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Introduction
Both in Africa and in the West, surgeons are often asked by our medical colleagues to drain pleural effusions through the insertion of chest tubes. In Africa, the most common reason for such a request is the post-pneumonic infected effusion or empyema. In the majority of cases the primary care is left to the medical service. While chest tubes are often sufficient to manage this problem, in certain cases the infection may require more sophisticated therapy. Therefore, it is incumbent on the surgeon to understand, in detail, the classification, pathophysiology, diagnostic and therapeutic approaches to pleural
space infections (PSI).

This review will concentrate on the post-pneumonic empyema including those associated with tuberculosis and HIV disease. It will deal briefly with post-traumatic pleural infections but not with those occurring after thoracic resection. For these the reader is referred to the following Reviews. (1; 2) It will review the clinical presentations and range of infectious agents as well as discuss the new therapeutic approaches of video-assisted thoracic surgery (VATS) and fibrinolysis, which have impacted the modern approach to loculated and chronic empyemas. Finally it will discuss the role of various surgical modalities in the treatment of complex empyemas.

**Pleural Effusions – Classification**

Three very good reviews outline the classification and approach to the patient with a pleural effusion. (3 - 5) Although pleural effusions can be diagnosed through physical examination (dullness to percussion, decreased breath sounds and vocal fremitus, shift of the trachea), they are most commonly found on chest x-rays. A standard upright posteroanterior chest x-ray can detect 150 ml of fluid and the costophrenic angle is blunted with up to 500 ml. The lateral decubitus chest ray is particularly sensitive; if there is layering of fluid 1 cm in thickness the effusion is accessible via thoracentesis - the standard diagnostic test.

Pleural effusions are first classified as transudates or exudates. Transudates, commonly a result of congestive heart failure, nephrotic syndrome or cirrhosis, are generally clear and straw coloured. Exudates occur with parapneumonic effusions, malignancy, tuberculous pleurisy, pulmonary embolism, collagen vascular disease, pancreatitis and other conditions. Transudates and exudates are distinguished on the basis of their protein content. An exudate is characterized by a protein content > 3.0 g/dL and LDH >200, but pleural/serum ratios are more accurate: protein >0.5; LDH > 0.6. (6) Sadly these tests are not available in every African hospital. Measurement of cell count, pH and glucose level and culture of the fluid are particularly important in infectious effusions (see below). Cytologic examination is important in the diagnosis of malignant effusions. Pleural biopsy may play a role. (7) Porcel (8) examined the characteristics of large or massive effusions in 153 patients and found that most were secondary to infections or malignancy.

**Empyema – Infected Effusions**

Para-pneumonic exudative effusions occur in up to 50% of pneumonias. Pleural space infections – empyemas need to be distinguished from these by the presence of an infectious agent, (although culture may be negative in up to 30% of PSIs), their ability to cause morbidity and their need for specific treatment. A number of excellent recent reviews discuss the nature and management of thoracic empyema. (9 - 13) The majority, 40-60%, are post-pneumonic. Infections after thoracic surgery and trauma make up the rest, with about 10% being idiopathic. A rare cause is the pyothorax associated lymphoma arising in chests treated with chronic pneumothorax. (14)

Empyemas have been divided into three stages: 1st or exudative, 2nd or fibrinopurulent and 3rd consolidative or chronic stage. Complex empyemas are multi-loculated. In the exudative stage drainage may not be necessary. However if frank pus is present or culture or gram stain is positive; if pH < 7.2, glucose < 35mg/dL, or LDH >1000 IU/L, then drainage is mandatory and should not be delayed. Azoulay et al (15) used reagent sticks to measure pH, protein content and leukocyte esterase levels and found good correlations with standard laboratory methods and ability to distinguish infectious exudates. This study is particularly relevant to the African context where laboratory facilities are practically non-existent. Where tests such as these may not be available it is better to err on the side of drainage.

Drainage is the sine qua non of empyema treatment. In the early stages before fibrinous deposits have fixed the lung to the underlying chest wall, drainage to an underwater seal must be maintained. In later stages open drainage with rib resection has traditionally been used. Undrained, delayed or inadequately drained pus results in pleural scarring and fibrosis, persistence of the lung collapse and maintenance of the infection. (16) A chronic empyema, which begins about 6 weeks after infection, requires surgical intervention aimed at obliterating the cavity either by VATS or thoracotomy with decortication of the lung and removal of the pleural peel, plus or minus lung resection, or with thoracoplasty bringing the chest wall down to the lung. Bronchopleural fistula complicates the decision process.

**Microbiology**

A wide range of infectious agents have been shown to cause PSI. While culture of pleural fluid must always be done, blood cultures should also be taken in febrile patients. Streptococcus pneumoniae (17) and staphylococcus aureus (18) are generally the most common pathogens in children, but anaerobes (19) and gram negative aerobes such as Klebsiella (20) may predominate in adults. Unusual organisms like Salmonella (21), Yersinia (22), Gemella (21) and fungal disease (24) may cause empyemas; hydatid cysts of the liver may rupture into the pleural space (25); even trichomonas (26) has been isolated. Tuberculous pleurisy is an important entity that will be discussed below.

**Imaging**

While the PA chest xray is the standard tool in the diagnosis of pleural effusion and empyema, other imaging techniques play an important role. (27) One of the major problems in the treatment of empyema is its failure to resolve with tube thoracostomy. (see below) This may occur as a result of the formation of septae and loculations in the pleural space resulting in multiple, non-communicating cavities. Ultrasound plays an important role in the diagnosis of this septation and can predict the success of simple thoracostomy and the need for alternative measures. (28) Image guided drainage can also be carried out.(29 ; 30) CT scan identification of a pleural peel accurately predicts the need for surgery. (31)

**Post-Pneumonic Empyema**

Interest has focused on which patients develop PSI. (33) Multiple factors including underlying patient health, bacterial virulence and promptness of drainage determine clinical outcome in PSI. (34 ; 35) In one retrospective study delaying drainage for 3 days after recognition was associated with an increase in mortality rate from 3% to 16%. Cell mediated immunity is depressed in empyema patients. (36) Treatment failure has also been associated with the presence of antibiotic resistant organisms (37) and with delay in diagnosis and referral.

**Children**

In the last 10 years, only two reports in English are available from Africa on the treatment of post-pneumonic PSI in children.(38 ; 39) In both the mean patient age was five. Fever, cough, dyspnea were the standard presentations with radiologic evidence of pleural effusion. Pneumococci or staphylococci were the most common organisms isolated. No patient in the Ethiopian study and one in the Nigerian study

received thoracotomy and decortication. This may indicate lack of or inadequate utilization of surgical services. The mortality rate ranged from 7-16%. In a recent study of 265 children with empyema from India (40), staphylococcus was the most common organism. Tube thoracostomy failed in 21% of cases classified as fibrinopurulent. Decortication was required in 25% of all thoracotomies, particularly when surgery was delayed. Eastham et al (17) present their experience with 47 children from north England. In 75% of cases an infectious agent was identified of which 86% were pneumococci, although this diagnosis could only be made through the isolation of bacterial DNA. The prior prescription of antibiotics in 96% of cases may have played a role in the lack of positive pleural cultures. PSI complicates 2-8% of pneumonias in children in the US. Schultz et al (41) report on 230 children in Texas over a 10 year period. 32% of pleural cultures were positive. The development and use of pneumococcal vaccine resulted in staphylococci being the most common organism isolated in the later period. Antibiotic resistance was a developing feature.

Adults

Nadeem et al (42) reported on 105 consecutive patients older than 10 years presenting to a Thoracic Surgical Unit in Peshawar, India. The mean duration of symptoms was 6 weeks with 38% having had an unsuccessful drainage prior to admission. The majority of patients required open surgery with a mortality rate of 7%. Cheng (43) reported on 72 patients from California treated with a non aggressive protocol with a mortality rate of 6%. Tsai et al (44) compared empyema in Tawainese adults older than 65 years with younger patients. The older patients had similar mortality rates, but higher morbidity, rates of fungal infection and an increased risk of associated malignancy.

Tuberculous pleurisy and empyema

Tuberculous pleurisy and empyema are discrete clinical entities requiring specific approaches. Pleural effusions may complicate up to 30% of cases of tuberculosis in Africa. (11,12) The association between AIDS and TB is well known. In tuberculous pleurisy the effusion occurs as part of the primary infection. The duration of symptoms is usually long with a mean of 4 months. Chest xray may or may not show typical findings of TB. Early on the pleural fluid shows a typical exudative character, later lymphocytes may predominate. Pleural levels of adenosine deaminase (ADA) are increased. Sputum may be positive for AFB in about 50% of cases. Mycobacteria are cultured in less than 50% of samples of pleural fluid; the yield is improved with histology and culture of pleural biopsies. While tuberculous pleurisy may resolve spontaneously over several months, ATB therapy is indicated.

Tuberculous empyema is a much more serious condition with massive contamination of the pleural cavity as a complication of pulmonary tuberculosis. The pleural fluid is purulent and AFB are more commonly identified. A bronchopleural fistula may be present. Al Kattan et al (45) report on 26 patients from Saudi Arabia. The empyemas were classified using pleural aspirates and CT scan findings. Aspiration and tube thoracostomy were adequate for exudative collections alone, but more advanced stages required other interventions. Decortication, pulmonary resections and open thoracostomies are important treatment modalities. Olgac et al (46) recommended decortication alone in patients with prolonged lung collapse and pleural infection secondary to tuberculosis.

HIV-positive patients

It is uncertain whether PSI is more common in HIV-positive patients but it is more serious. Borge et al (47) reported on 23 HIV-positive patients who were all intra-venous drug users. Most empyemas were secondary to community-acquired pneumonia with staph aureus and gram negative bacilli being the most common organism. Closed thoracostomies and fibrinolytic therapy was used. Patients with AIDS had higher risk of bronchopleural fistula and prolonged hospital stay. Khwaja (48) found that AIDS patients with CD4 counts < 200 had more complex empyemas requiring open drainage and decortication.

Post-Traumatic Empyema

Tube thoracostomy is appropriate and necessary treatment for traumatic pneumothorax and hemothorax. (49) Empyema and pleural fibrosis are significant risks in undrained hemothoraces. Bailey (50) reviewed complications of tube thoracostomy. Empyema occurs in about 2%. Maxwell et al (51) found that post-traumatic empyemas were related to the degree of underlying (particularly penetrating) lung injury and duration of tube placement. Concurrent antibiotics did not appear to be preventative.

Treatment

Antibiotics

Antibiotic therapy, active against the common pathogens causing PSI, should be initiated parenterally in all cases of empyema, before culture reports are available. Since these include pneumococcus, staph aureus, anaerobes and gram negatives, a broad spectrum penicillin with beta-lactamase resistance along with an anaerobic agent is a good choice. Amoxicillin/clavulinate or cefuroxime plus metronidazole are reasonable combinations. Palacios et al (52) found that cefuroxime was as effective as dicloxacillin/chloramphenicol in children. Teixeira et al (53) found significant differences in pleural antibiotic levels among various agents. Aminoglycosides, which are inactivated in pus and low pH, should probably be avoided. Paganini et al (54) found that PSI from penicillin resistant organisms was no more virulent. Surgeons should be aware of local antibiotic resistance.

Nutritional support

Empyema patients are often nutritionally depleted. Nutritional assessment and support is vital to the resolution of the underlying infection.

Drainage

In 2000 the American College of Chest Physicians published a Consensus Statement on the treatment of parapneumonic effusions. (55) They divided patients into 4 groups, on the basis of risk of poor outcome and used quantity of fluid, presence or absence of loculation, fluid culture reports, and pH of pleural fluid, to develop recommendations regarding the necessity of drainage. Basically if the effusion is small and free flowing, the culture negative and the pH>7.2 drainage is unnecessary (groups 1 & 2). If the effusion is greater than ½ hemothorax OR loculated OR culture positive OR pH<7.2 drainage is recommended (groups 3 & 4).

The main cause of treatment failure, morbidity and mortality in empyema is the development of loculated, undrained pus resulting in pleural scarring, fibrosis and chronicity of infection requiring surgical intervention. The objective of treatment is not only to resolve the infection but prevent this progression to chronicity. To succeed prompt and complete evacuation of infected fluid must be achieved.
A number of treatment modalities are available. These include:

**Thoracocentesis** – Repeated ultrasound guided thoracocentesis has been compared to closed thoracostomy in a small study. (54) Excluding patients with massive empyema resulting in mediastinal shift, both modalities had similar number of treatment failures. Intra-pleural fibrinolysis was used as deemed necessary in both groups. I believe that this modality should only be used in the earliest and most responsive cases and mandates extreme vigilance.

**Closed thoracostomy** – Closed chest tube drainage has been the standard first line therapy for empyema throughout the last century. Large bore tubes have historically been inserted to underwater seal and suction applied. Used with antibiotics alone, these have a significant failure rate of up to 50%. Repeated chest x-rays must be taken to ensure prompt evacuation of all fluid. Chest tubes should not normally be clamped. If drainage ceases a chest x-ray should be taken to assess if there is kinking or if residual fluid remains. The tube can be irrigated. If the tube is malfunctioning or drainage less than 100 in 24 hours, it should be removed. A simple suture for closing thoracostomy incisions has been described. (55) If significant fluid remains the next level of intervention should be undertaken. Huang et al (56) determined that pleural fluid WBC<6400/uL and loculation were independent predictors of failure of tube thoracostomy. Pierrepoint et al published a study using historical controls which showed pigtail catheters to be superior to standard chest tubes in preventing the need for surgical intervention. (30)

**Fibrinolysis** – The intra-pleural instillation of fibrinolytic agents has been used to breakdown loculations. Schiza et al (59) reviewed the agents used. Generally 250,000 IU of streptokinase is diluted in 20-100 ml saline and instilled via the chest tube which is clamped for 2-4 hours. Twice daily instillations for three days are routine. This regime is applicable for children as well. (60) Fever and allergic responses have been the most common side effects. The treatment does induce the presence of anti-streptokinase antibodies. (61) The efficacy of fibrinolysis has been carefully scrutinized. Cameron et al (62) examined the published RCTs for the Cochrane Database and concluded there was insufficient evidence to recommend their use. This lack of evidence has recently been resolved with the publication of the MIST study from the UK. (63) This large, multicenter RCT in adults clearly showed no difference between saline and streptokinase chest tube instillation in terms of treatment failures, need for surgery or mortality. Need for surgery and mortality rate were similar in both groups at 15%. A recent RCT from India showed no difference in short term results between streptokinase and saline (none of their patients failed) but a significant reduction in need for delayed surgery in those with multiloculated empyemas who had received streptokinase. (64) Another RCT from South Africa showed a significant improvement in treatment success and avoidance of surgery in streptokinase treated patients after seven days. (65) A recently published RCT from Greece also showed an improved success rate and lowered mortality rate with fibrinolysis compared to tube drainage alone. (66) While the MIST study certainly casts doubt on the value of fibrinolysis, further RCTs and meta-analyses can be anticipated. Although fibrinolysis may not be useful, agents such as DNase, which actually reduce the viscosity of the pus, may prove to be of value. (67)

**Surgery**

The unresolved fibrinopurulent or chronic empyema has always been the province of the surgeon. Open thoracostomy with rib resection and Eloesser flap has been the standard method of open and evacuating the cavity. Thoracotomy and decortication with or without pulmonary resection has historically been reserved for chronic empyemas where lung re-expansion is prevented by pleural fibrosis. The development of video-assisted thoracoscopy (VATS) in the 1980s changed that. (68) Now early exploration of the entire pleural cavity under direct vision could be undertaken without the morbidity of a thoracotomy. However, during this same period, the use of fibrinolysis and the proliferation of imaging techniques, with the application of image guided drainage, have in many cases delayed surgical referral with resulting negative consequences. Avansino et al (69) using a meta-analysis of 23 years of reports on empyema therapy in children has shown that primary operative therapy compares favourably with non-operative therapy. The failure rate is significantly reduced with primary operative therapy as are mortality rates, re-intervention rates, hospital stay, duration of tube and antibiotics. Gates et al (70) focusing on VATS reached similar conclusions. Other individual reports have done the same. (71- 73) Considering recent doubts cast on the value of fibrinolysis, it is clear that all cases of stage 2 empyema which do not resolve promptly with tube thoracostomy or which have thick, multiloculated fluid should have prompt surgical referral. The same is true for all stage 3 empyemas. The Recommendations of the British Thoracic Society BTS (disregarding the comments on fibrinolysis) would form a good basis for therapeutic approach. (74) In light of this the following recommendations can be made:

**Open thoracostomy, rib resection and Eloesser flap**

This historical approach to open surgical drainage is indicated when closed drainage is unsuccessful. VATS is unavailable and adhesive have fixed the lung to the overlying pleura. (75) A variable number of ribs can be resected. It is particularly suitable when the patient is not fit for general anaesthesia. BTS2.16 The cavity has historically been treated with sterilizing solutions such as Dakin’s. Maruyama et al (76) describes a slightly different approach.

**VATS**

Where facilities are available VATS is the procedure of choice for any empyema not promptly (4-8 days) and completely responding to closed thoracostomy. BTS2.15 General anaesthesia and double lumen endotracheal intubation is part of this highly technical, but very effective, modality. (77) Angelillo Mackinlay et al in 1996 favourably compared VATS with open thoracotomy and recommended RCTs to define its role. (78) Sadly only one RCT comparing immediate VATS with fibrinolysis has been published. VATS was deemed to be more effective as a result of a significantly higher treatment success rate, shorter hospital stay and duration of chest drainage. “Medical thoracoscopy”, carried out under local anaesthesia and sedation, has been described. (79)

**Open thoracotomy with or without decortication**

In settings where VATS is not available but where there is adequate surgical expertise, open thoracotomy and drainage of abscess is indicated in stable patients whose empyemas do not respond promptly (4-8 days) and adequately to closed thoracostomy. (80) BTS2.15 Decortication is added if a thick pleural peel prevents expansion of the lung. (81) Lung resection may be necessary if there is a bronchopleural fistula or severely damaged lung.
Empyema

Thoracoplasty

In patients with chronic empyema, collapsed lung and pleural fibrosis who are not fit for thoracotomy, a thoracoplasty can be done to collapse the chest wall onto the lung thereby obliterating the cavity.

Pneumonectomy

Extra-pleural pneumonectomy can be carried for serious damaged lungs in the presence of chronic empyema. (82) Most cases are associated with chronic tuberculosis. This is an operation for experts.

Recommendations

1. All undiagnosed pleural effusions should be aspirated and have their protein and LDH content measured and compared with serum levels. Exudates should have cell counts and differentials, pH and glucose determination, gram and acid fast staining and culture. Urine reagent sticks may be used in the absence of formal chemical analysis.
2. Drainage is appropriate for all parapneumonic effusions which are greater than ½ hemothorax OR loculated fluid OR culture or gram stain positive OR pH<7.2. Other criteria such as frank pus, glucose<35mg/dL or LDH>100IU/L should also be considered.
3. Streptococcus pneumonia and staphylococcus aureus are the major pathogens in children; gram-negative aerobes and anaerobes predominate in adults.
4. Tuberculous pleurisy needs to be distinguished from TB empyema. The former needs only ATB therapy, the later the full gamut of empyema strategies.
5. Chest tubes are important in traumatic pneumo- and hemothorax, but they should be removed as soon as air and blood drainage cease. Risk of post-traumatic empyema is a reflection of underlying lung injury.
6. Ultrasound examination should be undertaken in all pleural effusions and especially those which do not resolve promptly with tube drainage. The presence of septations is an indication of an increased risk of failure of tube drainage and the need for surgical drainage.
7. Antibiotic protocols should be started before definitive culture reports are available. These include amoxicillin/clavulinic acid or a second generation cephalosporin such as cefuroxime plus an anaerobic agent like metronidazole. In patients with penicillin allergy, a fluoroquinone like ciprofloxacin, a carbapenem like imipenem, or perhaps chloramphenicol may be substituted.
8. Nutritional assessment and support should be offered to all empyema patients.
9. Empyemas should be classified as stage 1 – exudative; stage 2 - fibrinopurulent and stage 3 - chronic.
10. Exudative empyemas (stage 1) which are less than ½ hemothorax, are not loculated, with negative gram stain and culture and with pH>7.2 can be treated without drainage. These should be followed very closely with xray and if necessary repeated thoracentesis to diagnose any progression to stage 2 and ensure resolution.
11. In large or loculated stage 1 and all stage 2 empyemas the first line therapy is prompt and adequate drainage, probably with closed tube thoracostomy. Multiloculated collections have a higher risk of failure with tube drainage.
12. Failure of prompt (4-8 days) radiologic or clinical response after tube drainage mandates surgical consultation.
13. In light of the MIST study, the role of intrapleural fibrinolysis in the management of empyema is in doubt.
14. VATS, if available, is the procedure of choice for the evacuation of refractory empyemas. VATS is probably one of the most useful minimally invasive procedures in the African setting and is recognized in the FCS syllabus of COSECSA.
15. In the absence of VATS, thoracotomy, with or without decortication, is indicated in multiloculated, inadequately drained empyemas.
16. All stage 3 empyemas require surgery as first line therapy. Thoracotomy with decortication is required. Lung resection may be necessary in some cases, particularly if there is a bronchopleural fistula. Some cases can be managed by VATS.
17. Open thoracostomy with rib resection and Eloesser flaps should be used in localized and inadequately drained empyemas, particularly when the patient’s condition is poor or expertise lacking.

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Questions

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