PLEURAL TISSUE VERSUS PLEURAL FLUID CULTURE IN MICROBIOLOGICAL DIAGNOSIS OF PLEURAL INFECTION: COMPARATIVE STUDY

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Abstract

Background and objectives: Managing pleural infection can be challenging due to the significant morbidity and mortality of this healthcare problem. Identifying the causative organism poses a significant difficulty, as traditional cultures have low sensitivity. To address this issue, this study aimed to investigate the role of pleural tissue culture in improving the microbiological yield for pleural infections.

Methods: This study was conducted at the Chest Department of Kasr Al-Ainy Hospital, Cairo University, and involved 30 patients diagnosed with pleural infection. Of these, 17 patients underwent ultrasound-guided true-cut needle biopsies, while 13 underwent thoracoscopic pleural biopsies. Tissue samples, pleural fluid, and blood were collected from all patients for culture and analysis.

Results: The mean age of patients was 39 ± 15 years, with 90% male. The incidence of intravenous drug addiction was 23%, and 73% had poor dental hygiene. Of the patients, 20% had diabetes. The pleural fluid culture was positive in 17% of patients (5 out of 30), and the blood culture was positive in 16.7% (2 out of 30). Most pleural tissue cultures were negative, with only 3.3% being positive.

Conclusion: Whether ultrasound-guided or thoracoscopic, tissue culture does not increase the microbiological yield compared to conventional pleural fluid culture. Therefore, further research is necessary to determine the potential benefits of medical thoracoscopy in diagnosing and managing pleural infections.

Keywords:

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1. INTRODUCTION

Pleural infection is a prevalent and challenging medical condition that, if not adequately managed, can lead to prolonged hospital stays and require more aggressive treatments (1).

Pleural infection is characterized by purulent pleural fluid or pleural effusion with a pH below 7.2, associated with signs of a chest infection or proven bacterial invasion of the pleural space. Identifying the causative organisms is a critical step in managing pleural infection. It permits a better choice of antimicrobial agents, resulting in improved treatment outcomes, lower complication rates, shorter hospital stays, and reduced healthcare costs (2).

Conventional pleural fluid cultures have limited sensitivity, with a reported sensitivity range of 40% to 60% (3). In recent years, pleural tissue culture has been adopted as an alternative approach to increase the diagnostic yield in pleural infections; however, its role in clinical practice has yet to be established. Real-time, ultrasound-guided pleural biopsy, performed by respiratory physicians, is a safe and easily performed procedure that is effective in diagnosing different pleural diseases. Medical thoracoscopy, also known as local anesthetic thoracoscopy (LAT), is a minimally invasive and safe procedure with well-established diagnostic and therapeutic purposes in various pleural diseases, including pleural infections (4).

Thoracoscopic pleural biopsies have been shown to have a higher diagnostic yield than conventional pleural fluid cultures. This method is likely because thoracoscopic biopsies are more extensive and allow for the sampling of pleural tissue, which may harbor a higher concentration of infectious organisms. Additionally, thoracoscopic biopsies allow for visualization of the pleural space, which can aid in identifying areas of infection and inflammation. In one study, thoracoscopic biopsies had a diagnostic yield of 89%, compared to 63% for pleural fluid cultures (5).

It is important to note that while thoracoscopy is a safe and effective procedure, it requires specialized training and equipment and should only be performed by experienced physicians. This study aimed to

compare the diagnostic yield of pleural tissue culture with that of standard pleural fluid culture in patients with pleural infection, plus assessing whether pleural tissue culture can improve the identification of causative organisms in pleural infections, which can aid in selecting appropriate antimicrobial therapy and improve treatment outcomes, thus may provide valuable insights into the utility of pleural tissue culture in managing pleural infection and may guide clinicians in selecting the most appropriate diagnostic approach.

2. METHODS

Patients and study design

A comparative cross-sectional study was conducted at Chest Department, Kasr Al Ainy Hospital, Cairo University, in collaboration with the Clinical and Chemical Pathology Department, Cairo University, from April 2018 to April 2021. The study received approval from the research ethic committee at Cairo University with the study code: MD-06-2019.

The study included 30 patients diagnosed with pleural empyema, based on pleural fluid aspirate that met at least one or more of the following criteria: grossly frank purulent, gram stain positive for bacteria, bacterial culture positive, acidic with a pH <7.2, low pleural fluid glucose (<55mg/dL), and CT evidence of pleural infection (6). However, patients who were under 18 years of age, had no pleural fluid available for analysis, had pleural infections caused by Mycobacterium tuberculosis or those associated with malignant effusion, had coagulation defects (prothrombin concentration <60%, platelets count <60 000/mm3), or were unable to give informed consent were excluded from the study.

Sampling and bacteriological examination

- **Pleural fluid sample:** Pleural fluid samplings were done using a syringe attached to a green needle, which was inserted into the pleural space using the technique described by BTS- British Thoracic Society, 2010; about 20-50 ml fluid was withdrawn and sent for biochemical analysis, including pH, lactate dehydrogenase (LDH), protein content, glucose; differential leucocytic count; Gram stain; and culture (7).
- **Pleural tissue sample:** The first 13 patients were subjected to medical thoracoscopy for tissue samples; rigid thoracoscopy was done in the lateral position; a single incision after giving local anesthesia with 2% lidocaine and sedation with midazolam, a small caliber trocar (14F) was introduced into the intercostal space in order to produce a pneumothorax. After enlarging the channel, a larger flexible trocar (10 mm) was introduced. Suction was then applied to remove the pleural fluid. A rigid thoracoscope of 7 mm diameter was inserted into the pleural cavity. When they were present, adhesions were lysed using biopsy forceps or cautery. The thoracoscope was connected to a video camera, and the lesions were viewed on a computer screen. Biopsies were taken from abnormal lesions. An intercostal drain was inserted post-procedure (8). The subsequent 17 patients were subjected to ultrasound-guided true-cut pleural biopsy; the patient was under local anaesthesia with 2% lidocaine, and the tip of the cutting needle was inserted through the guide channel into the pleural superstratum. The number of punctures depended on the quality of the specimens and the patient's tolerance (9). All specimens were immediately sent to the laboratory for further culture and sensitivity.
- **Microbiological examination:**

1. Pleural fluid culture: Specimens were prepared for Gram and Leishmann staining through cytocentrifugation and placing one drop of sediment on two slides. The Gram-stained film was used to identify polymorphs and organisms, while the Leishmann-stained slide was used for the differential total leucocytic count. Blood agar, chocolate agar, and McConkey agar plates were inoculated with 2-3 drops of a sediment of specimen after centrifugation to perform an aerobic culture. Additionally, up to 1 ml of the specimen was inoculated into 5 ml of brain heart infusion broth. Incubation occurred at 35-37°C in ambient air for 3-4 days for blood agar and MacConkey plates and at 35-37°C with 5% CO2 for chocolate agar plates. Media were observed for macroscopic evidence of growth every 24 hours. Brain heart infusion broth was examined for turbidity every 48 hours, and subcultured on blood, chocolate and MacConkey agar plates, if present. However, Neomycin blood agar was inoculated for anaerobic culture with 2-3 drops of the sediment of specimen after centrifugation and 1 ml of the specimen was added to 5 ml thioglycolate broth. Plates were incubated under anaerobic conditions at 35-37°C for seven days. The thioglycolate broth was examined every 48 hours for turbidity and subcultured on neomycin blood agar if present, followed by incubation under anaerobic conditions.

2. Pleural tissue culture: Aerobic culture involved cutting a portion of the pleural tissue with a sterile scalpel and inoculating one piece onto blood agar, chocolate agar, and MacConkey agar plates. Plates were then incubated and observed daily for bacterial growth. Blood agar and MacConkey plates were incubated at 35-37°C in ambient air for 3-4 days, while chocolate agar plates were incubated at 35-37°C with 5% CO2 for 3-4 days. One piece of tissue was saved without cutting for the smears. In addition, another portion was cut with a sterile scalpel to conduct anaerobic culture. A smaller piece was immediately placed on neomycin blood agar, while another piece was placed into thioglycolate broth and incubated at 35-37°C. The plates were streaked for isolation and incubated under anaerobic conditions

for seven days. The broth was observed every 48 hours for turbidity, subcultured on neomycin blood agar if turbidity appeared, and incubated under anaerobic conditions. To prepare the smear for Gram staining, touch prep smears were made after inoculation to prevent contamination. A fresh tissue cut was touched to a slide to prepare the smear. Gram staining was performed on the smear to evaluate the culture, allowing for the recording of the relative numbers of WBCs, epithelial cells, and bacterial and fungal morphotypes.

3.Blood culture: For blood culture: Aerobic BACTEC™ vials were inoculated and placed in a BACTEC™9120 fluorescent series instrument (Becton Dickinson, USA) for 5-7 days. CO2 production from metabolizing organisms caused an increase in the fluorescence of the vial sensor, indicating positive blood culture. Positive vials were subcultured on blood, chocolate, and MacConkey agar plates and Gram-stained. The plates were then incubated and examined as previously described (10). If bacterial growth was detected on aerobic culture plates, standard microbiological techniques were used for identification, followed by antimicrobial susceptibility testing (11).

4.Antimicrobial susceptibility testing: The antibiotic susceptibility of the isolates was determined using the modified Kirby Bauer disk diffusion method. The antibiotics used for Gram-negative organisms included amikacin, amoxicillin-clavulanic acid, ampicillin, cefepime, cefoperazone, cefoxitin, cefotaxime, ceftazidime, ceftriaxone, cefuroxime, ciprofloxacin, gentamicin, imipenem, levofloxacin, meropenem, ofloxacin, piperacillin/tazobactam, and trimethoprim/sulfamethoxazole. For Gram-positive organisms, antibiotics used were penicillin, cefoxitin, ciprofloxacin, clindamycin, erythromycin, doxycycline, gentamicin, linezolid, levofloxacin, ofloxacin, and trimethoprim/sulfamethoxazole, along with E-test for vancomycin susceptibility testing. Antimicrobial discs were obtained from Mast Group Ltd., UK, and stored according to the manufacturer's instructions. The susceptibility testing was performed and interpreted following the methodology and breakpoints defined by the Clinical and Laboratory Standards Institute (CLSI) (CLSI, 2020). Escherichia coli ATCC 25922, Staphylococcus aureus ATCC 25923 and Pseudomonas aeruginosa ATCC 27853 were used as quality control reference strains for antimicrobial susceptibility testing. The diameters of the inhibition zones were recorded and interpreted as sensitive, intermediate, or resistant, according to the CLSI guidelines 2020 (12).

STATISTICAL ANALYSIS:

The statistical package for the Social Sciences (SPSS) version 26 (IBM Corp., Armonk, NY, USA) was used to code and enter the data. The quantitative data were summarized using mean, standard deviation, minimum, and maximum. Categorical data were summarized using frequency (count) and relative frequency (percentage). The Chi-square test was used to compare categorical data. In cases where the expected frequency was less than 5, the Exact test was used instead. P-values less than 0.05 were considered statistically significant.

3. RESULTS

Characteristics of patients

Table (1) showed that the mean age of the patients was 39 years, with a standard deviation of 15 years. Furthermore, most of the patients (90%) were males. Among the patients, 20% had diabetes mellitus (DM), while poor dental hygiene was the most common issue observed in 73.3%. Additionally, 23.3% of the patients had a history of intravenous drug addiction, the diagnosis of infective endocarditis was confirmed by transthoracic echocardiography in approximately 10% of the patients, and around one-third had comorbidities.

Microbiological culture of different biological samples modalities

Table (2) showed that six of the 30 patients included in the study tested positive for cultures. One patient had positive pleural tissue, fluid, and blood cultures, while four had positive pleural fluid cultures but negative blood and fluid cultures. The pleural fluid culture results indicated that 83.3% of patients had "No growth" results. The remaining patients showed Pseudomonas, Pseudomonas MDR, Klebsiella, Acinetobacter growth, and mixed growth of Gram-negative organisms. Blood cultures were negative in 93.3% of patients, with only one patient showing growth of Klebsiella MDR and another showing growth of Staph-aureus. Surprisingly, most pleural tissue cultures were negative (96.7%), with only one patient showing growth of Acinetobacter and Klebsiella.

Furthermore, in **Table (3)**, only one patient had positive results in all samples. Blood culture was only positive, specifically for Staphylococcus aureus in one case, who was an intravenous drug abuser and was diagnosed with infective endocarditis, with negative pleural fluid and pleural tissue cultures. In four other patients, the causative organism was only identified by pleural fluid culture, while pleural tissue and blood cultures were negative.

Table (1): Basic characters of patients with empyema

Factors	**Total (n=30)**	
	Mean	**SD**
Age	39	15
Sex	N	%
Female	3	10%
Male	27	90%
DM		
Yes	6	20%
No	24	80%
Dental		
Poor	22	73%
Normal	8	27%
IV drug		
Yes	7	23%
No	23	77%
Endocarditis		
Yes	3	10%
No	27	90%
Comorbidity		
Yes	10	33%
No	20	67%

N: number, **SD:** Standard deviation

Table (2): Organisms in different culture modalities

Culture	**Total (n=30)**	
1- Blood	**N**	**%**
♦ **No growth**	28	93.3%
♦ **Growth**	2	6.6%
➢ **Staph aureus**	1	3.3%
➢ **Klebsiella (MDR)**	1	3.3%
2- Pleural fluid	**N**	**%**
♦ **No growth**	25	83.3%
♦ **Growth**	5	16.7%
➢ **Pseudomonas MDR**	1	3.3%
➢ **Pseudomonas**	1	3.3%
➢ **Mixed growth (-ve)**	1	3.3%
➢ **Klebsiella**	1	3.3%
➢ **Acinetobacter**	1	3.3%
3- Pleural biopsy	**N**	**%**
♦ **No growth**	29	96.7%
♦ **Growth**	1	3.3%
➢ **Acinetobacter + Klebsiella**	1	3.3%

N: number

Table (3): Comparing between the three different modalities of culture

Positive samples	**Blood**	**Pleural fluid**	**Pleural biopsy c/s**
Sample.1	Klebsiella (MDR)	Mixed growth (-ve)	Acinetobacter + Klebsiella
Sample.2	Staph aureus	No growth	No growth
Sample.3	No growth	Klebsiella	No growth
Sample.4	No growth	Pseudomonas	No growth
Sample.5	No growth	Acinetobacter	No growth
Sample.6	No growth	Pseudomonas MDR	No growth

4. DISCUSSION

Pleural infection is an inflammatory process caused by various pathogens, and the primary treatment is antimicrobial agents along with prompt drainage of the infected fluid. Empirical antibiotic selection is typically used until the causative agent can be identified, reducing broad-spectrum antibiotics and improving patient response to treatment while minimizing side effects and antibiotic resistance. However, traditional cultures may not always identify the offending organism (13).

The current study found that the mean age of patients with empyema was 39±15 years; most were males (90%). The vast essential risk factors for infection in our cohort were poor dental hygiene and intravenous drug addiction; in 73.3% and 23.3% of patients, respectively. Previous studies support these results; hence, the age of thirty and male predominant was typical in patients with empyema in two recent studies (14-15). However, other study found that older age than sixty and female patients were more likely to have empyema (16). Moreover, poor dental hygiene and intravenous drug addiction were considered potential risk factors associated with pleural infection in smaller studies (14, 17). Despite the smaller percentage of cases, it could be due to underestimating the community-associated stigma with IV addiction.

Considering the pleural fluid culture, the current results revealed that only a small proportion (17%) of patients had positive culture results, while the majority (83%) showed no growth. Among the positive cultures, various organisms were identified, including Pseudomonas, Pseudomonas MDR, Klebsiella, Acinetobacter, and mixed growth of Gram-negative organisms. These findings are consistent with those of **Psallidas et al.** who reported positive cultures in only 20% of cases, with different patterns of biogram, including Staph aureus (MSSA), mixed anaerobes, Klebsiella pneumonia, and anaerobes (16). The low sensitivity of pleural fluid culture has been reported in many studies, with rates ranging between 40-60% (18-20). However, some studies have reported even lower rates of positive cultures; they reported negative pleural fluid cultures in 80% and 91% of cases, respectively (17, 21).

These findings suggest that pleural fluid culture may have limited diagnostic value, and other diagnostic tests may be necessary to confirm the diagnosis of pleural effusion. Additionally, the variability in culture results may reflect differences in patient populations, underlying medical conditions, and the use of antibiotics before collecting pleural fluid samples.

Furthermore, the blood culture results of our cohort exposed that only a small proportion (16.7%) of patients had positive cultures, with the growth of klebsiella MDR in one patient and staph-aureus in another. These findings were consistent with those of **Psallidas et al.,** who reported positive blood cultures in only 10% (2/20) of cases, with the growth of anaerobe and methathelin resistance Staphylococcus aureus (16). Notably, in both studies, the patients with positive blood cultures had negative pleural fluid and pleural tissue cultures, suggesting that blood culture may be a more sensitive diagnostic test than pleural fluid or tissue culture. However, it should be noted that the low rate of positive blood cultures may be influenced by several factors, such as the timing of blood culture collection, the volume of blood collected, and the use of antibiotics before blood culture collection. Additionally, some organisms may be more likely to cause pleural infection than bloodstream infection, which may further contribute to the low rate of positive blood cultures in patients with pleural effusion.

In our study, the majority (96.7%) of pleural tissue cultures were negative, with only one patient showing growth of Acinetobacter and Klebsiella. These results came in contrast to the findings of **Psallidas et al.** who reported positive tissue cultures in 45% (9/20) of cases, with the growth of Streptococcus, Streptococcus intermedius, K. pneumonia, S. aureus (MMSA), Staphylococcus epidermidis, S. intermedius, and anaerobes (16). The higher rate of positive tissue cultures in the **Psallidas** study may be due to the use of pleural biopsy, which had the highest diagnostic yield of all techniques, and the assumption that microbes are more likely to be located on the parietal pleural surface, which has a better blood supply and nutrition than the pleural fluid.

In the **Psallidas** study, the pleural biopsy was the only microbiologically positive sample obtained in 25% of cases. This data underscores the importance of using multiple diagnostic techniques, including pleural fluid, pleural tissue, and blood cultures, to increase the likelihood of identifying the causative organism. Moreover, the limited antibiotics penetration and efficacy to the pleural space may have contributed to the negative culture results. These findings are consistent with those of **Kheir et al.** who reported that pleural fluid culture was positive in only 18.75% of cases, with two additional patients showing positive pleural biopsy cultures (22). He used novel thoracoscopic biopsies for tissue culture, which may have increased the diagnostic yield.

Overall, the low yield of culture techniques in our study and others highlighted the need for alternative diagnostic tests. Additionally, the use of antibiotics prior to sampling should be carefully considered and documented, as it may impact the diagnostic accuracy of culture techniques.

Our study had some limitations; the first was a small sample size (30 patients), which may restrict the generalizability of the findings to other populations; the second was the study conducted in a single center; the third was using antibiotics prior to

sampling in all patients, which may have impacted the diagnostic accuracy of the culture techniques.
In summary, in the present study, while pleural fluid culture may be a more sensitive diagnostic test for pleural infection than blood culture or tissue culture, the low rate of positive cultures highlights the need for additional diagnostic tests, such as imaging studies or biomarker analysis, to confirm the diagnosis of pleural effusion. Further research is needed to understand better the factors that influence the diagnostic accuracy of pleural fluid culture in patients with pleural effusion, plus to identify the most effective diagnostic strategies for pleural infection.

5. DECLARATIONS

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Author's contribution
Main Idea: Prof Raef Hosny.
Collection of Data: Naglaa Bakry, Yasmin Hamdy, Dina Sobhy.
Pleural Biopsy: Raef Hosny, Yasmin Hamdy, Dina Sobhy.
Sample Analysis: Sherifa Tarek.
Statistical data analysis: Naglaa Bakry, Dina Sobhy.

All Authors shared in reviewing and accepting final paper.

COMPETING INTERESTS
All authors declare no conflict of interest. Each author has revised and approved the final version of the manuscript independently.

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