology 2003; 228: 370-8.*
37. *Weinstein M, Restrepo R, Chait PG, et al. Effectiveness and safety of tissue plasminogen activator in the management of complicated parapneumonic effusions. Pediatrics 2004; 113: 182-5.*
38. *Simpson G, Roomes D, Reeves B. Successful treatment of empyema thoracis with human recombinant deoxyribonuclease. Thorax 2003; 58: 365-6.*
39. *Lim TK, Chin NK. Empirical treatment with fibrinolysis and early surgery reduces the duration of hospitalization in pleural sepsis. Eur Respir J 1999; 13: 514-8.*
40. *Kalfa N, Allal H, Montes-Tapia F, et al. Ideal timing of thoracoscopic decortication and drainage for empyema in children. Surg Endosc 2004; 18: 472-7.*
41. *Wait MA, Sharma S, Hohn J, Dal Nogare A. A randomized trial of empyema therapy. Chest 1997; 111: 1548-51.*
42. *Luh SP, Chou MC, Wang LS, et al. Video-assisted thoracoscopic surgery in the treatment of complicated parapneumonic effusions or empyemas: Outcome of 234 patients. Chest 2005; 127: 1427-32.*
43. *Brutsche MH, Tassi GF, Gyorik S, et al. Treatment of sonographically stratified multiloculated thoracic empyema by medical thoracoscopy. Chest 2005; 128: 3303-9.*