Disorders of the Pleural Space: Gas, Liquid, and Solid

Guest Editors: Joseph S. Friedberg and Takashi Nakano
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Editorial
Disorders of the Pleural Space: Gas, Liquid, and Solid

Joseph S. Friedberg¹ and Takashi Nakano²

¹Division of Thoracic Surgery, Department of Surgery, University of Pennsylvania, Philadelphia, PA 19104, USA
²Division of Respiratory Medicine, Department of Internal Medicine, Hyogo College of Medicine, Nishinomiya, Hyogo 19104, Japan

Correspondence should be addressed to Joseph S. Friedberg, joseph.friedberg@uphs.upenn.edu

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This special issue focuses on the pleural space, a unique region of the human body affected by some of the earliest described maladies in medical science yet remaining a mystery in both purpose and function. The two pleural spaces, defined by the bony thorax, diaphragm, and mediastinum, are each occupied by the lungs. Consequently, the pathophysiologic disorders of the space involve not only benign and malignant disorders that take the form of solid masses or effusions, but also gaseous disorders as well.

Ongoing air leakage through the surface of a lung will result in collapse and, if ongoing, will result in a fatal pneumothorax. These are some of the most common problems encountered in the pleural space and are treated, along with other maladies, with tube access of the pleural space. Although a common procedure, it requires technical precision and judgment to avoid potentially disastrous complications, as detailed in this special issue. Embryologic development of the pleural structures, discussed in this special issue, results in planes of dissection and paths of least resistance that can result in unusual and unexpected patterns of air accumulation when the air leaks within the lungs.

The net negative pressure within the pleural space and the positive pressure in the pulmonary arterial circulation and the lymphatic circulation maintain a dynamic equilibrium in pleural space, the net effect being a minimal amount of fluid at any given time despite a high flow from the visceral to parietal pleural surfaces. Perturbation of this delicate balance results in fluid accumulation. Because of the extraordinary number of factors involved in maintaining this balance, it can be very difficult to diagnose the reason for the fluid buildup. Within the context of the overall clinical picture, the diagnosis is often rendered by analysis of the fluid itself. As described in this special issue, there are many tests and criteria accessible to the clinician to diagnose the etiology of the fluid accumulation. When the fluid is caused by a malignancy or noninfectious benign process, it is typically necessary to intervene and stop the fluid accumulation. The most common approach remains pleurodesis, affecting a symphysis between the visceral and parietal pleural surfaces for the purpose of obliterating the space. Using talc for this purpose remains one of the most common, and arguably best, techniques and is described in this special issue.

When the fluid does accumulate and becomes infected, it is called an empyema, and this too can easily escalate into a fatal condition without prompt and appropriate treatment. Although drainage, as first described by Hippocrates over 2000 years ago, remains a critical element of the treatment, there are now multiple tools and techniques available to the clinician to combat this common and lethal disorder. A review of this important topic is covered in this special issue. Although the pleural space is highly resistant and resilient in the face of infectious challenges, the ultimate clearance and recovery most often hinges on full lung expansion with pleural-pleural apposition. When an empyema is not drained early enough, the lung can become encased in a fibrous peel that precludes reexpansion and results in a chronic space. Ideally, the fibrous peel can be surgically resected to reexpand the lung and fill the space. At times, however, the lung will no longer fill space, and this results in a challenging and deadly situation that warrants surgical intervention. As described in this special issue, this can take the form of opening the space to allow full drainage to obliterate the space by filling it with healthy vascularized tissue and/or collapsing the chest wall to meet the lung surface.

The pleural space is a fascinating and enigmatic region of the body maintained in balance by a symphony of
homeostatic mechanisms. Perturbation of this balance by benign or malignant processes can lead to a myriad of problems, unique to the pleural space. Addressing these problems requires an understanding of the embryology, anatomy, and physiology and then combining this knowledge with sound judgment, scientific analysis, meticulous technique, and, at times, a dash of detective work. We hope you enjoy this special issue as it explores these topics.

Joseph S. Friedberg
Takashi Nakano
Review Article

Thoracomyoplasty in the Treatment of Empyema: Current Indications, Basic Principles, and Results

Petre Vlah-Horea Botianu and Alexandru Mihail Botianu
Surgical Clinic 4, University of Medicine and Pharmacy of Târgu Mures, Gh. Marinescu 66/1, Târgu Mures, Romania

Correspondence should be addressed to Alexandru Mihail Botianu, botianu_alexandru@yahoo.com

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1. Introduction

Despite obvious recent advances, empyema remains a challenge for modern medicine. It is a common disease in chest medicine involving important costs and resources, the overall mortality is still high, and the best treatment is still to be defined [1–3]. Surgery is particularly very reluctant to the principles of evidenced-based medicine and very much of the current practice is based on “local protocols” and “personal experience” [4]. The recent recrudescence of tuberculosis (TB) has also brought to attention the pleural complications of this disease [5]. The aim of this paper is to present the current indications, principles, and results of thoracomyoplasty procedures for empyema.

2. Historical Background

Empyema is known since Hippocrates, who described the clinical signs and recommended open drainage using cautery [6]. However, lack of knowledge about the pleural physiology made difficult the early attempts of surgical treatment.

Modern management of the empyema starts with the work of the Empyema Commission led by Bell and Graham during World War I. This Commission was created by the US Army to find a solution to the high mortality of patients with parapneumonic empyema. They found that most deaths were the result of the open pneumothorax with lung collapse and respiratory failure that occurred after drainage. They realized the importance of the negative pleural pressure and of the closed drainage and made clear recommendations that are still valid in our days. As a result of the recommendations of the Empyema Commission, there was a dramatic decrease of the mortality of parapneumonic empyema from an average of 30% to 4.3% [7, 8].

Thoracoplasty was introduced at the end of the 19th century as a procedure to obliterate empyema cavities by collapsing the chest wall [9]. Many procedures have been described and used, more or less original and more or less popular. The most “radical” was the operation described by Schede [10], which involved resection of the ribs, intercostal spaces, and parietal pleura overlying the empyema; healing of the empyema was achieved by putting in close contact the visceral pleura with healthy tissues represented by the chest wall muscles and subcutaneous fat [10–12].

The operation of thoracoplasty was further developed mainly as a technique to achieve healing of TB by collapsing...
the lung and had an important contribution to the development of what is now called general thoracic surgery [13]; however, its popularity declined after the introduction of tuberculostatic drugs in the years following immediately the 2nd World War [14]. In our days, thoracoplasty is performed mainly as a solution for chronic empyema and most authors use the technique described by Andrews [15, 16], with or without different modifications [17–19].

Muscle transposition was performed at the beginning of the 20th century by surgeons like Abrashanoff [20], Robinson (1915), Eggers [21], or Archibald [22], but most data published before 1960 were case reports or small series. The technique did not become very popular mainly due to the absence of conditions allowing major thoracic surgery (anesthesia, transfusion, antibiotics, etc.). It became popular in the 1980–90s mainly due to the work of the surgeons (thoracic and plastic-reconstructive) from the Mayo Clinic who showed the value of different muscle flaps in the treatment of severe intrathoracic infections [14, 23, 24].

3. Modern Indications

From the very beginning, it must be clearly stated that thoracomyoplasty procedures address to a very small group of patients with empyema. First of all, most patients with parapneumonic effusions and empyema can be cured by antibiotics and thoracocentesis or tube-thoracostomy, with no need to perform major surgery [25]. If this is required, the first option is lung decortications, which obliterates the space by reexpanding the lung and has several very important advantages: no chest wall mutilation, functional recovery of the collapsed lung, and no significant long-term sequelae [26]. The possibility to perform this procedure using a minimally invasive approach makes it even more attractive by reducing the morbidity and the postoperative pain and by improving the esthetic aspect [27]. Decortications performed through video-assisted thoracic surgery (VATS) is now the first option for most patients with empyema requiring major surgery [28].

However, lung decortication (open or VATS) requires two major conditions in order to be successful. First, there must be a cleavage plane allowing to decorticate the lung; if this plane does not exist or is not clearly defined, the procedure becomes difficult or even impossible due to the bleeding and air leaks that occur during the dissection. Second, the underlying lung parenchyma must have the ability to reexpand and completely obliterate the pleural space. If these two conditions are not fulfilled, lung decortications becomes a hazardous and very risky procedure and thoracomyoplasty becomes an option that should be taken into consideration [29].

Therefore, thoracomyoplasty for empyema is nowadays indicated in the following situations:

(i) absence of a cleavage plane allowing to decorticate the lung,
(ii) inability of the lung to reexpand and completely fill the pleural space,
(iii) postoperative empyema, where decortication is not possible or has failed,
(iv) presence of bronchial fistulae: their safe closure is mandatory and suture-reinforcement using muscle flaps, with or without a thoracoplasty, is a good and safe option,
(v) presence of unresectable lesions in the lung parenchyma: this diseased space must also be filled with well-vascularized tissue.

TB empyema is not by itself an indication for thoracomyoplasty, although, in the past, different collapse techniques were used to treat TB. However, TB patients with prolonged medical treatments and parenchyma lesions present more frequently with the aforementioned features, making them candidates for thoracomyoplasty. In our experience with this kind of surgery, almost one half of the cases had different forms of TB disease.

Thoracomyoplasty involves opening of the chest, resection of some parts of the chest wall, and dissection of muscle flaps on large areas. Therefore, it is a major procedure and the ability of the patient to tolerate it should be clearly assessed when planning the surgery. The preoperative evaluation should be basically the same as for any major thoracic procedure [30]. Due to the esthetic disturbance of the chest, thoracomyoplasty procedures are less attractive for young and female patients.

This kind of surgery involves a certain degree of chest wall mutilation and some functional impairment. As a matter of fact, one of the main objective of the modern techniques is to minimize these adverse effects. However, these aspects must be clearly discussed with the patient before the operation and a written consent should be obtained [31, 32].

4. Basic Principles and Techniques

4.1. Preoperative Preparation. It is essential in this kind of surgery. Most patients present with an altered biological status secondary to the infection and significant associated diseases requiring a careful reequilibration. Antibiotics should be administered according to the sensitivity of the microorganisms involved. Local control of infection should be achieved by thoracocentesis, tube-thoracostomy, or even open-window. Daily lavages of the empyema cavity are required to achieve an operative field as clean as possible.

4.2. Planning the Procedure. It must be done very carefully and several factors should be clearly assessed:

(i) location and dimensions of the empyema cavity, which can be well evaluated using modern CT scans with 3D reconstructions;
(ii) presence or absence of bronchial fistulae, whose safe closure is mandatory;
(iii) available flaps—previous surgery may damage some of the vascular pedicles, making some flaps impossible to raise—that is, myocardial revascularization
using the mammary artery or subcostal laparotomy compromise the ipsilateral rectus abdominis, standard posterolateral thoracotomy sections, the latissimus dorsi, and so forth;

(iv) the morbidity generated by the use of a certain flap and the complexity of the mobilization.

4.3. Technical Details. In most cases a posterolateral thoracotomy skin incision is made. After sectioning of the subcutaneous fat, the latissimus dorsi and the serratus anterior are mobilized partially to allow access to the empyema cavity. After entering the empyema cavity, the topography of the lesion is carefully evaluated and the final decision is made. We prefer to start with a complete mobilization of the flaps, according to the topography of the lesions:

(i) the latissimus dorsi muscle:

(a) the standard mobilization is based on the thoraco-dorsal vessels, resulting in a large flap that reaches almost any part of the thorax [33]; it is probably the most used flap in both plastic-reconstructive and thoracic surgery,

(b) the reversed latissimus dorsi flap is based on the secondary blood supply represented by some perforator branches from the last intercostal and first lumbar vessels: it is a much more difficult flap with a variable anatomy and limited arch of rotation, but it may be a good solution for defects located in the supradiaphragmatic area [34, 35];

(ii) the serratus anterior has as main blood supply a branch from the thoraco-dorsal vessels (not recognized by the Nomina Anatomica) which allows the mobilization of the entire muscle. The secondary blood supply represented by the lateral thoracic vessels supports only a limited portion of the muscle. When a full mobilization of the serratus anterior is performed, it results a flap with a volume that is comparable with the latissimus dorsi and can reach any point located in the upper half of the thorax, including the hiliar region [35, 36]. Due to the common blood supply, the latissimus dorsi and the serratus anterior may be raised together using the thoraco-dorsal vessels;

(iii) the pectoralis major may be raised in more ways:

(a) using the thoracoacromial vessels, which results in a flap with good mobility that is useful for defects located in the apex of the chest,

(b) using the perforator branches from the internal mammary and the anterior intercostal vessels, which results in a flap with a limited mobility suited for defects located in the upper paramediastinal area [37, 38];

(iv) the rectus abdominis flap can be raised using the superior epigastric vessels, which continue the internal mammary artery and vein; although the tip of this flap may reach the base of the neck, it is usually used for defects located in the lower half of the chest [39];

(v) the omentum—although it is not a muscle, it is used with the same purposes and principles; it is mobilized using the left or right gastroepiploic vessels and brought inside the chest through a small diaphragmatic opening. It is an excellent material for closure of large bronchial fistulas [40];

(vi) other flaps rarely used to fill an infected pleural space include the trapezius, subscapularis, infraspinatus, external oblique, and teres major. In the available literature, there is no important experience with them and they should be taken into consideration mainly when other more common neighbourhood muscles are not available [41, 42].

Introduction of the flaps inside the chest requires a second opening, which is done by a limited rib resection (10–15 cm length, no more than one rib) to allow safe passage of the flap and its blood supply. The flaps must reach the defect without any tension or torsion. At the end of the procedure, the muscle flaps must remain with a good blood supply, both arterial and venous. As for any procedure that involves muscle flaps, severe ischemia with necrosis will result in complete failure of the operation [32].

Associated thoracoplasty is often necessary to achieve complete obliteration of the infected pleural space. In opposition to many classic procedures based on extensive rib resection, thoracoplasty should be as limited as possible to avoid major chest deformity and long-time sequelae. Rib resection must never expand beyond the edges of the empyema cavity. We also believe that preservation of the first rib is mandatory to avoid shoulder asymmetry and functional disturbances. When mobilized carefully, the muscle flaps may fill most of the empyema cavity, as well as the dead angles and the cul-de-sacs, thus reducing the extent of the rib resection. The resection of the ribs should be made using a subperiosteal plane, thus allowing some regeneration of bone tissue, which improves the long-time rigidity of the chest wall. Creation of intercostal flaps is very easy after thoracoplasty, by simply sectioning the remaining pleuro-periosto-intercostal plane through the bed of the resected ribs.

At the end of the procedure, the empyema cavity must be completely obliterated by this combination of muscle flaps and thoracoplasty. Especially for big cavities, a certain compromise must be found to avoid both mobilization of multiple muscle flaps and an extensive chest wall resection (Figures 1 and 2).

Drainage of the empyema cavity is mandatory; we usually use an irrigation-aspiration system that allows not only drainage of the cavity, but also postoperative lavages with different antibiotic and disinfectant solutions. If the mobilization of the flaps is an extensive one (as it happens in most cases), the subcutaneous space must also be drained to avoid postoperative seroma. The wound is closed primarily with separate stitches [30, 35].
Figure 1: Anatomic drawing of the blood supply of the most used extrathoracic muscle flaps that are transposed inside the chest to obliterate infected spaces. From Miller et al.—Single-stage complete muscle flap closure of the postpneumonectomy space: a new method and possible solution to a disturbing complication, Ann Thorac Surg 1984; 38: 227-31.

Figure 2: TB empyema with multiple bronchial fistulae solved by thoracomyoplasty—personal collection. (a) Aspect of the cavity with multiple large bronchial fistulae (encircled area). (b) The latissimus dorsi and serratus anterior flaps. (c) Closure-reinforcement of the bronchial fistulae. (d) Final aspect at the end of the procedure. Note the associated rib resection and the complete obliteration of the empyema cavity with the use of the muscle flaps.
5. Personal Experience and Results from the Literature

We started to use thoracomyoplasty with extensive mobilization and intrathoracic transposition of flaps since 2003 and have recently published a detailed analysis of our first 76 cases [35, 43, 44]. This is a group of desperate patients with intrathoracic infections that were not amenable for lung decortication and/or resection. As particular clinical and pathological aspects of our small series, we mention the high proportion of

(i) active TB cases (36 cases, 47%) with 28 patients still having positive bacteriologic cultures and 7 patients with multi-drug-resistant infections,
(ii) postoperative empyema (13 patients, 17%),
(iii) frank intrapleural rupture of a pulmonary cavity (18 patients, 24%),
(iv) bronchial fistulae (26 patients, 34%).

In our series, we encountered an overall mortality of 5% (4 patients). Local complications included recurrence of the intrathoracic infection in 4 patients (5%) that required a modified open-window procedure, minor skin necrosis solved by simple excision in 3 patients (4%), and external thoracic fistula solved by local lavages in 2 patients (3%). Postoperative hospitalization ranged between 4 and 180 days with an average of 40 ± 5 days (confidence level: 95%). At 3-month followup, 66 patients (91%) of the survivors returned to an almost normal life compared with their preoperative status.

Other authors have recently published their experience with this kind of surgery (with or without different technical details) with quite similar results, showing that in selected cases thoracomyoplasty may be a valuable solution [19, 45–49]. There seems to be a an overall mortality around 5% with a success rate (defined as chest closure and cure of the empyema with no recurrence of the intrathoracic infection) of over 90%.

There are many unsolved problems since due to the rarity of these procedures and the great heterogeneity of the patients we cannot talk about randomized studies or even fair retrospective comparisons. As a direct result, some questions are still to be answered: which is the best flap and when and how a certain flap should be mobilized, what is the number of flaps that should be mobilized, what should be the extent of rib resection, and so forth.

6. Conclusions

Thoracomyoplasty remains a valuable surgical solution for difficult empyema cases not amenable to lung decortication. Its value comes from the fact that it may be one of the last solutions for some desperate cases. It achieves healing by immediate complete obliteration of the empyema cavity. Compared to classic thoracoplasty procedures—including the operation described by Andrews—the use of muscle flaps mobilized using techniques borrowed from plastic-reconstructive surgery helps improving the results mainly by limiting the extension of the rib resection and by filling the empyema cavity with a well-vascularised tissue, which is able to fight against infection and promote healing. Although not commonly indicated in our days, thoracic surgeons should be familiar with this kind of procedures [50].

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Review Article

The Radiological Manifestations of the Aberrant Air Surrounding the Pleura: In the Embryological View

Shih-Yi Lee,1,2 Chih-Hao Chen,2,3 Chin-Yin Sheu,2,4 Julie Hua Ying Tai,5 Sheng-Hsiung Yang,1,2 and Chao-Hsien Chen2,6

1 Division of Pulmonary and Critical Care Medicine, Mackay Memorial Hospital, Main Branch Hospital, Taipei 10449, Taiwan
2 Mackay Medicine, Nursing and Management College, Taipei 10449, Taiwan
3 Department of Thoracic Surgery, Mackay Memorial Hospital, Main Branch Hospital, Taipei 10449, Taiwan
4 Department of Diagnostic Radiology, Mackay Memorial Hospital, Main Branch Hospital, Taipei 10449, Taiwan
5 Semmelweis University, Budapest, Hungary
6 Division of Chest, Internal Medicine, Mackay Memorial Hospital, Main Branch Hospital, Taipei 10449, Taiwan

Correspondence should be addressed to Shih-Yi Lee, leesyi5538@yahoo.com.tw and Julie Hua Ying Tai, juliehuayingtai@gmail.com

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The radiological manifestations of the aberrant air surrounding the pleura are varied because of the air outlining the organs in and out of the visceral space. The continuity of the visceral space from the neck, mediastinum to the retroperitoneum is originated from embryological development, which is compatible with the findings through laboratory experiments, cadaveric anatomy, and thoracic computer tomography image. We reviewed the embryo development to understand the anatomy of body cavity, which can determine the radiological findings of pneumomediastinum and pneumothorax.

1. Introduction

During respiration, both lungs freely expand and collapse in the pleural space within the thoracic cavity. The pleural cavity, namely, is a space lined with pleura. The parietal pleura accompanied with ribs, muscles, and skin constitutes the thoracic wall. The visceral pleura covers the surface of both lungs (Figure 1).

The visceral pleura overlies both lungs in addition to the organs in the mediastinum [1] (Figure 2). It encloses a space, which is known as visceral cavity. The visceral cavity is continuous from the neck to upper abdomen (the level of T2 to L1). These anatomical relationships are established as early as embryo development and greatly influence the radiological signs of aberrant air surrounding the pleura, pneumothorax, and pneumomediastinum [2–4].

Embryo development occurs in the period of 3rd to 8th week of gestational age. The three layers of the germ disc (ectoderm, mesoderm, and endoderm) gives rise to specific tissues and organs [5]. The following cephalo-caudal and lateral foldings of the germ disc establishes the primal spatial relationships of the fetus among different tissues and organs, including thoracic and abdominal cages, pleura and peritoneum, trachea, and intestine.

In this review, we will focus on the formation of the continuum of visceral space during embryo development and its relationships to the radiological signs of aberrant air surrounding the pleura.

2. The Body Cavity Formation

After fertilization of the human ovum, the zygote procedes to several stages of development: morula, blastocyst, implantation, bilaminar germ disc, trilaminar germ disc, embryonic period, and fetal period.

In the embryonic period, the lateral folding of the trilaminar germ disc forms the embryo in three-layer tube-like shape (Figure 3). This establishes the primitive anatomical
Figure 1: The thoracoscopic image shows the pleura overlaying the tissue and organs in the thoracic cavity: chest wall (1) and the lung (2).

Figure 2: The thoracoscopic image shows the pleura overlaying the tissue and organs in the mediastinum: heart (1), descending aorta (2), inferior pulmonary ligament (3), and diaphragm (4).

Figure 3: Diagram shows the model of lateral folding of germ disc.

Figure 4: Lateral folding of germ disc in the level of pharyngeal arches. Diagram shows the cells in the mesoderm proliferates and neural tube is forming.

relationships of the embryo: ectoderm on the surface, mesoderm in the middle, and endoderm inside. Nevertheless, this also shows the anatomical relationships of embryo on the level of pharyngeal arches [5] (Figure 4).

The embryo below the level of pharyngeal arches develops to the body cavity, which is originated from the mesoderm on each side of the midline. The cells in the lateral plate of mesoderm starts to divide into the parietal and visceral mesoderms to form the intracellular cavities. The results of the lateral folding develops the parietal mesoderm and the ectoderm to form the body wall; the visceral mesoderm and endoderm to form the gut wall; the intracellular cavities within the mesoderm to form the intraembryonic coelomic
The visceral space around the esophagus, stomach, intestine, trachea, descending aorta, and azygos vein is called posterior mediastinum compartment, or post-vascular space [4, 6] (Figure 6). The visceral space from the neck to the upper abdomen, surrounded by the visceral fascia, is originated from the visceral mesoderm. The intraembryonic coelomic cavity of embryo is separated into the thoracic and abdominal cavities, after the pleuroperitoneal membrane and the transverse septum transforms into the diaphragm. The visceral facia in these two cavities, which is originated from the visceral mesoderm, becomes visceral pleura and peritoneum. The diaphragm does not hinder the continuity of the visceral mesoderm overlaying the gut. Therefore, the visceral space is continuous in the posterior mediastinum [4, 6] (Figure 6).

The space surrounding the pericardial and aortic fascia is known as middle mediastinum compartment or vascular space [7]. The formation of the pleuropericardial membrane of embryo separates to create a pericardial cavity within the thoracic cavity (Figure 7). However, the pericardial cavity and the post-vascular space of the thoracic cavity remains continuous by the vascular fascia (Figure 6). The angiogenic cell clusters, which are derived from the visceral mesoderm, transform into the cardiovascular system. These angiogenic cell clusters form the bilateral endocardial tubes. Accompanied with the cephalocaudal and lateral flexion of the germ disc, one end from each endocardial tubes fuse in the midline to develop the heart (Figures 7). The other end of the endocardial tubes unite in the midline of the embryonic shield to form the aortic arches. The aortic arches arise from the aortic sac and terminate at the dorsal aorta, forming lastly the arch of aorta. Since the aortic sac is the most distal part of the truncus arteriosus of the heart [5], the heart in the pericardial cavity is connected to the descending aorta through the aortic arch. Hence, the pericardial cavity and post-vascular space are continuous through the aortic fascia [6, 7] (Figure 7).

In the Zylak classification of mediastinum, the thoracic space anterior to the pericardium is the anterior mediastinum. Since the thymus originated from the third pharyngeal arch migrates caudally and medially into the anterior portion of the thoracic cavity [5], the upper portion of anterior mediastinum is continuous to the neck.

The peribronchial and visceral spaces are continuous through each hilum. The lung bud is the respiratory primordium, which is an outgrowth of the ventral wall of the foregut. The right lung bud is divided into three branches, while the left one is divided into two branches. It then extents caudally and laterally, and penetrates into the thoracic cavity [5] (Figure 6). Therefore, the hilum where the lung buds enter pleural cavity becomes the channel between lung interstitium and visceral space.

### 3. The Compartmentalization of the Mediastinum and the Continuum of the Visceral Space of the Mediastinum

Although the body cavity is further divided into thoracic, abdominal, and pericardial cavities by the pleuropertitoneal and pleuropericardial membranes, the cavities remain continuous throughout the visceral space [5].

### 4. The Radiological Manifestations of Aberrant Air Surrounding the Pleura

The embryonic development of compartmentalization of the mediastinum, and the continuum of the visceral space and its surrounding tissues, is associated well with the findings of the laboratory experiments [6, 8], cadaveric anatomy [7],
Figure 6: Diagram shows that the formation of the continuity of the fascial planes connects cervical soft tissue with the mediastinum to the retroperitoneum. The space between fascia permits aberrant air arising in any of these areas to spread elsewhere.

5. Conclusion

The embryo development establishes the anatomy of body cavity. The compartmentalization in the body cavity and the continuum of the visceral space has significant impact on the radiological manifestations of pneumomediastinum and pneumothorax. It is crucial to review the radiological manifestations of the aberrant air surrounding the pleura from the embryological view.

Conflict of Interests

The authors declare no conflict of interests.

Disclosure

One of the authors certifies that all his affiliations with or financial involvement in, within the past 5 years and foreseeable future, any organization or entity with a financial interest in or financial conflict with the subject matter or materials...
Figure 7: Heart and pericardial cavity formation. Diagram shows that bilateral angiogenic cell cluster originated from the mesoderm fused in the midline along with lateral folding of germ disc and forms the heart and the visceral pericardium. The parietal mesoderm then forms the fibrous and serous layer of parietal pericardium.
1: peribronchial space
2: neck
3: chest wall
4: pleural cavity
5: mediastinum
6: peritoneum
7: pericardial cavity
8: paracardial space
9: thymic region
E: esophagus
T: trachea
Thy: thymus
(a)

Figure 8: Continued.
Figure 8: Air flow in the pneumomediastinum: peribronchial space (1); neck (2); chest wall (3); pleural cavity (4); mediastinum (5); retroperitoneum (6); pericardial cavity (7); paracardial space and diaphragm (8).
discussed in the paper are completely disclosed (e.g., employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, royalties).

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Review Article
Management of Infectious Processes of the Pleural Space: A Review

Ankur Girdhar, Adil Shujaat, and Abubakr Bajwa

Division of Pulmonary and Critical Care Medicine, UF College of Medicine at Jacksonville, 655, 8th Street west, Jacksonville, FL 32209, USA

Correspondence should be addressed to Ankur Girdhar, ankurgirdhar@yahoo.com

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Pleural effusions can present in 40% of patients with pneumonia. Presence of an effusion can complicate the diagnosis as well as the management of infection in lungs and pleural space. There has been an increase in the morbidity and mortality associated with parapneumonic effusions and empyema. This calls for employment of advanced treatment modalities and development of a standardized protocol to manage pleural sepsis early. There has been an increased understanding about the indications and appropriate usage of procedural options at clinicians’ disposal.

1. Introduction

Any effusion that occurs secondary to an infectious process in the lung parenchyma such as pneumonia or lung abscess is defined as a parapneumonic effusion. A complicated parapneumonic effusion requires an invasive procedure for resolution and usually a bacterial organism can be cultured from the pleural fluid [1]. When a parapneumonic effusion progresses to become frank pus, it is labeled as empyema. Parapneumonic effusion and empyema are both important medical conditions associated with significant morbidity and mortality.

Infection of the pleural space affects approximately 60,000 individuals in the USA annually and has approximately 15% mortality [2]. About 40% of all patients diagnosed with pneumonia have an associated pleural effusion, out of which only a few require active intervention for resolution [1, 3, 4]. Recent epidemiologic studies have indicated that the incidence of empyema has been increasing in the last two decades [5, 6].

In view of the increasing incidence and considerable mortality and morbidity associated with pleural infections, there is a need to utilize modern principles of empyema management that will promote early diagnosis and prompt pleural drainage. It has been observed that any delay in initiating effective drainage can result in prolonged hospital stay, requirement of an invasive procedure for drainage, and further increase in mortality and morbidity [1, 7–9] (Table 1).

2. Pathophysiology of a Parapneumonic Effusion

Any inflammation due to an infectious process in the lung parenchyma leads to disturbance in the delicate balance between formation of pleural fluid and its clearance resulting in accumulation of fluid in the pleural space. This pleural fluid initially can be sterile but if left untreated can progress to become an empyema. This progression occurs in three stages (Table 2) [10].

At the very beginning, inflammation due to pneumonia in the lung parenchyma increases vascular as well as visceral pleural membrane permeability by molecules like vascular endothelial growth factor (VEGF) and there is outpouring of inflammatory fluid in the pleural space [11]. This is known as the exudative phase. At this stage, the pleural fluid is nonviscous, free-flowing, and readily drained by thoracentesis or chest tube. During this stage, pleural fluid culture is negative for bacteria, fluid pH is >7.20, the glucose
level is within the normal range and lactate dehydrogenase remains <3 times the upper limit of normal [12].

If the inflammation proceeds unabated, it leads to purulent and increasingly viscous pleural fluid, which is now rich in inflammatory cytokines like IL-1 and TNF-α. IL-1 induces mesothelial cells to release transforming growth factor (TGF-β) which is one of the most potent fibrogenic agents ever discovered [13]. This second stage called fibrinopurulent phase is characterized by positive parapneumonic effusions [14]. Pleural infection during this stage may respond to antibiotics and chest tube drainage but often requires invasive intervention. This is because of the continuing inflammation that there is a deposition of fibrin over the visceral pleura which in turn results in the formation of adhesions that impede lung re-expansion during attempts at fluid drainage. When the pleura is inflamed, the amount of fibrin that is laid down is the result of the balance between fibrinogenesis and fibrinolysis. Fibrogenesis occurs when the factors that favor fibrogenesis such as TNF-α, TGF-β, and plasminogen activation inhibitor-1 (PAI-1) are dominant. Fibrinolysis occurs when more fibrin is being broken down than is being created [15]. If a fibrinopurulent effusion remains undrained, fibroblasts eventually deposit fibrotic tissue that encases the lung in inelastic peels [16–18]. At this organizing phase, thick pleural peel restricts chest mechanics and often requires surgical decortications to address restrictive impairment.

### 3. Bacteriology

The bacteria isolated from infected pleural effusion vary significantly between community- and hospital-acquired infections. Maskell et al. conducted a large prospective MIST 1 trial (Multicenter Intrapleural Sepsis Trial 1) in 2005 [19]. In their study, 430 subjects were enrolled from 52 centres in the United Kingdom. Positive pleural cultures were found in 232 (54%) of the subjects. The most common pathogen isolated was Staphylococcus milleri group (29%), followed by Staphylococcus (21%) and Streptococcus pneumonia (16%). Only 15% of effusions had anaerobes. Less common organisms responsible for community-acquired infection include other staphylococci, enterobacteria, Haemophilus influenzae, Pseudomonas spp., tuberculosis, and Nocardia. In an earlier study [20], it was reported that nosocomial pleural infections were most commonly caused by methicillin-resistant Staphylococcus aureus (27%), other staphylococci (22%) and enterobacteria (20%). Similar results were seen in a recent study of empyema in the intensive care unit setting by Tu et al. [21]. They found that Klebsiella pneumoniae was the most isolated microbe and also there was a high prevalence of polymicrobial infection. Even though the MIST 1 trial showed a low incidence of anaerobic organisms causing pleural infections, it is well known that they are difficult to isolate by culture of fluid and/or blood. Previous studies have shown that anaerobic bacteria were cultured in 36

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### Table 1: Pleural infections staging and recommended drainage [7].

| Category | Pleural space anatomy | Pleural fluid chemistry | Risk of poor outcome | Drainage |
|----------|-----------------------|-------------------------|----------------------|----------|
| 1        | Minimal free-flowing effusion (<10 mm on lateral decubitus) and Gram stain and culture results unknown | Very low | No |
| 2        | Small to moderate free-flowing effusion (≥ 10 mm and less than one half hemithorax) and Negative Gram stain and culture | Low | No |
| 3        | Large, free-flowing effusion (≥ one half hemithorax), loculated effusion, or effusion with thickened parietal pleura or Positive Gram stain and/or culture | Moderate | Yes |
| 4        | Empyema pus | High | Yes |

### Table 2: Different stages in the evolution of an infected pleural effusion with associated pathological changes and pleural fluid findings.

| Phase         | Pathology                      | Pleural fluid findings |
|---------------|--------------------------------|------------------------|
| Exudative     | Increased permeability of vascular and visceral pleural membranes VEGF     | Nonviscous Free flowing Readily drained Pleural fluid Cx negative |
| Fibrinopurulent| Fibrin deposition on visceral pleura Locules formation IL-8, TNF-α | pH > 7.20 Glucose within normal ranges LDH < 3 times ULN Viscous More viscous Pleural fluid Cx positive Typical "complicated" effusion |
| Organizing    | Fibroblast entry Pleural peel TGF-β | Thick pus Very viscous pH < 7.20 Glucose < 40 LDH > 3 times ULN |

LDH: lactate dehydrogenase. 
ULN: upper limits of normal. 
VEGF: vascular endothelial growth factor. 
IL-8: interleukin 8. 
TNF-α: tumor necrosis factor-alpha. 
TGF-β: transforming growth factor-beta.
to 76 percent of human empyemas [22, 23] with predominant organisms isolated being *Fusobacterium nucleatum*, *Prevotella* sp, Peptostreptococcus, and the *Bacteroides fragilis* group although B. fragilis is relatively rare [22, 24, 25].

4. Therapeutic Approaches to Manage Pleural Infections

There are very few randomized trials regarding management of pleural infections. This limits the evidence base to small observational reports and expert opinions leading to considerable variation in the treatment of individual patients. Depending on institutional expertise, the management of pleural infections can range from noninvasive treatment such as observation and antibiotic therapy to aggressive as well as invasive procedures like therapeutic aspiration, tube thoracostomy and intrapleural fibrinolytics, thoracoscopy, thoracotomy, or open drainage [12].

In recent times, application of these treatment modalities has been greatly aided by advanced imaging studies. With various imaging as well as treatment options at our disposal, there is a need for development of a multidisciplinary approach that can coordinate pulmonary, thoracic surgery, and interventional radiology expertise.

4.1. Antibiotics. Almost all patients with parapneumonic effusion will need antibiotic coverage. This coverage can be to treat the pneumonia or empirical coverage for a suspected pleural sepsis [1]. Even if the pleural fluid cultures are negative and there is a strong suspicion of pleural infection, clinician should initiate an empiric anaerobic coverage as an anaerobic infection will not grow well on culture media. According to the bacteriology listed for a community-acquired infection before the first choice will include intravenous amoxicillin with clavulanic acid or a combination of a second-generation cephalosporin (e.g., cefuroxime) and metronidazole or clindamycin if patient is penicillin allergic.

Figure 1: A series of CT images done in patient with parapneumonic effusions. (a) CT image showing a free flowing pleural effusion (r) with a meniscus formation (arrow). There is also some fluid in the fissure on the left side (L). (b) A loculated pleural effusion with loculations seen in the pleural space (arrows). (c) A chronic pleural effusion showing marked pleural thickening (arrows).
patients with nosocomial empyema need adequate Gram-negative coverage, as Gram-negative infections are more common in nosocomial empyemas. Coverage should include at least a carbapenem or an antipseudomonal penicillin (e.g., piperacillin/tazobactam), or third- or fourth-generation cephalosporins (e.g., ceftazidime, cefepime) with metronidazole. If there is a suspicion for MRSA, coinfection vancomycin or linezolid can be added. The single exception is that aminoglycosides may be inactivated at low pleural fluid pH [27].

4.2. Serial Thoracentesis. Therapeutic thoracentesis has been used for the treatment of parapneumonic effusions for almost two centuries [28]. In recent times, treating empyema or complicated parapneumonic effusions with serial therapeutic pleural aspirations has been largely abandoned. There have been no controlled studies comparing therapeutic thoracentesis with small-tube thoracostomy in the treatment of patients with complicated nonloculated parapneumonic effusions. Most of the recommendations are from some centers [29, 30] who advocate that patients should have daily therapeutic thoracentesis with or without pleural lavage in case of recurrence of infected effusions after initial thoracentesis to allow the pleural fluid to freely flow without any formation of locules until antibiotics resolve the infection. This approach may require an average of eight thoracentesis in >2 to 4 weeks. This was shown in a recent study done by Simmers et al. [31] in which they were able to successfully treat 24 of 29 patients with parapneumonic effusions by means of alternate-day ultrasound-guided pleural aspirations. This approach required that the patients undergo an average of 7.7 ± 3.5 thoracentesis with an average hospitalization of 31 days.

4.3. Chest Tube Drainage. Current indications for chest tube drainage are the aspiration of frankly purulent pleural fluid, the identification of organisms on pleural fluid Gram stain or culture, or a pleural fluid pH < 7.2 in the clinical setting of a pneumonic illness [32]. As an exception in a very large simple parapneumonic effusion, chest tube drainage may be done for symptomatic relief. According to old literature, chest tube drainage is most commonly achieved by a standard (24–28 french) intercostal chest drain, that is, positioned in the dependent part of a free-flowing pleural effusion (most often the posterior costophrenic recess). Using an imaging modality like ultrasound for inserting chest tube is advised as thickened parietal pleura, adhesions, or loculations often complicate insertion. Complete re-expansion of the lung, as demonstrated by repeat imaging, resolution of clinical and laboratory signs of infection, and avoidance of surgical drainage, defines successful drainage.

Till recent times, the common thinking was that smaller bore chest drains are likely to fail in the presence of pus with a high viscosity. However, some prospective studies [33–35] have found that 8- to 12-french pigtail catheters or 10- to 14-french catheters inserted with the Seldinger technique under US or CT guidance (Figure 2) were at least as effective as larger catheters inserted without imaging. Occlusion of the smaller drains can be avoided by the use of suction (20 cm H2O) and regular flushes (e.g., 30 mL normal saline every 6 hours). If the patient has not demonstrated significant improvement within 24 h of initiating tube thoracostomy, either the pleural drainage is unsatisfactory or the patient is receiving the wrong antibiotics. Unsatisfactory pleural drainage can be due to the tube being in the wrong location, loculation of the pleural fluid, or a fibrinous coating of the visceral pleura, which prevents the underlying lung from expanding. If drainage is inadequate, ultrasonography or a CT scan should be obtained to delineate which of the above factors is responsible. Data is still lacking to define the right time to remove the chest drain and thus general recommendations are to remove the drain when the daily output falls to less than 150 cc for 2 consecutive days, in the setting of clinical and radiographic improvement.

The evidence base developing for small bore drains estimates a failure rate of 19% with their use in draining empyema [36]. A very recent study [35] of 71 complicated parapneumonic effusions and 70 empyemas drained with ultrasonographically guided small catheters showed a success rate of 80% (48/60) when the initial ultrasonography did not reveal significant loculations. In those patients with a complex septated pattern on ultrasonography, the success rate was still 51% (41/81). Authors concluded that the threshold for using fibrinolytics and large-bore catheters should be low in empyema.

Long-term indwelling catheters (Figure 3) are being increasingly used to drain malignant pleural effusions. Development of infection in the pleural space has been cited as a complication of this product. An article was published in 2008 [37] with two reports of use of indwelling catheters to treat pleural infection. The first case had a persistent bronchopleural fistula and the second case had esophageal rupture due to necrotizing TB lymphadenitis resulting in development of empyema in both cases. These cases suggested that small-bore indwelling catheters can have as successful outcomes as open drainage procedures and in addition provide patients with better quality of life during sustained pleural drainage. The current understanding is that during the early phase of pleural infection, short-term fine-bore pigtail catheter drainage can be useful, while for chronic pleural infection, long-term drainage can be effective without the problems of catheter blockage or tract infection. This approach needs validation with larger patient samples and randomized trials.

4.4. Intrapleural Fibrinolytics and DNase. Drainage of pleural fluid becomes challenging when there is formation of loculations inside the pleural cavity which resist drainage with a single chest tube. This has generated considerable interest in the use of intrapleural fibrinolytic agents and DNase (Table 3), which may facilitate fluid drainage by dissolving fibrinous adhesions. Development of dense layers of fibrin and loculations in a complicated parapneumonic effusions and empyemas are as a result of the procoagulant state within the pleural space as discussed in the pathophysiology of pleural infections. It, therefore, seems
highly plausible that intrapleural fibrinolytics given early in the fibrinopurulent phase should prevent loculations and promote pleural drainage. Small studies \[38–41\] have reported the beneficial effects of therapy with streptokinase, urokinase, and rtPA for avoiding surgery and improving the radiographic appearance of loculated effusions. Based on these early reports of efficacy from smaller studies, the BTS \[26, 42\] and the ACCP \[7\] (Table 1) guidelines have recommended fibrinolytic drugs as possible management options.

Till date, the largest randomized control trial of fibrinolytic therapy is the Multicenter Intrapleural Sepsis Trial (MIST1) done by Maskell et al. \[19\]. Study centers in this trial placed small-bore chest tubes (median size, 12F) without image guidance in 427 patients with complicated parapneumonic effusions (pleural fluid pH < 7.20, with signs of infection, or positive findings from a pleural fluid Gram stain or culture) or frank empyema and instilled streptokinase or placebo. The trial observed no benefits from streptokinase administration in terms of survival, decreased hospital stay, or need for surgery. However, there was a criticism about the methodology and implementation of this trial \[43–45\]. Patients did not undergo CT scanning or US imaging to identify locules or place chest tubes, and correct tube positioning was not confirmed after placement. There were concerns about the generalization of findings as no standardized protocols were used across the 52 centers to direct antibiotic or other treatments or to select patients who

Table 3: Various intrapleural fibrinolytics (Adapted from Colice et al. \[7\]).

| Fibrinolytic       | Dose        | Instillation | Duration       |
|--------------------|-------------|--------------|----------------|
| Streptokinase      | 250,000 IU  | 100–200 cc NS| QD for up to 7 days |
| Urokinase          | 10,000 IU   | 100 cc NS    | QD for up to 3 days |
| t-PA               | 10–25 mg    | 100 cc NS    | BID for up to 5 days |

t-PA: tissue plasminogen activator.
IU: international units.
NS: normal saline.
QD: every day.
BID: twice a day.

Figure 2: CT images after chest tube drainage. (a) Image shows placement of pigtail catheter (arrow) in the posterior recess confirmed with CT. (b) Placement of small-bore pigtail catheter (arrowheads) in the small loculated effusion with the help of CT guidance.

Figure 3: A pictorial representation of a chronic indwelling catheter (Aspira) which is tunneled beneath the skin to enter the pleural cavity at a distant site. This assembly prevents introduction of infection in the pleural cavity and can provide long term drainage of infected pleural effusion.
had not responded to fibrinolysis for surgery. Many of these centers lacked on-site surgical expertise and contributed only small numbers of patients. Even the drainage techniques were questioned as study design permitted small-bore chest tubes but did not report on pleural drainage volumes. Furthermore, streptokinase was mailed to study centers after randomization, which delayed fibrinolysis. Mortality as one of the endpoints was doubted as patients with serious concomitant illnesses that made survival beyond three months unlikely were excluded from the study. It was speculated that use of intrapleural streptokinase might yield better results in improving short-term mortality in a carefully selected patient population [43]. These deficiencies do not invalidate this large randomized trial, but concerns remain about the validity of its results with regards to younger, more severely ill patients and in different health care settings.

Streptokinase often loses effectiveness due to immune-mediated neutralization; therefore, studies [40, 46, 47] have been done using rtPA as the primary fibrinolytic. These studies estimate success rate of 86% with rtPA.

Similar results as in MIST1 were found in a meta-analysis [48] done subsequently to evaluate the benefit of fibrinolytic therapy in pleural sepsis. A Cochrane review [49] that included some studies (n = 761) also failed to show a reduction in death among patients who received fibrinolytic therapy (28 versus 33 percent). In view of conflicting results in different studies, currently there is not enough evidence to support routine fibrinolytic therapy for every patient with parapneumonic effusions.

Deoxyribose nucleoprotein content plays a major role in increasing the viscosity of pus in the pleural space. Intrapleural fibrinolytics have negligible effects on decreasing the viscosity of empyema pus in contrast to agents that depolymerize DNA, such as human recombinant deoxyribonuclease. Benefit of intrapleural human recombinant DNase in the treatment of empyema following failure of streptokinase has been reported only in case reports [50]. In a recent UK trial comparing the effects of intrapleural tPA, intrapleural fibrinolytics and both combined with placebo showed insignificant response in pleural infection resolution with tPA or DNase alone. On the other hand, the combination of tPA-DNase instilled in the intrapleural space improved fluid drainage and reduced the frequency of surgical referral and the duration of the hospital stay [51]. These initial case reports and trial hint toward a potential new therapy which can improve outcomes of semi-invasive therapies.

4.5. Thoracoscopy. Thoracoscopy is a technique which is able to provide a minimally invasive access to the pleural space to suction viscous pleural fluid, lyse adhesion in loculated pleural effusions, and place chest tubes in dependent regions of pleural fluid under direct visualization [12]. Loculations can be broken down, the visible pleural space completely drained, and an intercostal chest tube can be optimally placed [12]. Thoracoscopy in comparison to thoracostomy has the advantage of having less postoperative pain, lower costs, shorter hospital stays, and better cosmetic results [52]. Available thoroscopic procedures include medical thoracoscopy and video-assisted thorascopic surgery (VATS).

Medical thoracoscopy (Figure 4) has been shown to provide resolution of tuberculous pleural effusions by
repeated adhesionolysis since early part of 20th century in Europe [53, 54]. Medical thoracoscopy is a cheap and quick procedure which can easily be done in an endoscopy suit with patient under conscious sedation and breathing spontaneously within 30–60 minutes [55]. Medical thoracoscopy is performed via single chest port in contrast to VATS, and does not require complete collapse of the lung. Limitation of medical thoracoscopy lies in its inability to fully examine the pleural cavity and to perform pleurectomy if needed. Additionally, debridement done using medical thoracoscopy is time consuming and cumbersome.

Again, there has been a lack of large randomized controlled trial for establishing the role of medical thoracoscopy. A recent case series [56] which analyzed the benefit of medical thoracoscopy for treatment of ultrasonographically stratified multiloculated pleural effusion showed a primary success rate of 91%. Taking in account patients who required additional chest tube insertion or second medical thoracoscopy procedure, the success rates further improved to 94%. 6% of cases required conversion to open drainage. This case series reported the use of intrapleural fibrinolytics as an adjunctive therapy after the thoracoscopy procedure in 49% of cases. Complications occurred in 9% of patients with no mortality observed due to the procedure itself.

VATS is a procedure which is performed by a cardiothoracic surgeon generally using a three-entry port and a double-lumen endotracheal tube. Using VATS, surgeons can also perform decortication and pleurectomy if needed. Even though VATS in comparison to medical thoracoscopy can provide the operator with a much larger access to the pleural

Figure 5: A schematic flow chart summarizing the various treatment modalities available for managing pleural infection and various stages where each of them may be used. Decisions regarding timing of each treatment option may vary according to institutional expertise. *Empyema or effusions with either gram stain or culture positive, pH < 7.2, glucose < 60 mg/dL, LDH < 1000.
space, it may still prove out to be inadequate to treat thick empyemas complicated by dense adhesions and multiple loculations. Studies on VATS procedure have reported a success rate of 60–100%. Currently, VATS is reserved for treating complicated fibrinopurulent effusions, with some surgeons using it during the organizing phase and then converting to thoracostomy if it fails [57–60].

4.6. Open Drainage. An open drainage procedure is employed when the minimally invasive procedures fail to achieve acceptable resolution, defined as re-expansion of lung to the chest wall. In the early exudative or fibrinopurulent stages, an open drainage procedure helps to control the pleural sepsis while the main aim in an organizing phase is to remove the fibrotic peel that encases the lung in order to help it to re-expand and improve chest dynamics [12, 61, 62].

Open drainage is achieved using two types of approaches. First being thoracotomy with drainage and subsequent closure of the chest with one or more drains left in the pleural cavity. Second approach involves creating a window in the pleural cavity by wall incision and rib resection, which provides continuous drainage of the chest cavity. This is called thoracostomy. Through the window in the chest wall drainage can be facilitated by inserting chest tubes. After complete removal of the empyema, chest tubes can be withdrawn. Thoracotomy procedure can also help in complete or partial decortication of the pleural membranes coated with fibrous tissue which will in turn expedite evacuation of thick pus in the pleural cavity and let the lung reexpand [63]. Debridement in comparison to decortication which is a major thoracic operation is less aggressive and can be better tolerated by patients who are markedly debilitated [64].

In a review of 25 patients [65] who underwent either decortication or debridement for empyema drainage, the outcomes were studied by measuring the change of the pleural cavity size before, immediately after surgery, and on followup. On followup imaging, the eventual size of the pleural cavity was not different between the two procedure groups (P < 0.937). Thus, almost similar results were achieved by debridement alone without decortication in patients presenting with empyema, despite the presence of an underlying trapped lung.

5. Conclusions

The management principles for pleural infection have come a long way from employing antibiotic therapy and thoracocentesis to the current availability of semi-invasive and invasive procedures. The key to successful management of pleural infection still remains to be early diagnosis and initiation of treatment. Due to the paucity of robust clinical trials, the treatment modality or the management approach chosen largely depends on individual and institutional expertise. Clinicians are encouraged to develop standardized protocols using best practices reported in the literature, for early identification and management (Figure 5).

Use of advanced imaging like ultrasound and CT scans widens the scope of diagnosing and treating effusions seen on a routine postero-anterior chest radiograph. Observation is usually adequate for a small (<10 mm) unseptated, free flowing effusions. Any other effusions warrant a diagnostic thoracentesis. If the aspirated fluid fulfills the criteria for being infected (pH < 7.2, glucose < 40 mg/dL, culture positive), a prompt plan for its drainage is needed. Currently, large bore tube thoracostomy is the treatment option of choice for patients with empyema, but data is accumulating for treating parapneumonic effusions with small-bore intercostal drains.

The use of fibrinolytics still remains controversial. Fibrinolytics will have more defined role for treating loculated parapneumonic effusions and empyema, particularly in young, acutely ill patients, poor surgical candidates, and in centres with inadequate surgical facilities. Early thoracostomy is an alternative to thrombolysis. Local expertise will dictate the choice between therapeutic thoracentesis, intrapleural fibrinolytics, and medical thoracoscopy as well as conversion to open drainage when thoracoscopy fails till randomized trials provide with better evidence.

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Roles of Talc Modulation on Cytokine Activation in Cancer Patients Undergoing Pleurodesis

Yehuda Schwarz and Alex Star

Department of Pulmonary Medicine, Tel-Aviv Sourasky Medical Center, Sackler Faculty of Medicine, Tel Aviv University, Tel-Aviv 64239, Israel

Correspondence should be addressed to Yehuda Schwarz, schwarz@tasmc.health.gov.il

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We investigate the mechanism of talc pleurodesis (TP) in 20 patients with recurrent malignant pleural effusion and 10 patients with nonmalignant pleural effusions. We measured IL-8 levels before and 6 h after TP and find a significant threefold increase (2.26 ng/mL ± 0.7 to 6.5 ng/mL ± 0.1), which explains the recruitment of inflammatory cells in these patients. We hypothesize that TP is enabled by stimulating the mesothelial cells (MS) to secrete FGF. A significant tenfold increase in FGF-b (0.05 ng/mL ± 0.02 to 0.44 ng/mL ± 0.6) was seen 24 h after talc instillation (P < 0.04). In order to examine whether FGF-b is secreted by MS cells, MS recovered from CHF patients with recurrent pleural effusions were cultured for 48 h in the presence or absence of increasing concentrations of talc (from 100 ng/mL to 1 mg/mL). They produced significant levels of FGF-b in a dose dependent manner (P < 0.005). We hypothesized that a successful pleurodesis involves an early enhanced recruitment of inflammatory cells through a rise of IL-8 followed by enrollment of fibroblasts from the submesothelial space through increased mesothelial FGF-b production.

1. Introduction

Recurrent pleural effusion in cancer patients is a common problem that significantly affects their quality of lives. Several palliative treatment options are available for malignant recurrent pleural effusion in cancer patients who are not responding to chemotherapy, repeated thoracocentesis, or chemical pleurodesis. The most widely used pleurodesis technique is based on the instillation of sclerosing agents into the pleural space. The therapeutic goal in the management of symptomatic patients with malignant pleural effusions is to achieve effective pleural sclerosis. The aim of the sclerosant agent is to irritate both pleurae and to induce mesothelial cell sloughing and subsequent formation of adhesions between the parietal and visceral surfaces. Although the agent must have irritant attributes, it needs to limit and even obviate adverse effects to the patient. Several sclerosing agents are used in clinical practice, among them doxycycline, minocycline, tetracycline, bleomycin, cisplatin, etoposide, fluorouracil, interferon-β, and corynebacterium parvum. Talc has minimal long-term adverse side effects and it was shown to be the most effective agent for preventing recurrences [1]. The mechanisms of pleurodesis have not yet been entirely understood. Diffuse pleural inflammation and fibrin deposition have been considered influential in the success of pleural symphysis [2]. In animal studies, histologic analysis of talc-treated pleurae [2] showed neutrophilic predominance at 24 h, followed by mononuclear infiltration into the subpleural connective tissue matrix and peripheral airspace of the lung. At day 7, the mononuclear infiltrate was accompanied by fibroblasts and collagen. Rodriguez-Panadero et al. [3] showed a significant increase of neutrophil count in the pleural fluid from patients whose pleurodesis treatment was successful. It is not clear how the presence of increased neutrophils in the pleural space contributes to the success of pleural symphysis, but it does indicate that the first step of neutrophilic recruitment is critical. The arrival of inflammatory phagocytic cells is mediated via the release of chemotactic cytokines by activated mesothelial cells [4]. Indeed, the ability of mesothelial cells to release
chemokines following stimulation by LPS, IL-1, or TNF-α has been reported [4]. Pleural effusions secondary to various diseases are associated with the presence of different inflammatory cells, but the formation of pleural adhesion is slow compared to adhesion following the instillation of talc and other sclerosing agents. Tetracycline, which was widely used in the past as a sclerosing agent, increases IL-8 and neutrophil predominance and release of growth-factor-like activity for fibroblasts [5, 6]. The deposition of efficient fibrin within the pleural space in malignant effusions to induce pleurodesis is scanty. In contrast, effusions induced by injury and inflammation the deposition of fibrin has been often demonstrated [7–10]. It was postulated by Kuwahara et al. that the pathogenesis for pleural fibrosis after pleural injury is through fibroblast recruitment to the pleural damage sites by mesothelial cells [11]. Those researchers used fibronectin as the chemotaxin and they showed a progressive time-dependent increase in fibroblast chemoattractant activity by pleural mesothelial cell throughout 96 h cultures. This secretion of a mesothelial cell-derived fibroblast chemoattractant may play a role in the response of the pleura to injury and in the pathogenesis of pleural fibrosis [11]. Fibroblast fibrinopeptides during fibrin formation stimulate local mesothelial regeneration and proliferation as shown by Griffith et al. [12]. Fibrin and collagen deposition in the pleural connective tissue and in intrapleural adhesions was reported by Hurewitz et al. after instillation of tetracycline and doxycycline for pleurodesis [13]. They showed also that fibroblasts were the predominant inflammatory cells at autopsies after 2 weeks of successful pleurodesis in rabbits. Enhanced proliferation of fibroblasts following asbestos exposure [14] and tetracycline [15] have also been reported. The mechanisms of talc pleurodesis have yet to be delineated, raising a number of unanswered questions. Is the role of talc in the pleurodesis process limited to an irritant (foreign body) effect that solely induces inflammation or does it have a direct effect on mesothelial and fibroblasts cells? Is the activation of mesothelial cells by the inflammatory process critical to the recruitment and proliferation of fibroblasts, and are the mesothelial cell responsible for fibroblast proliferation? Do mesothelial cells from cancer patients react to talc the same degree as mesothelial cells from normal subjects?

1.1. Clinical Relevance. During the evolution of the disease, cancer patients suffer from recurrent pleural effusion that endangers their lives and significantly reduces their quality of life. They are in need of medical support and frequently require immediate treatment. Although talcpleurodesis is effective, it causes side effects and morbidity. By understanding the fibrotic process produced by talc, we will be able to prevent most of those side effects and lower the risk of injury to the already compromised health of these patients.

We hypothesized that successful induction of pleurodesis involves a cascade mechanism in which there is early enhanced recruitment of inflammatory cells to the pleural space through secretion of chemokines (mainly IL-8). This inflammatory “soup” allows enrollment and proliferation of fibroblasts from the submesothelial space to the plural space by secretion of fibroblast growth factor production by the mesothelial cells. These steps are induced directly and primary by talc.

2. Methods

2.1. Clinical Protocol

2.1.1. Study Population. 20 patients with recurrent malignant pleural effusions and 10 patients with nonmalignant pleural effusions. Patients are followed during their hospitalization for the talcage procedure and at the outpatient pulmonary and oncology clinics after discharge. Chest X-rays are performed before and shortly after talcage, and before discharge. Pulmonary function tests are also performed before and after talcage. A clinical chart is used to track any failure of pleurodesis induction.

2.1.2. Thoracocentesis. Diagnostic thoracocentesis is performed under local anesthesia, using the Bard®I-Cath intravenous placement unit (Bard Ltd., UK) No. 16 connected through a three-way stopcock to a syringe.

2.1.3. Pleural Fluid Examination. Fluid is examined routinely for cytology, levels of glucose, LDH, protein, cholesterol, and cultures. Pleural fluids from the diagnostic thoracocentesis are collected immediately before talcage, and at 6h and 24h after Talcage and frozen at −70°C until cytokine measurement.

2.1.4. Talcage Slurry Procedure. Instillation of talc (slurry procedure) via tube thoracostomy (Sherwood Medical, Ireland) is performed after full expansion of the lung. Two 2 g of certified USP asbestos-free talc (Biolabs, Israel) sterilized at 150°C is mixed in 100 mL of normal saline solution under sterile conditions, and instillation is performed through the tube thoracostomy at bedside. The tube is clamped for 2 h and the patient undergoes rotational maneuvers. Drainage monitoring and volumes are recorded until drainage falls below 150 mL/24 h at which point the thoracostomy tube can be extracted [16].

2.2. In Vitro Protocol

2.2.1. IL-1 Mediation. The following experiment is designed to clarify whether IL-8 production is mediated by primary IL-1 activation. Cells recovered from pleural thoracocentesis are cultured for 24 h in 1640 RPMI 10% FBS in the presence or absence of IL-1 receptor antagonist (1 μg/mL/10^6 cells) and talc (1 μg/mL/10^6 cells). Supernatants are collected for IL-8 measurements.

2.2.2. Talc Studies. Normal mesothelial cells recovered by thoracocentesis from patients with intractable congestive heart failure are cultured at equal concentrations in 1640 RPMI 20% FBS until confluence. Cell viability is tested by trypan blue dye exclusion. Cytospin preparations of pleural fluid cells are performed by counting the cells before culture by cytopsins and reconstituting them at a concentration...
of $7.5 \times 10^{-5}$ mix-cell/mL in RPMI-20% FCS. They are exposed to graded concentrations of talc in serum-free medium at increasing concentrations from 100 ng/mL to 1 mg/mL for 24 h in order to establish a dose-response curve. Supernatants for measuring cytokines and growth factors are collected after centrifugation to remove excess talc and cells.

2.2.3. Cytokine Measurement. IL-8 and human fibroblast growth factor levels are quantified by sandwich-type enzyme-linked immunoassays ELISA (R & D systems, USA).

For the IL-8 and hFGF ELISAs, flat-bottomed 96-well microtiter plates are coated with an excess murine monoclonal antibody to either IL-8 or hFGF. The pleural fluids from the diagnostic thoracentesis and supernatants from the mesothelial cell culture medium stimulated by serial dilutions of talc are then added. After incubating, any unbound protein is removed by washing with phosphate-buffered saline (PBS) and an enzyme-linked polyclonal antibody specific to either IL-8 or hFGF is added. The antibody binds the antigen that had been immobilized during the first incubation period. Substrate solution is added to the wells after another washing with PBS. The presence of IL-8 or hFGF is quantified by comparing the optical density (OD) of the samples with the standard curve.

2.3. Statistical Analysis. Data were analyzed with the SigmaStatstatistical software package (Apple Computer, Cupertino, CA, USA) and expressed as mean ± SD. The differences between the group means were analyzed by analysis of variance (ANOVA), with use of the Student-Newman-Keuls test. Data were considered statistically significant at $P < 0.05$.

Isolated pleural fluid cells are characterized as pleural mesothelial cells (PMCs). In general, approximately 500 mL of centrifuged transudative pleural fluid yields 12 confluent 3.5 cm diameter Petri dishes of mesothelial cells within 5 to 12 days when cultured as described. The mesothelial cells were positively stained for vimentin, cytokeratin, and hyaluronic acid mucin [17]. Cell morphology was defined by phase-contrast microscopy as having a cobblestone pattern, and numerous microvilli were noted on transmission electron microscopy. All cells were utilized at the second passage in 3.5 cm diameter Petri dishes.

3. Results

3.1. IL-8 Production in Malignant Pleural Effusion. We found that pleural fluid obtained from patients suffering from recurrent malignant pleural effusion had elevated IL-8 levels (4.52 ng/mL ± 4.4) compared to the pleural fluid obtained from noncancer patients suffering from nonmalignant, noninfectious pleural effusion (0.2 ng/mL ± 0.4) ($P < 0.05$) (Figure 1).

3.2. Talc Stimulates IL-8 Secretion at Early Steps of the Pleurodesis Process. The IL-8 levels in malignant pleural effusion showed an early (6 h) significant threefold increase due to talc instillation (2.26 ng/mL ± 0.7 to 6.5 ng/mL 0.1). (Figure 2).

3.3. Talc Stimulates Confluent Mesothelial Cells to Release C-X-C Chemokine-IL-8. PMC cultures were stimulated with varying doses of talc (2 to 64 mg/cm²) for 24 h in tissue culture plates. Cell viability was documented by trypan blue dye exclusion and vi-intensity character-visual inspection with phase-contrast microscopy. Viable cells were expressed as the percent viable cells of all cells. The PMC viability decreased with increasing talc concentration. PMC viability at a talc concentration of 64 mg/cm² was about 75%. Cultured mesothelial cells released small amounts.

There was a significant ($P < 0.04$) tenfold increase in FGF-b levels (0.05 ng/mL ± 0.02 to 0.44 ng/mL 0.6) 24 h after talc instillation (Figure 3).

Moreover, normal mesothelial cells were cultured in vitro with talc in order to determine whether the mesothelial cells are the ones responsible for the rise in FGF-b levels after talc: they produced significant levels of FGF-b in a dose-dependent manner ($P < 0.005$) (Figure 4).

4. Discussion

In this work, we demonstrated cytokine IL-8 elevation in early stages of talc pleurodesis compared to basic fibroblast
growth factor (bFGF) increases in later phases. We also showed that pleural mesothelial cells were either partially or completely responsible for both IL-8 and bFGF elevation.

Current thinking of chemical pleurodesis [18–20] suggests that an acute inflammatory reaction is initiated in the pleural space following the administration of talc, with an influx of neutrophils and mononuclear cells associated with an increase in interleukin-8 and other cytokines in pleural fluids. During the next step, pleural mesothelial cells secrete significant amounts of bFGF that stimulate fibroblast proliferation. The fibroblasts synthesize collagen, resulting in pleural adhesions between visceral and parietal pleurae, and bFGF simultaneously promotes secretion of TGF-β and VEGF that accentuates fibrosis.

Our results demonstrate that pleural IL-8 levels from patients with malignant pleural effusion were higher compared to IL-8 levels in patients with nonmalignant, noninfectious pleural effusion (P < 0.05). We also reported a threefold increase of IL-8 at 6 hours after talcage (P < 0.005). A number of investigations have shown that mesothelial cells actively contribute to the acute inflammatory process in talc pleurodesis. Genofre et al. [21] evaluated submicroscopic features of active pleural remodeling associated with talc pleurodesis and stated that talc acutely induces a prominent injury to the mesothelial cells.

The mesothelial cells exposed to talc can actively produce proinflammatory cytokines, such as IL-8 [18, 22], VEGF [18], and bFGF [20]. Marchi et al. [19] demonstrated that WBC, neutrophil percentage, and IL-8 levels were increased in the first 24 h after talc exposure. Acencio et al. [23] investigated the acute response of rabbit pleural mesothelial cells challenged with talc. Cultured rabbit pleural mesothelial cells were exposed to and assessed for the production of IL-8, VEGF, and TGF-β. At 6 h, the IL-8, VEGF, and TGF-β levels produced by talc-exposed mesothelial cells increased significantly and remained elevated for up to 48 h. The investigators concluded that pleural mesothelial cells may actively mediate the primary inflammatory pleural response in talc-induced pleurodesis injection, whereas VEGF and TGF-β1 levels were initially lower and increased with time. Therefore, our results confirm the data of other investigators on early involvement of cytokine IL-8 in the talcage procedure that induces recruitment of inflammatory cells in this process.

We hypothesized that a successful pleurodesis induction involves an early enhanced recruitment of inflammatory cells through a rise of pleural IL-8 concentrations followed by enrollment of fibroblasts from the submesothelial space through increased mesothelial bFGF production. We found a ten-fold increase of the bFGF level in pleural fluid 24 hours after talcage that confirms the above hypothesis.

bFGF has been characterized as a key factor in successful pleurodesis as well as in the formation of pleural effusions. It is a member of the FGF family. This group of molecules, similarly to the TGFβ superfamily, are pleiotropic regulators of cell responses that are involved in a diverse range of biological functions, including proliferation, differentiation and wound healing. Like TGFβ, bFGF has also been implicated in pleural fibrosis and can stimulate mesothelial cell proliferation in vitro and in vivo.

We speculate that talc induces pleurodesis-fibrosis by direct stimulation of mesothelial cells to secrete bFGF. We established mesothelial cell cultures from CHF patients with recurrent pleural effusions and incubated them with different concentrations of the talc. The cells produced significant levels of bFGF in a dose-dependent manner. These results support data of Antony et al. [20] who showed that talc can induce release of bFGF from mesothelial cells. Patients with higher pleural fluid bFGF levels after talc pleurodesis were more likely to develop successful pleurodesis. An increase in fibroblast proliferation was stimulated by incubation in pleural fluid from these patients, which was reduced by anti-bFGF antibodies. Antony et al. [20] demonstrated that talc pleurodesis is partly driven by mesothelial-derived bFGF. Furthermore, those authors demonstrated that patients with extensive pleural carcinomatosis and minimal intervening normal mesothelium had significantly lower quantities of bFGF in their pleural fluid compared to those with limited disease who subsequently developed successful pleural...
sympysis. These findings suggested that mesothelium free of tumor was necessary for successful pleurodesis [19]. A recent study also showed that an intact pleural mesothelium is critical in modulating the metastatic potential of cancer cells within the pleural space. Malignant cells secrete angiogenic factors that promote tumor growth, proliferation of endothelial cells and invasion of surrounding tissue by neovascularization. Talc-treated pleural mesothelium counteracts these effects by releasing endostatin, an anti-angiogenic factor which may be responsible for tumor containment within the pleural space and accounts for the improved clinical outcome of patients with malignant pleural effusions successfully pleurodesis with talc [24]. Lee et al. [25] demonstrated that talc causes apoptosis of lung cancer cells in a dose- and time-dependent manner. However, this process is selective and spares the normal mesothelium.

The mechanism that determines pleural sympysis involves the action of different growth factors, such as bFGF and TGF-β and, especially, vascular endothelial growth factor (VEGF). Ribeiro et al. [26] studied the acute effects of VEGF blockade on the expression of inflammatory cytokines and pleural fluid accumulation in rabbits that received intrapleural injections of either talc or silver nitrate. The animals pretreated with anti-VEGF antibody showed significant reductions in pleural fluid volumes after talc or silver nitrate injection. IL-8 levels, vascular permeability, and macroscopic pleural adhesion scores were also reduced in the groups that received bevacizumab. That study showed that bevacizumab interferes in the acute phase of pleural inflammation induced by silver nitrate or talc, reinforcing the role of VEGF as a key mediator in the production of pleural effusions.

Teixeira et al. [27] assessed the influence of the anti-VEGF antibody (bevacizumab) on pleurodesis induced by talc or silver in rabbits: antibody anti-VEGF interfered in the pleurodesis induced by both agents, and the anti-VEGF antibody inhibited adhesions between the pleural layers.

Collectively, our results provide experimental evidence that cytokine IL-8 levels were elevated during the early hours of pleural effusion after talc instillation and that this preceded the appearance of inflammatory cells in the pleural cavity. Profibrotic growth factor bFGF levels increased 24 hours after pleurodesis when fibroblasts started to proliferate in the pleura and produced collagen [19, 20]. We also found that pleural mesothelial cells secrete both IL-8 and bFGF. Our present results closely agree with previous works of others that showed interactions among resident and inflammatory cells and cytokines and growth factors in the pathogenesis of tissue fibrosis during pleurodesis [18, 20, 22, 23]. These interactions lead to excessive matrix production with fibrosis and scar formation in the pleural cavity. Although fibroblasts have been implicated as the effector cells in pleural fibrosis, other resident cells, foremost among them, mesothelial cells, may directly or indirectly play important roles as well.

Pleural injury and fibrosis are characterized by excessive fibrin production. The pleural loculations evolve into fibrous adhesions under the influence of profibrotic mediators, such as bFGF and TGF-β, leading to the deposition of collagen and the formation of adhesions between the visceral and parietal surfaces. Elucidation of the specific steps involved in inflammation and fibrin turnover in pleural injury during pleurodesis will lead to better understanding of this process and to the development of novel sclerosants with potential clinical applications.

At least two mechanistic pathways are likely to be involved in talc-induced pleural fibrosis: (i) the generation of cytokines and inflammation and (ii) the production of growth factors stimulating fibroblast proliferation and collagen synthesis. bFGF is considered to be the most potent profibrotic mediator, but the roles of other fibrogenic mediators need to be further studied as targets for pleurodesis. Although the mechanisms involved in pleural fibrosis are unclear, recent evidence suggests that they may be associated with the upregulation of genes for profibrotic mediators, such as bFGF and TGF-β [28]. However, further studies are required to establish a molecular mechanism in the development of pleural fibrosis.

In summary, talc pleurodesis is the consequence of sclerosant instillation and can manifest itself as diffuse pleural thickening and fibrosis. Although its pathogenesis is not completely known, it is likely that the complex interactions between resident and inflammatory cells and profibrotic mediators are integral to the development of pleural fibrosis. It is generally accepted that the primary target cells for pleural fibrosis are subpleural fibroblasts, however, our results as well as those of other studies suggest that mesothelial cells may also play a significant role in the pathogenesis of this condition, both by initiating inflammatory responses and producing profibrotic growth factors. A greater understanding of the biology of these growth factors may allow therapeutic manipulation of these cytokines to create pleurodesis and to stimulate pleural adhesion/fibrosis.

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Review Article
Pleural Fluid Analysis: Standstill or a Work in Progress?

T. Hassan, M. Al-Alawi, S. H. Chotirmall, and N. G. McElvaney
Respiratory Research Division, Educationand Research Center, Royal College of Surgeons in Ireland, Beaumont Hospital, Beaumont Road, Dublin 9, Ireland

Correspondence should be addressed to S. H. Chotirmall, schotirmall@rcsi.ie
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Pleural fluid analysis yields important diagnostic information in pleural effusions in combination with clinical history, examination, and radiology. For more than 30 years, the initial and most pragmatic step in this process is to determine whether the fluid is a transudate or an exudate. Light’s criteria remain the most robust in separating the transudate-exudate classification which dictates further investigations or management. Recent studies have led to the evaluation and implementation of a number of additional fluid analyses that may improve the diagnostic utility of this method. This paper discusses the current practice and future direction of pleural fluid analysis in determining the aetiology of a pleural effusion.

1. Introduction
Pleural effusions are associated with a number of medical conditions causing fluid accumulation via differing yet synergistic mechanisms including increased pleural membrane permeability, increased pulmonary capillary pressure, decreased oncotic pleural pressure, and lymphatic obstruction. Pleural fluid analysis yields important diagnostic information in most cases of pleural effusions. Standard workup includes determining whether the effusion is transudative or exudative, an important differentiation aiding the physician in narrowing the differential diagnosis (Figure 1). Despite this, several experts propose that such a categorical division represents outdated practice as it does not permit establishing a definitive cause of the effusion. A variety of nonroutine tests may be performed during pleural fluid analysis either as lone or additional diagnostic tools to further determine a definitive cause for an effusion in the appropriate setting. This paper will discuss the current practice and future prospective direction for the use of pleural fluid analysis in determining the aetiology of a pleural effusion in a variety of clinical settings.

2. Have We Moved on from Light’s Criteria?
The primary aim when investigating a pleural effusion is to establish the correct diagnosis with minimal investigation. Prior to the advent of Light’s criteria, most physicians initially determined whether an effusion was transudative or exudative based on the pleural protein level [1]. Serum and fluid albumin gradients of greater than 12 g/L also indicated exudates, however, when used in isolation, these criteria have low sensitivity [2].

Light’s criteria have recommended for use when a pleural protein is between 25 and 35 g/L and defines exudative pleural effusions as having either (1) a ratio >0.5 between total pleural and plasma protein, (2) a ratio >0.6 between pleural and plasma lactate dehydrogenase (LDH), and (3) pleural LDH higher than two thirds of the normal serum level. The sensitivity of Light’s criteria in identifying exudative pleural effusions is high (98%); however, its ability to exclude transudates remains low. For instance, prospective work by Porcel et al. reported an almost 100% sensitivity for exudates but found that approximately one-fifth of patients with congestive cardiac failure on diuretics also met Light’s criteria for an exudate [3]. Despite this deficiency, Light’s criteria
remain superior to clinical judgement for discriminating between transudates and exudates. A prospective study of \( n = 249 \) patients directly comparing clinical suspicion to Light’s criteria reported that the former was significantly less accurate to the latter (84% versus 93%, \( P < 0.01 \)) (6), illustrating the criteria’s importance in routine clinical practice [4].

Most studies to date have focused on making Light’s criteria more practical without affecting its discriminatory power. For example, it has been suggested that serum LDH in isolation does not increase the value of the two other criteria components [5]. This is supported by a Brazilian study proposing new criteria to differentiate the two effusion types [6]. By quantifying exclusively total pleural protein and LDH without the need of serum samplings, this study showed a diagnostic yield comparable to that of Light’s criteria.

Other studies have additionally generated a number of nonroutine biochemical measurements on pleural fluid that may discriminate transudates from exudates, for instance pleural fluid bilirubin with pleural: serum ratio of \( >0.6 \) is suggestive of an exudate with a sensitivity and specificity of 90.6% and 96.2%, respectively [7]. An early case series has demonstrated that pleural fluid cholesterol \( >60 \text{ mg/dL} \) is indicative of an exudative effusion with high sensitivity [8], whilst another study utilizing both LDH and pleural cholesterol measurements revealed similar sensitivity to
distinguish between the two types of effusion [9]. Vascular endothelial growth factor (VEGF), an important mediator of angiogenesis and vascular permeability, may be another key mediator and thus marker in the identification of exudates due to the increased pleural endothelial permeability it confers. In one study of n = 79 patients, median levels of VEGF in exudates were approximately twice that of transudates [10]. In addition, elevated tumor necrosis factor alpha (TNF-α) levels are found in both infectious and malignant pleural effusions, but rarely transudates [11]. Other biochemical parameters that have been examined to aid transudate versus exudate differentiation include alkaline phosphatase, creatine kinase, and uric acid which possessed diagnostic accuracies lower than the traditional Light’s criteria [12].

Some of these studies have proposed new and alternative criteria avoiding venepuncture consequently reducing investigations and diagnostic costs. However, these criteria vary in their cut-off points to best discriminate the two forms of effusion. To date, Light’s criteria remain robust with diagnostic accuracy of 96% and for now remains the optimal method to separate pleural transudates from exudates.

3. Cardiac Pleural Effusion: Extending beyond the Transudate/Exudate Boundary

Cardiac failure remains the most common cause of transudative pleural effusions. A single study has revealed that 28% of cardiac-related pleural effusions were misclassified as exudative due to the use of diuretics [13]. Brain natriuretic peptide (BNP) is a neuroendocrine hormone secreted from the ventricular walls in response to increased pressures and stretch conferred on cardiomyocytes impacting upon the renin-angiotensin system to increase diuresis and vasodilation [14]. BNP is cleaved to NT-proBNP, and detection of the cleaved product in serum has been used to distinguish cardiac failure from primary pulmonary causes of dyspnoea. This marker has been demonstrated to possess diagnostic usefulness during pleural fluid analysis. A study by Long et al. demonstrated that, although levels of pleural BNP have a statistically significant correlation with NT-proBNP, the latter is a far more accurate diagnostic tool during evaluation of cardiac pleural effusions [15]. In addition to high sensitivity and specificity, pleural NT-proBNP is shown to be superior to Light’s criteria for the identification of cardiac-based pleural effusions [16]. Meta-analyses have shown that the number of misclassified effusions from application of Light’s criteria was significantly reduced with the use of NT-proBNP [17]. However, there is a need for caution as levels of NT-proBNP are physiologically raised in the elderly and renal failure populations requiring further studies to evaluate its role in these groups. Importantly, NT-proBNP measurement is difficult and costly when compared to application of traditional criteria such as the albumin gradient in assessing pleural effusions [18]. Measuring pleural NT-proBNP should therefore be reserved for settings where a suspected cardiac effusion meets exudative criteria but a high index of clinical suspicion remains. Alternative markers have been studied in the assessment of cardiac pleural effusions, for example, normal complement levels (C3 and C4) are reported to have a high negative predictive value in this setting [19].

4. The Promise of Biological Pleural Markers to Determine the Aetiology of Pleural Exudates

The most challenging aspect of investigating exudative pleural effusions is differentiating the likelihood of inflammatory parapneumonic versus malignant disease both major causes of exudates in routine clinical practice. Tuberculous effusions are an additional important consideration owing to long-term treatment strategies. Biochemical analyses such as protein, pH, and microbiologic assessment remain the standard investigations during this process. Additionally, cytological examination of suspected malignant pleural effusion (MPE) can result in false-negative rates of up to 40% [20]. The diagnostic yield for cytology, however, depends on the tumour type; highest for ovarian (83%) and less so for breast (78%), lung (57%), and mesothelioma (41%) primaries. Overall, standard testing to determine the underlying cause of exudates has a suboptimal accuracy requiring other parameters such as clinical suspicion and radiology to play an associative role.

4.1. Pleural Fluid Appearance. Pleural fluid appearance is a nonspecific and undermined tool in the assessment of a pleural effusion. Prior work has suggested that malignancy is the leading cause of gross bloody effusions (47%) [21] and further confirmed by Porcel and Vives who reported that pleural effusions with significantly higher red blood cell counts occurred in those who subsequently had malignant rather than nonmalignant effusions [22]. In a separate study assessing patients without any prior diagnosis of malignancy, an association between blood-stained effusions and the presence of malignant cells on cytological examination was described [23]. Conversely, a larger retrospective study assessing patients diagnosed with cancer who underwent thoracocentesis revealed no difference between the presence of blood and the ability to predict positive pleural fluid cytology [24]. Therefore, due to low sensitivity and specificity of bloody effusions to indicate malignancy in the setting of an exudate, pleural fluid appearance should not be emphasized as a diagnostic tool to establish MPE as it can be relatively nonspecific.

On the other hand, there are cases where the appearance of pleural fluid may be helpful. The best described setting is one of a milky appearance suggestive of chylothorax or pseudochylothorax that can be differentiated by centrifugation. Although reliable where present, the gross appearance of a chylothorax has been described as nonmilky half the time [25]. Chylothorax may alternatively give the appearance of bile-stained fluid. However, pleural triglyceride analysis is a more definitive test with a level greater than 110 mg/dL reflecting a 99% chance that the fluid is chyle. For infective-related pleural effusions, an anchovy-brown fluid may indicate amoebic liver abscess whilst black fluid suggests Aspergillus infection [26].
4.2. Cell Count Differential. Differential cell count of pleural fluid may also provide clues to the origin of an exudative pleural effusion. Neutrophilic predominance indicates an acute injury of the pleural surface that may occur in parapneumonic settings, pulmonary embolism, and subphrenic abscesses. In chronic, long standing pleural injury, the fluid becomes populated by lymphocytes. Two-thirds of lymphocytic predominant effusions are the result of malignancy or tuberculosis (TB) [27]. Eosinophilic pleural effusions, defined as a pleural effusion that contains at least 10% eosinophils, most commonly occur during conditions associated with the presence of blood or air in the pleural space such as pneumothorax and malignancy. Interestingly, although eosinophilia is nonspecific and can occur in benign-related effusions, a percentage of pleural eosinophils >40% indicates an extremely low likelihood of malignancy [28].

4.3. Markers of Pleural Inflammation. Pleural biological markers have been proposed as an alternative means to determine the cause of exudative pleural effusions. C-reactive protein is an acute-phase reactant widely used as a marker of inflammation and tissue injury. Pleural CRP is found to be higher in benign versus malignant exudates with a sensitivity and specificity of 93.7% and 76.5% for parapneumonic effusion [29, 30]. This finding has been supported by further studies revealing an almost 100% sensitivity for a cutoff value of 5.3 mg/dL to identify parapneumonic versus tuberculous or malignant effusions [31]. Interleukin-8 (IL-8), a proinflammatory cytokine, and CRP together may differentiate complicated from uncomplicated parapneumonic effusions with sensitivities of 84% and 72% and specificities of 82% and 71%, respectively [32]. Interleukin-6 (IL-6), an alternative proinflammatory cytokine induced by lipopolysaccharide (LPS) as a marker of system activation, has also been shown to effectively differentiate infective from malignant effusions with highest levels in tuberculous rather than parapneumonic effusions [33]. In spite of this, elevated IL-6 has also been found in MPE, particularly following pleurodesis. Elevated TNF-α is also useful in differentiating tuberculous from malignant effusions [34]. Studies supporting the utility of pleural proinflammatory cytokines during pleural fluid analysis revealed that a low absolute neutrophil count may give a diagnosis of empyema with a sensitivity rate of 78.6% and a specificity rate of 88.4% in the presence of elevated IL-8. Similar findings are reported with IL-1 [35, 36].

Other features of pleural fluid analysis that discriminate infection from inflammation in the complicated versus noncomplicated setting include pleural soluble triggering receptor of myeloid cells-1 (sSTREM-1), procalcitonin, and lipopolysaccharide binding protein (LBP) [37]. Pleural pneumococcal antigen assays have been explored and may be more sensitive than the equivalent urinary assays for the establishment of microbial-induced pneumonias [38]. Parapneumonic effusions secondary due to S. pneumoniae are further shown to have positive antigen testing in pleural fluid whilst negative results from concurrent urine sampling.

A prospective study of n = 72 patients set out to discriminate exudates with multiple pleural biological parameters including adenosine deaminase (ADA), CRP, carnoembryogenic antigen (CEA), IL-6, TNF-α, and VEGF found ADA and CRP to be the most reliable of the group assessed [39]. ADA concentrations >45 U/L and CRP <4 mg/dL most likely indicated tuberculous effusions, whilst ADA <40 U/L and CRP >6 mg/dL suggested a parapneumonic origin. The latter ADA levels in combination with CRP <4 mg/dL on the other hand, were most likely malignant in origin. In a specialized subgroup of lung transplant recipients, normal or high complement levels within pleural fluid indicate a secondary cause, for example, parapneumonic effusion rather than those attributable to the surgery itself [19].

Despite the large volume of work in-progress, larger and more robust studies are necessitated before we can safely recommend the use of nonroutine and costly biological markers as standard to improve the diagnostic accuracy during the routine workup of an exudative pleural effusion.

4.4. Pleural Tuberculosis. Pleural tuberculosis displays important pleural fluid features that significantly contribute to the diagnostic process. Such features preclude the need for invasive investigation such as thoracoscopy or pleural biopsy. Microbiologic assessment remains paramount directly aiding treatment strategy. Microscopic examination of Ziehl-Neelsen stained pleural fluid detects acid-fast bacilli in <5% of non-HIV cases [40]. Addition of Lowenstein-Jensen media culture increases this positive yield to approximately 35%. Nucleic acid amplification confers better statistics for diagnosis and has specificity between 90%, and ~97%; however, sensitivity may be as low as 60% [41].

ADA is a T-cell (CD4+) metalloenzyme whose presence in high levels within pleural fluid strongly indicated tuberculosis particularly in high prevalence areas. High pleural ADA is also detected in non-TB settings including malignancy, rheumatoid arthritis, systemic lupus erythematosis, and parapneumonic effusions. In view of this, it is important to acknowledge that two ADA isoenzymes exist; ADA 1 and 2 with the latter related in increased levels in the tuberculous setting. In meta-analyses of 63 studies, ADA is reported to have a sensitivity of 92% and a specificity of 90% [42], whilst within the setting of a lymphocytic predominant effusion, ADA >40 U/L is almost exclusively secondary to tuberculosis. Paradoxically, retrospective study of 221 patients has illustrated that ADA levels >250 U/L do not generally occur in tuberculosis related effusions [43]. Such levels are in fact found in patients with empyema or lymphoid-related malignancies. Therefore, whilst the measurement of pleural fluid ADA remains a useful diagnostic tool for tuberculous pleurisy, it should be interpreted in parallel with clinical findings and other traditional methods such as the tuberculin skin test to reach a diagnosis. Such a combination of clinical features with pleural ADA measurement has excellent diagnostic value with a sensitivity and specificity rates of 95% and 97%, respectively. Therefore, experts have recommended measuring ADA levels in low-prevalence areas as a concentration <40 U/L almost exclusively rules out tuberculosis-driven effusions [44].
Measurement of pleural interferon-γ, an alternative cytokine derived from lymphocytes, may also be utilized in the diagnosis of tuberculous effusions. However, like ADA, elevated levels of interferon-γ are reported in empyema and malignancy. Even though the sensitivity and specificity of this marker is lower than that of ADA, joint sensitivity and specificity utilizing both together increases to 96% and 93%, respectively [45]. A single prospective study of n = 63 patients illustrated that interferon-γ gamma assays (IGRAs) including the commercially available QuantiFERON-TB Gold and T-SPOT-TB performed poorly compared to interferon-γ levels >0.31 IU/mL as a cut-off value [46]. Use of IGRA is currently not recommended due to variability in results when compared to other markers such as ADA that appear superior.

Other biological parameters including pleural IL-6, IL-1β, neopterin, leptin, lysozyme, and soluble FAS ligand have extensively been studied in the setting of tuberculous pleural effusions. Neopterin is a pteridine, released by activated macrophages and shown to be elevated in tuberculous effusions [47]. Conversely, leptin, an adipose-derived hormone, has been shown to be reduced to a greater extent in tuberculous effusions when compared to other exudative effusions with a sensitivity and specificity of 82% [48]. Lysozyme also released from activated macrophages similarly have a sensitivity of 85% and specificity 61% for the identification of tuberculous effusions. SC5b-9, a product derived from the binding of C5b-9 complexes to the S protein, is elevated in effusions secondary to TB particularly at a cut-off value of >2 mg/L. Such measurements have also been studied to aid differentiating tuberculous from malignant pleural effusions [49]. Pleural interferon-γ inducible 10 kDa protein (IP-10), interleukin-12 p40, and matrix metalloproteinase (MMP) levels [50–52] are additional markers elevated in pleural fluid from tuberculous effusions compared with malignant and other benign settings. Despite this, their significant variability in sensitivity and specificity coupled with costs for routine use preclude the introduction of such measures into routine clinical practice. What is probably most feasible is a combination of these tests used synergistically at a reduced cost. For example, a study has shown that a combination assay including ADA, interferon-γ, and nucleic acid amplification for TB will have superior sensitivity and specificity as compared to a single test alone and offers a future promise in the workup of tuberculous effusions [53].

4.5 Tumour Markers. Nodularity, pleural and diaphragmatic thickening are highly indicative of malignant pleural disease with a positive predictive value of 100%. Despite this, such features are not always present and pleural fluid cytology thus plays a crucial role in the diagnosis of malignancy. MPEs are positive in 40–60% of cases [54], and it is common practice to require a large volume (>500 mLs) of fluid to reach a diagnosis by cytology. Interestingly, a recent prospective study on n = 121 thoracocentesis showed that diagnostic accuracy was dependent on the volume of pleural fluid obtained with a recommendation of >150 mL, whilst another prospective study examining n = 44 patients concluded that samples >50 mL similarly did not increase diagnostic yields [55, 56]. Work on noninvasive tumour biomarkers remains ongoing and if successful may avoid invasive investigation such as pleural biopsy or thoracoscopy.

Well-described tumour markers such as carcinoembryonic antigen (CEA), cancer antigen 125 (CA 125), 15-3 (CA 15-3), and neuron-specific enolase/cytokine fragment (CYFRA) 21-1 have limited usefulness in the routine workup of a suspected malignant pleural effusion. CA 125 is a well-described tumour marker implicated in ovarian malignancy and has reported high levels in pleural fluid compared to serum in this setting [57]. High pleural CA 125, however, is also observed in squamous and adenocarcinomatous malignant effusions and may have a prognostic role [58]. Pleural CEA was one of the first markers to be evaluated in lung cancer. It is overexpressed in metastatic adenocarcinoma possessing prognostic relevance in terms of median survival and treatment response [59]. Although CEA has been shown to be specific, sensitivity remains low (<50%) with variable cut-off values precluding routine use. Metastatic breast cancer is another common cause for malignant pleural effusions with CA 15-3 used for both diagnosis and therapeutic monitoring [60]. CYFRA 21-1, a cytokerin tumour marker has both diagnostic and prognostic roles in nonsmall cell lung cancer [60]. However, due to relatively poor sensitivity for a single test, a use of a combination of tumour markers such as CA 125 and CYFRA 21-1 for adenocarcinoma and CEA, CA 15-3, and CYFRA 21-1 for squamous cell cancer of the lung has been recommended. In a study involving n = 243 and n = 173 patients with malignant and benign effusions, respectively, selected cut-off values had to be 100% specific to classify correctly 54% of the malignant effusions [61]. Discriminating pleural fluid cut-off values were generally higher than those found in serum, a finding that does not justify the routine use of measuring classic tumour markers in the workup of pleural effusions. Despite this, one particular study has in fact demonstrated that in cases of suspicious MPE and negative cytology and in the absence of an obvious primary source that the measurement of tumour markers may be helpful as an alternate diagnostic tool [62].

The diagnosis of a mesothelioma-related pleural effusion remains difficult as few studies have reported markers with a high positive predictive value. Increased levels of pleural CA-15-3, hyaluronic acid, and spliced forms of CD44, such as exon v6 (CD44v6), have been reported; however, a discrepancy exists in the literature for CYFRA 21-1 to differentiate between mesothelioma and other pleural malignancies [63]. Alternatively, mesothelin, a cell surface glycoprotein that may be cleaved into the soluble mesothelin related protein (SMRP), is a moderately sensitive but highly specific marker in serum studies [64]. Studies also support the use of pleural fluid levels of mesothelin with 98% specificity and 67% sensitivity in mesothelioma compared to benign effusions [65, 66]. Pleural SMRP measurement also diagnosed mesothelioma more reliably than cytological examination alone [65, 67]. Consequently, such a measure could be considered for patients with undiagnosed pleural effusions, particularly if mesothelioma is a concern.
4.6. Rheumatological-Related Pleural Effusions. Rheumatological-related pleural effusions usually have pleural biochemical characteristics such as protein, pH, and glucose similar to other noninfective causes of exudates. Serum rheumatoid factor (RF) and antinuclear antibody (ANA) are more sensitive and specific for the diagnosis of rheumatoid arthritis (RA) and systematic lupus erythematosus (SLE); however, their measurement in pleural fluid does not possess the same diagnostic accuracy for disease-related pleural effusions. RF titres may be measured in pleural fluid and are often >1:320 in rheumatoid pleuritis. Despite this finding, this measurement is rarely practiced in the clinical setting as the pleural levels often reflect serum values. One particular study confirmed this fact as it reported no additional diagnostic value above that of serum analysis alone [70]. Cyto logical assessment looking for “ragocyte” cells that consist of white blood cells with phagocytic intracellular inclusions is described in rheumatoid pleuritis but generally has low specificity. Pleural ANA is additionally not specific to SLE and may occur in malignancies. Interestingly, however, one study has suggested that pleural ANA measurement possesses good negative predictive value for SLE pleuritis and may be useful in this context [71]. Conversely, an alternative study of n = 266 patients has shown no additional value in measuring pleural ANA in the setting of SLE pleuritis [72]. Pleural ant double stranded DNA (dsDNA) also has good negative predictive value, whilst complement activation of pleural fluid in both RA and SLE has also been evaluated but is not routinely practiced in the clinical setting due to its low specificity [73].

5. Conclusion

Since the introduction of Light’s criteria in the 1970s, other proposed criteria and recommendations to overcome some of its drawbacks have been suggested, however, Light’s criteria have remained biochemically the most robust for differentiating exudates from transudates. This allows easier diagnosis for an underlying cause of a pleural effusion, avoiding unnecessary investigation. Nevertheless, most transudates are in fact secondary to congestive heart failure where clinical judgement and disease-specific markers such as NT-proBNP have been proven to be superior. Other useful disease-specific markers include ADA in the diagnosis of tuberculous effusions. Discriminating malignant and benign pleural effusions in the setting of an exudate remains a challenge. While there is no substitute to the histologic demonstration of malignancy, the role of tumour markers may emerge to have a larger contribution in the future as a complementary tool in the setting of MPE particularly when considering the invasiveness and lack of universal accessibility to thoracoscopy. Although workup of pleural effusions is a mix of both old and new measures, novel technologies such as global gene profiling and proteomics enable the identification of “fingerprints” for disease-specific markers that will undoubtedly improve our approach in the diagnosis for a definitive cause of a particular pleural effusion. Such future improvements do illustrate major advances from the simplistic transudate-exudate separation and do suggest that pleural fluid analysis is in fact a work in progress.

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Review Article
Tube Thoracostomy: Complications and Its Management

Emeka B. Kesieme,1 Andrew Dongo,1 Ndubueze Ezemba,2 Eshiobo Irekpita,1 Nze Jebbin,3 and Chinenye Kesieme4

1 Department of Surgery, Irrua Specialist Teaching Hospital, PMB 8, Irrua, Edo State, Nigeria
2 National Cardiothoracic Center, University of Nigeria Teaching Hospital, Enugu, Nigeria
3 Department of Surgery, University of Port-Harcourt Teaching Hospital, PMB 6173, Port-Harcourt, Nigeria
4 Paediatric Intensive Care Unit, Irrua Specialist Teaching Hospital, PMB 8, Irrua, Edo State, Nigeria

Correspondence should be addressed to Emeka B. Kesieme, ekesieme@gmail.com

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Background. Tube thoracostomy is widely used throughout the medical, surgical, and critical care specialties. It is generally used to drain pleural collections either as elective or emergency. Complications resulting from tube thoracostomy can occasionally be life threatening. Aim. To present an update on the complications and management of complications of tube thoracostomy. Methods. A review of the publications obtained from Medline search, medical libraries, and Google on tube thoracostomy and its complications was done. Results. Tube thoracostomy is a common surgical procedure which can be performed by either the blunt dissection technique or the trocar technique. Complication rates are increased by the trocar technique. These complications have been broadly classified as either technical or infective. Technical causes include tube malposition, blocked drain, chest drain dislodgement, reexpansion pulmonary edema, subcutaneous emphysema, nerve injuries, cardiac and vascular injuries, oesophageal injuries, residual/postextubation pneumothorax, fistulae, tumor recurrence at insertion site, herniation through the site of thoracostomy, chylothorax, and cardiac dysrhythmias. Infective complications include empyema and surgical site infection. Conclusion. Tube thoracostomy, though commonly performed is not without risk. Blunt dissection technique has lower risk of complications and is hence recommended.

1. Introduction

Tube thoracostomy is the most commonly performed surgical procedure in thoracic surgery. As a life saving procedure, general surgeons, intensivists, emergency physicians, and respiratory physicians may at one time or the other be required to perform tube thoracostomy.

The first documented description of a closed tube drainage system for the drainage of empyema was by Hewett in 1867 [1]. However during the Second World War, the experience gained in military and civilian hospitals contributed to the development of tube thoracostomy in chest trauma management, and, at the time of the Vietnam war, it has become the standard of care for management of chest trauma [2]. In 1992, Lilienthal reported the postoperative use of chest tube following lung resection for suppurrative diseases of the lung [3].

Tube thoracostomy is an invasive procedure and complications can result due to inadequate knowledge of thoracic anatomy or inadequate training and experience. These complications can simply be classified as technical or infective. Trocar technique is by far associated with a higher rate of complication [4, 5].

2. Methods

A literature review on tube thoracostomy was done from 1970 to date using manual library search, journal publications on the subject, and Medline. Full texts of the materials, including those of relevant references, were collected and studied. Information relating to the techniques, complications, and management of these complications were extracted from these materials.

3. Results

There are two principal methods of tube thoracostomy: the blunt dissection technique and the trocar technique.
The trocar technique is associated with a higher rate of intrathoracic organ injury [4]. A combination of both trocar technique and blunt dissection technique has been described [4]. Complications of tube thoracostomy can be classified as either technical or infective. Technical causes include tube malposition, blocked drain, chest drain dislodgement, reexpansion pulmonary edema, subcutaneous emphysema, nerve injuries, cardiac and vascular injuries, oesophageal injuries, residual/postextubation pneumothorax, fistulae, tumor recurrence at insertion site, herniation through the site, chylothorax, and cardiac dysrhythmias. Infective complications include empyema and surgical site infection including cellulitis and necrotizing fasciitis.

4. Discussion

4.1. Applied Anatomy. A sound knowledge of the anatomy of the thorax is important to avoid some complications of tube thoracostomy.

The intercostal spaces are filled with intercostal muscles, with the vein, artery, and nerve lying in the costal groove along the inferior margin of the superior rib from above downwards and situated between the second and the third layer of muscles (Figure 1). To avoid the neurovascular bundle, it is normally advocated that the drain be located in the interspace just superior to the rib. However, puncture done as close as possible to the superior margin of the inferior rib may lead to laceration of the collateral intercostal artery [6]. Recent study has shown that the ideal spot should be 50–70% of the way down the interspace [7]. Injury to this neurovascular bundles remain possible complication of the procedure.

British Thoracic Society (BTS) has recommended the triangle of safety as the site for insertion for intercostal drain [8]. This area is bordered by the anterior border of the latissimus dorsi, the lateral border of the pectoralis major muscle, a line superior to the horizontal level of the nipple, and an apex below the axilla (Figure 2). A survey of junior residents on the anatomical landmarks when inserting an intercostal drain revealed that 45% were placed outside the safe area of chest drain insertion with the most common error (20%) being a choice of insertion too low [9].

The midaxillary line is the most commonly advocated position for tube thoracostomy; the innermost layer of intercostal muscle being poorly developed at this point, and comprising thin intracostals, which blend with the internal intercostal layer except where separated by neurovascular bundles [10]. A more anterior position will lead to injury to the muscles and breast tissue while a more posterior position is more uncomfortable and has risk of drain leakage. The long thoracic nerve lies behind the midaxillary line on the surface of serratus anterior and deep to the fascia and segmentally supplies this muscle.

In full expiration, the two domes rise as high as the 4th dorsal intervertebral space on the right and 5th space on the left; hence, when a chest tube is placed too low, there is a high probability of abdominal placement. Inferior placement of chest tubes will not only perforate the diaphragm but will also damage intra-abdominal organs. The same will also apply to other conditions that elevate the diaphragm, for example, late pregnancy, gross obesity, massive ascites, and intraabdominal tumours [10].

Each lung is invested by and enclosed in a serous pleural sac that consists of visceral and parietal pleura. Parietal pleura is subsequently divided into costal, diaphragmatic, cervical, and mediastinal pleura. The anatomical relationship to mediastinal structures explains injuries to these organs when a chest tube is inappropriately placed too far into the chest.

The right lung consists of three lobes (upper, middle and lower) separated by the horizontal and oblique fissures while the left consists of two lobes (upper and lower) separated by an oblique fissure. The position of the oblique fissure in either lung can be shown by a line drawn from the spinous process of the second thoracic vertebra around the side of the thorax to the sixth rib in the midclavicular line while the horizontal fissure runs at the level of the fourth costal
cartilage and meets the oblique fissure in the midaxillary line. Chest tubes placed laterally in the fifth, sixth or seventh intercostal space will enter the chest near the oblique fissure and if directed centrally can enter the fissure [11]. Both the lung parenchyma and the fissures are thus potential sites of tube malposition.

5. Complications

5.1. Tube Malposition. Tube malposition is the commonest complication of tube thoracostomy [5, 12]. It is more common when tubes are inserted under suboptimal conditions and in urgent tube thoracostomy. Trocar technique of chest tube insertion has been shown to increase the risk of tube malposition compared with the blunt dissection technique [5].

Complication rates of tube thoracostomy have been found to be higher in the critically ill patients with about 21% of tubes placed intrafissurally and 9% intraparenchymally [13].

Tube malposition has been defined by CT confirmation in 4 locations: intraparenchymal, fissural, extrathoracic, and angulation of the drain in the pleural space [4]. In this review, tube malposition will be classified as intraparenchymal tube placement, fissural tube placement, chest wall tube placement, mediastinal tube placement, and abdominal tube placement.

5.1.1. Intraparenchymal Tube Placement. Intraparenchymal chest tube placement occurs more likely in the presence of pleural adhesions or preexisting pulmonary disease [14]. It may be dramatic if there is associated injury to pulmonary vessels. However, clinical manifestation may be absent, and the only clue to the diagnosis of tube malposition may be inadequate drainage of air and fluid. The routine frontal and lateral radiographs taken after chest tube insertion may be unreliable in demonstrating the exact location of the tube. In contrast, chest computerized tomographic (CT) scan has been shown to be superior and more accurate than plain radiographs in assessing malpositioned chest tubes and also in providing additional valuable information with significant therapeutic impact [5, 12]. The drawback of computerized tomographic scan of chest in the developing countries is its unaffordability.

5.1.2. Fissural Tube Placement. The probability of interlobar malpositioning is significantly higher when using the lateral approach of tube thoracostomy as opposed to the anterior approach. Curtin et al. found no significant difference between intrafissural and those located elsewhere in the following outcome measures: duration of thoracostomy drainage, quantity of pleural fluid drained, need for further tubes, length of hospital stay, appearance on last chest radiograph before discharge and need for surgical intervention [15]. This finding contrasts the result of Stark et al. that showed that tubes that lie within the fissure correlated with a lengthy and complicated hospital course [12].

On anteroposterior chest radiograph, an interfissural tube is more likely to extend centrally or superiorly in a straight line or follow a gentle curve from its point of entry unlike the normally placed tube in the anterior or posterior pleural space, which will be angulated or will follow a sharp curve at its point of entry [11]. Lateral radiograph confirms the position. Malfunctioning interfissural tubes should be repositioned or replaced to improve function.

5.1.3. Chest Wall Tube Placement. Subcutaneous tube placement is a rare complication with reported incidence between 1–1.8% [16]. An unstable chest wall secondary to multiple rib fractures, haematoma, and hurried chest tube insertion was suspected to be the etiological factor in a case reported by Ozpolat and Yazkan [17]. It can be identified clinically by tube malfunctioning and the lack of fluctuation of the fluid level in the drainage system and radiologically by subcutaneous position of the chest tube. This complication can be minimized by blunt dissection technique. Subcutaneous tube should be removed and replaced correctly into the pleural cavity.

5.1.4. Mediastinal Tube Placement. Placing chest tubes far into the thorax can result in perforation of heart, injuries to large vessels, perforation of the oesophagus, and nerve injuries. Details of these injuries will be discussed separately under cardiovascular injuries, oesophageal perforation, and nerve injuries.

5.1.5. Abdominal Placement. Triangle of safety has been advocated as the correct site for tube thoracostomy. Abdominal placement of tube usually occurs when tube thoracostomy is performed too low below this area. Injuries to the spleen, liver, and stomach have all been reported secondary to inadvertent passage of tube through the diaphragm [18]. Perforation of intra-abdominal viscera by chest tube is also possible in acquired diaphragmatic rupture with visceral herniation [19]. Injury to hollow viscus requires repair. The extent of surgery on a perforated solid viscus depends on the degree of injury.

5.2. Blocked Drain. Nonfunctional drain may be due to kinking (Figure 3), angulation, clot formation within the lumen or the presence of debris, or lung tissue. Smaller drains tend to kink or clot easier than larger drains especially when used in the setting of trauma [20]. A cardinal sign of blocked chest tube drain is failure of fluid within the tube to fluctuate with coughing or respiration. This ineffective drainage will result in undrained or unresolved pleural collection. Tension pneumothorax can also result in cases of ongoing air leak. Milking or stripping can be used to unblock semisolid contents, for example, blood clots or fibrin clots blocking the lumen of the tube. However, this is controversial and debatable as the negative pressure created may damage lung tissue. Chest drain should be unkinked in cases of kinking causing blockage.
5.3. Chest Drain Dislodgement. This can be partial or total. It can be prevented by meticulous care and good technique of drain anchorage. The use of mattress suture or a stay-in closure suture to secure the chest tube is recommended [8]. The use of purse-string suture in securing chest drain is complicated by poor cosmetic results and increased risk of skin necrosis. The seal provided by purse-string suture does not prevent air leaks [21]. The ideal suture to secure the tube should be strong and nonabsorbable, for example, “1” silk should include adequate skin and subcutaneous tissue to ensure it is secure [8]. A dislodged chest tube should be reintroduced with aseptic precaution through a new site.

5.4. Reexpansion Pulmonary Edema (REPE). This is an uncommon but fatal complication that can occur following tube thoracostomy for pneumothorax or pleural effusion. Mortality rate of up to 20% has been reported [22].

Reexpansion pulmonary edema has also been reported following transthoracic endoscopic sympathectomy for primary hyperhidrosis [23], reexpansion of lung after decortications [24], reexpansion after excision of giant mediastinal tumour [25], and following puncture of a giant bulla [26]. It usually occurs on the side ipsilateral to the reexpanded lung though cases of reexpansion pulmonary edema occurring on the side contralateral to the reexpanded lung [27] and even bilateral reexpansion pulmonary edema have been reported [28].

The aetiology of REPE is unknown, but certain hypotheses have been suggested. The most important pathophysiological mechanism appears to be increased endothelial permeability and loss of integrity of the alveolar capillaries leading to exudation of protein-rich fluid. The factors responsible for this include:

(a) Lung collapse itself: Destruction of pulmonary microvascular endothelium occur, probably due to anoxic stress, mechanical stress exerted on the endothelium by blood cells, and changes in lymph flow.

(b) The mechanical stress to normal vessels during reexpansion

(c) Increase in oxygen-free radical and increase of activity of its scavenger, catalase, in a reexpanded lung [29]. Oxygen-free radical may injure capillary endothelium. This hypothesis is supported by the observation that inhalation of oxygen at FiO₂ of 0.4 prevents pulmonary edema when lungs are reexpanded [30].

(d) Increase in leucocyte sequestration, interleukin-8 (IL-8), monocyte chemoattractant protein-1 (MCP-1) [31]. An increase in the level and activity of xanthine oxidase has also been reported [32].

(e) Low levels of surfactants have been noted in chronically collapsed lung [35]. Decrease of alveolar surfactant activity is said to include pulmonary edema by drastically lowering the intrapleural pressure and further lowering the perivascular pressure of the pulmonary microvessels.

This increase in IL-8 and monocyte chemoattractant protein (MCP) does not only occur in the affected lung, but also occurs to a lesser extent in the contralateral lung, partly explaining the phenomena of contralateral and bilateral reexpansion pulmonary edema [31, 33]. However, the main cause of contralateral REPE is thought to be secondary to the compression atelectasis of the contralateral lung associated with shift of mediastinum [34].

The risk factors for developing REPE in a patient include young age (<40 years), collapse of the affected lung for more than 3 days, large pneumothorax (>30% of single lung), application of significant negative pleural pressure suction and rapid lung reexpansion [22, 36, 37].

Clinical picture varies from asymptomatic radiologic findings to dramatic respiratory failure with circulatory shock. Patient usually becomes symptomatic within 2 hours after rapid lung reexpansion. There may be frothy sputum production associated with tachypnea, tachycardia, and cyanosis. Auscultation may reveal rales, and chest radiograph will reveal the presence of pulmonary infiltrates with ground glass appearance.

Prophylactic measures include recognizing patients at high risk, leaving thoracostomy tubes initially off suction, preferring underwater seal drainage rather than negative pressure apparatus, and ensuring that fluid exceeding 1 L must not be removed rapidly if the pleural pressure is not being monitored. The goal should be to keep the pleural pressure above −20 cm H₂O [38].

Treatment includes haemodynamic support (vigorous resuscitation and vasopressors), administration of supplemental oxygen, and, if need be, mechanical ventilation with positive end-expiratory pressure (PEEP). In cases of unilateral REPE, positioning the patient in lateral decubitus position with the affected side up will reduce intrapulmonary shunting and improve oxygenation [39]. The use of NSAIDS is not evidence based. Diuretics should be avoided due to the hypovolaemic status.
5.5. **Subcutaneous Emphysema.** Development of subcutaneous emphysema is a known complication of tube thoracostomy. It usually presents as subcutaneous crepitation demonstrable clinically or as an occult radiologic finding (Figure 4). Extensive subcutaneous emphysema may present with extreme discomfort, disfigurement, anxiety, upper airway obstruction [40], and pacemaker dysfunction [41].

Subcutaneous emphysema following chest tube insertion is more commonly associated with trauma, bronchopleural fistula, large and bilateral pneumothoraces, and mechanical ventilation. There is an established association with prolonged drainage, poor tube placement, tube blockage, side port migration, and a greater number of chest tubes. It results in a longer length of hospital stay and increased mortality [42].

Subcutaneous emphysema resulting from chest tube insertion is usually minor and self-limiting. Other modalities that have been tried in managing extensive subcutaneous emphysema include infraclavicular blow-holes (incising the skin and subcutaneous fascia to allow air to escape) [43], insertion of fenestrated angiocatheter into the subcutaneous tissue [44], subcutaneous pigtail [45], or large bore drains [46]. These modalities are rarely necessary.

5.6. **Nerve Injuries**

5.6.1. **Horner’s Syndrome.** Horner’s syndrome has been reported in the adult and paediatric populations [47, 48]. It is an oculosympathetic paresis, resulting from interruption of second-order preganglionic neurons and manifest as miosis, ptosis, hemifacial anhidrosis, and enophthalmos. Horner’s syndrome results from direct pressure of the tip of the chest tube on the sympathetic chain in the medial portion of the apex. A thin endothoracic fascia separates the parietal pleura from the ganglion [49]. This complication is therefore avoided by not placing the tip of the tube close to the apex.

The malpositioned tube should be pulled 2-3 cm back as soon as possible after radiological confirmation. The resolution can be complete, partial, or absent depending on the degree of injury to the ganglia.

5.6.2. **Phrenic Nerve Injury.** Diaphragmatic paralysis is an uncommon complication of tube thoracostomy, mostly reported in the paediatric population [50, 51]. The underlying aetiology is injury to the phrenic nerve secondary to tube malposition. Clinical suspicion should be confirmed by chest radiograph, fluoroscopy, nerve conduction studies, and magnetic resonance imaging (MRI). MRI may reveal haematoma in the region of the chest tube tip and phrenic nerve fibers [51]. Chiladiti sign occurring probably as a result of diaphragmatic paralysis has been reported by Gulati et al. [52].

Diaphragmatic paralysis following tube thoracostomy can be prevented by correct positioning of the chest tube tip at least 2 cm distant from the vertebrae [51]. Prompt recognition and correction of malpositioned tube or selection of softer chest tube is advised. Symptomatic cases with intractable respiratory distress should be managed by diaphragmatic plication.

5.6.3. **Injury to Long Thoracic Nerve.** Injury to long thoracic nerve of Bell causing winging of the scapula has been reported as a possible complication of tube thoracostomy [53]. Physiotherapy is the hallmark of treatment. Recovery of full muscle strength and complete recovery is possible after 6 months of regular physiotherapy.

5.6.4. **Ulnar Neuropathy.** This is a rare, though significant, complication associated with tube thoracostomy. Repositioning of tube leads to significant improvement. Management of persistent symptoms is expectant, with early upper extremity range of motion and strength exercise [54].

5.7. **Cardiac and Vascular Injuries**

5.7.1. **Cardiac Injuries.** Perforation of the heart is a rare catastrophic complication of tube thoracostomy. Injuries with perforation of the (R) atrium [55], (L) atrium [56], (R) ventricle [57], and the (L) ventricle [58] have all been reported. Predisposing factors in patients reported were thoracic deformities, enlarged cardiac chambers, trauma, and emergency respiratory conditions.

Miesel et al. reported perforation of the (R) atrium using trocar type thoracotomy technique in a patient with kyphoscoliosis [55]. Perforation of the (R) ventricle has occurred due to poor knowledge of the anatomy of the postpneumonectomy space by operating physician [57].

Perforation of the heart leads to immediate return and continuous stream of blood emerging from the chest tube leading to marked hypotension, haemorrhagic shock, and death. Prompt intervention is required. Perforation should be repaired by polypropylene suture via a thoracotomy.

5.7.2. **Injury to the Pulmonary Artery.** Injuries to the pulmonary artery and pulmonary artery pseudoaneurysm are rare serious complications of chest tube insertion [59–62].
5.7.3. Occlusion of Subclavian Artery. Subclavian artery ob-
be between 50–70% of the way down an interspace to avoid
aspect. The safest zone to perform tube thoracostomy should
neurovascular bundles on the groove located on the inferior
traumatized. Dissection during tube insertion should be
of chest tube. Intercostal arteries may bleed profusely when
This is a cause of haemorrhage during the insertion
Fistula.

5.7.4. Intercostal Artery Injury and Chest Wall Arteriovenous
5.7.3. Occlusion of Subclavian Artery. Subclavian artery ob-
5.7.4. Intercostal Artery Injury and Chest Wall Arteriovenous
Fistula. This is a cause of haemorrhage during the insertion
of chest tube. Intercostal arteries may bleed profusely when
traumatized. Dissection during tube insertion should be
done above the superior border of the rib to avoid the
neurovascular bundles on the groove located on the inferior
aspect. The safest zone to perform tube thoracostomy should
be between 50–70% of the way down an interspace to avoid
the variably positioned superior intercostal neurovascular
bundle and the inferior collateral artery [7]. Systemic
arteriovenous fistula (SAVF) involving an intercostal artery
and subcutaneous vein can result after tube thoracostomy
[67]. The clinical manifestations of a traumatic SAVF may
be immediate or delayed, ranging from 1 week to 12 years.
The classical physical signs are pulsatile mass, palpable thrill,
and machinery murmur. Chest radiography may reveal bone
density with bone erosion. However, the gold standard
for investigation is selective angiography. Modalities of
treatment include surgery and more recently, transcatheter
embolization.

5.8. Residual/Postextubation Pneumothorax. This is avoided
during the removal of chest tube by maintaining a sustained
valsalva manoeuvre to forcibly inflate the lung against
the chest wall with breathing suspended until the purse
string is tied. Residual pneumothorax may be secondary to
persistent air leak from underlying pathology. Repeat tube
thoracostomy is indicated if pneumothorax is significant or
if it is secondary to persistent air leak. However, in persistent
air leak, chest tube should not be removed prematurely.
Small residual/postextubation pneumothorax requires no
intervention.

5.9. Esophageal Perforation. Esophageal perforation follow-
ing closed tube thoracostomy drainage has been reported
both in the normal esophagus and at the site of esophageal
anastomosis/myotomy following repair of esophageal atresia
[68, 69].

Drainage of enteric contents is pathognomonic of this
condition. Diagnosis is confirmed by contrast studies. The
goal of management is to eliminate the source of soilage and
to ensure adequate nutrition.

Conservative management with feeding gastrostomy was
used to manage a reported case [70], but surgery is the
mainstay of treatment. Options of surgery include primary
repair with or without buttressing of suture lines, muscle
flap closure, exclusion and diversion, drainage, and resection.
This complication can be avoided by early recognition and
repositioning of chest tube.

5.10. Fistula

5.10.1. Acquired Bronchocutaneous Fistula. Bronchocuta-
nous fistula is a pathologic communication between the
bronchus, pleural space, and subcutaneous tissue. Acquired
bronchocutaneous fistula has been reported as a complica-
tion of tube thoracostomy [71]. Because of constant air leak,
this complication needs to be treated immediately to prevent
devastating pulmonary infection. Treatment options include
endoscopic repair, parietal pleurectomy, and pleurodesis.

5.10.2. Pleurocutaneous Fistula. Pleurocutaneous fistula is
declared as a pathologic communication between the
pleural space and the subcutaneous tissues. Pleurocutaneous fistula
secondary to tube thoracostomy has been reported in few
studies [72]. Patients with pleurocutaneous fistula exhibit no
physical signs. Computerized tomographic scan of the chest
is usually the mainstay of diagnosis; however, chest ultra-
sonography has been found to be useful both as a tool for
making diagnosis and following up these patients. Treatment
is directed both at the casual agent and predisposing factor.

5.11. Tumor Recurrence at Insertion Sites. Tumour recurrence
is possible at thoracostomy tube insertion sites. This may be
a manifestation of a local spread or distant metastasis, and
this complication is more related to the postsurgical proce-
dure rather than percutaneous chest tube placement itself.
Hayes-Jordan et al. reported 2 cases of tumor recurrence
at thoracostomy tube insertion sites after intraoperative
gross spillage of pleuropulmonary blastoma and malignant
epithelial thymoma [73]. Caution must be exercised to avoid
spillage of tumours at the time of resection especially in
tumours that are relatively resistant to chemotherapy and
radiotherapy. Treatment will depend on the response of the primary tumour to the modalities of surgery, chemotherapy, or radiotherapy.

5.12. Cardiac Dysrhythmia. Arrhythmias may rarely complicate chest tube insertion [74–76]. These may result from mechanical stimulation of the heart or its covering, the pericardium or due to irritation of the vagus nerve. Sudden death due to a profound unresponsive bradycardia has been observed following tube thoracostomy that resulted in haemorrhage and irritation of the vagus nerve [74].

In patients that presented with atrial fibrillation following chest tube insertion, factors that suggested that the tube was the culprit included the close association between the time the chest tube was inserted and the onset of arrhythmias, cessation of arrhythmias following tube withdrawal, no further occurrence of arrhythmias, location of kinked chest tube by chest radiograph, and proximity to the right atrium [75, 76]. Antiarrhythmic agents are not beneficial in this condition. Chest tube should be withdrawn and the effect on arrhythmias monitored.

5.13. Herniation of a Lung Bulla through Insertion Site. A previous thoracostomy site may serve as a weak point on the chest wall allowing herniation. Three cases of herniation of emphysematous bullae through a previous tube thoracostomy site have been reported [77–79]. The reported cases were mainly managed by surgical excision through a thoracotomy though there is room for conservative management of herniated bullae.

5.14. Chylothorax. Chylothorax has been reported as a late complication of traumatic chest tube insertion with injury to the thoracic duct [80]. This complication should be included in the differential diagnoses of patients presenting with chylothorax after tube thoracostomy. Line of management may be conservative (limited oral intake and supplementation with medium chain triglycerides (MCTs), which directly enter the portal system) or surgical.

5.15. Infectious Complication. Closed tube thoracostomy is classified as “clean contaminated” and hence risk of infection of wound is 7.7%. Studies of empyema secondary to tube thoracostomy have reported complication rates as low as 1% and as high as 25% [81, 82]. Studies have shown that the rate of empyema is higher when pleural effusion was present before tube thoracostomy [81]. The presence of pleural effusion allows nosocomial colonization from respiratory tract leading to subsequent empyema.

The usefulness of prophylactic antibiotics following tube thoracostomy has remained controversial. Prophylactic antibiotics have been found unnecessary in patients with primary spontaneous pneumothorax who require closed tube thoracostomy [83]. This has been shown not only to be very cost effective but also prevent complications from antibiotics abuse.

Concerning tube thoracostomy following chest trauma, there is insufficient evidence to support the blanket use of prophylactic antibiotics for all patients though antibiotics prophylaxis is appropriate for those at an increased risk of developing infectious complications.

Many studies have revealed significant reduction in empyema and pneumonia in patients who sustained chest trauma and require tube thoracostomy and were placed on prophylactic antibiotics compared with placebo [84, 85]. However, based on flawed methodology, these conclusions cannot be supported. Empyema occurs more frequently after penetrating chest trauma than blunt chest trauma as penetrating injuries allow direct entry of microorganisms into the pleural space.

Surgical site infection can range from cellulitis to necrotizing soft tissue infection. Tube thoracostomy drainage for empyema thoracis has a higher probability of giving rise to necrotizing soft tissue infection. Prevention of wound site infection is by adequate skin preparation. Cellulitis usually responds to antibiotics.

Necrotizing fasciitis after tube thoracostomy has been reported complicating empyema thoracis [86], secondary spontaneous pneumothorax for tuberculosis [87] and in patient with Werdnig-Hoffman disease [88].

Infection usually begins as an area of redness that will later give rise to dusky and purplish skin, signs of tissue necrosis, purulent discharge, bullae, severe pain, and subcutaneous emphysema with systemic features. Chest radiograph will reveal the presence of gas in the subcutaneous plane. Line of management involves antibiotics, aggressive surgical debridement, and repeat debridement as the case may be. Once infection is controlled, skin grafting is done. Free flap is seldom required but must be considered when treating more complex defects. Microsurgical reconstruction with latissimus dorsi free flap has been used for pleural reconstruction and wall stabilization [89]. The use of hyperbaric oxygen is being encouraged as it has a bacteriocidal effect, improve polymorphonuclear function, and enhance wound healing.

6. Conclusion

Tube thoracostomy is not without risk. Blunt dissection technique has lower risk of complications and is hence recommended. It is important to keep to the triangle of safety to limit these errors. Most of these complications are preventable and when they occur, they must be adequately and correctly managed.

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