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Research Article

# Prevalence and Microbiology of Secondary Bacterial Infections of Chest Tube Drains in Patients with Confirmed Tuberculous Pleural Effusion, Retrospective Study from TB Endemic Country

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## Abstract

**Introduction:** Secondary bacterial infections of chest tubes placed to drain tuberculous pleural effusions are common but has not been studied before. The aim of this study is to estimate the frequency of these secondary bacterial infections in patients with suspected drain infections based on clinical signs and symptoms and to assess the prevalence, microbiological and biochemical profile of their pleural fluid samples and the effect of the presence of the tuberculous effusion and the ongoing anti-TB chemotherapy on this prevalence.

**Methods:** This is a multicenter retrospective observational study. We enrolled 690 patients with confirmed TB effusion being treated with first class anti-TB drugs and chest tube drain. Strict exclusion criteria were applied. Patients were divided into two groups, group A (220 patients), who had suspected secondary bacterial infection of their chest tube drains and who developed signs or symptoms of drain infections. Group B (470 patients), who had no suspected secondary bacterial infection in their chest tube drains. Pleural fluid samples and cultures and insertion site samples were taken from both groups then cytochemical and microbiological profiles were assessed.

**Results:** In biochemical analysis: there were statistically significant differences between groups A and B regarding the levels of LDH (1466.9 ± 6169.4 U/l versus 255.2 ± 445.4 U/l; P < 0.001) which was significantly higher in group A. In the other hand, glucose was significantly higher in group B (109.4 ± 82.2 mg/dl versus 131.6 ± 76.4 mg/dl; P < 0.001). In Cytological analysis, the percentages of total nucleated cells (mainly neutrophils) were significantly higher in group A, while the percentages of lymphocytes were significantly higher in group B. In microbiological analysis, pleural fluid cultures were positive in 34% of group A samples and were positive in only 6% of group B samples. Insertion site cultures were positive in 14% of group A samples and 4.2% of group B samples. The PPV and NPV of chest tubes drain culture for insertion site infection for group A were 36.5% and 97.5% respectively, and for group B were 37.5% and 97.8% respectively. Gram positive bacteria were the most prevalent bacterial isolates from both groups A and B, 74% and 48% respectively. Staphylococcus aureus species were the predominant bacteria in both groups A and B, 63% and 42.8% respectively. Gram negative bacteria were more prevalent in group B (42%) with Pseudomonas species were the most common gram-negative bacteria (21%).

**Conclusion:** Clinical features is a good evidence for the presence of secondary bacterial infection of chest tube drains in patients being treated for tuberculous effusion and this was confirmed by bacterial cultures. In addition, the presence of ongoing pleural mycobacterial infection and anti-TB drug treatment has not altered the causative bacteria profile from what has been reported for other cases. Staphylococcus aureus and Pseudomonas species being the more prevalent organisms.

***Keywords:*** *Retrospective Study; Tuberculous Pleural Effusion (TPE); Secondary Bacterial Infection (SBI); Insertion Site Infection (ISI); Pleural Co-Infection*

## Abbreviations

TPE: Tuberculous Pleural Effusion; SBI: Secondary Bacterial Infection; ISI: Insertion Site Infection

## Introduction

### Secondary bacterial infections of chest drains in Tuberculous effusion

Tuberculosis is one of the well-known, mostly-curable diseases. It accounts for millions of active disease cases and deaths worldwide. According to the last World Health Organization report that was released in October 14, 2020, there were an estimated 10 million people fell ill with tuberculosis worldwide [1]. Tuberculous pleural effusion (TPE) is the second most common form of extrapulmonary tuberculosis [2]. TPE is a self-limited disease, however, treatment is warranted in some cases. The drug treatment of TPE is the same as that for pulmonary TB [3]. Other treatments include chest tube drains and surgery [4,5].

Although the risk of infection transmission is low with chest tube placement, however, secondary bacterial infections (SBI) of chest drain still happened like any other intrahospital procedure-related infection [6]. Clinical and microbiological features usually help to diagnose these infections [7]. Many bacterial organisms were reported to be the cause of these pleural SBIs. However, SBIs of chest tube drains in patients with TPE and who are receiving anti-TB drugs were not studied before and to our knowledge our study is the first retrospective observational study that figure this out.

## Aim of the Study

The aim of this study was to estimate the frequency of SBIs in chest tube drains in patients with confirmed tuberculous effusions who has suspected drain infections based on clinical signs and symptoms. And to assess the prevalence, microbiological and biochemical profile of these pleural fluid samples and the effect of the presence of the TPE and the ongoing anti-TB chemotherapy on this prevalence.

## Methods

### Study design

This multicenter retrospective observational study was carried out at three tertiary hospitals in Jeddah, Saudi Arabia during a period of three years from February 2017 to March 2021. Relevant information such as age, sex, culture and sensitivity were collected from the records after taking approval from Institutional Ethics committees and individual written consent. Patient who had concurrent immunodeficient state (e.g. HIV infection, organ transplant and post-chemotherapy) or those who had received antimicrobial therapy in the last three months before the study were excluded. In addition, we excluded patients with chest tubes inserted at other centers. We make sure that all patients had negative bacterial culture of their pleural fluid after admission. All of our patients in this study were diagnosed with uncomplicated tuberculous pleural effusion using either VATS pleural biopsy or PCR detection of mycobacterium tuberculosis in pleural fluid or both and were treated with both first line anti-tuberculous medications and intercostal chest tube drainage during admission. A total of 764 patients were reviewed in the study but 74 patients were excluded as they did not meet the inclusion criteria, however, 690 patients of age more than 18 years with uncomplicated tuberculous effusion were included in this study (Figure 1). Those 690 patients were divided into two groups, group A and group B. Group A, 220 patients, were patients who had suspected secondary bacterial infection of their chest tube drains and who developed signs or symptoms of drain infections such as, new onset fever, redness, tenderness, or pus around drain insertion site or in the drain tube. Group B, 470 patients, were patients who had no suspected secondary bacterial infection in their chest tube drains. Pleural fluid samples and insertion site samples were taken under full aseptic measures and collected into sterile containers (EDTA, ethylenediaminetetraacetic acid coated tubes or heparin treated tubes) from all patients in both groups. Only one

sample (the first sample) was taken into consideration in the study analysis for each patient thus resulting in one sample for each patient. All samples were sent for gram staining, bacterial culture (bedside inoculation) and cytochemical analysis. Automated Multichannel Analyzers were used to assess pleural fluid cytochemical parameters. In the microbiological labs, samples were cultured on 5% sheep blood agar, MacConkey agar, chocolate agar and anaerobic media incubated at 37°C for 24 hours. Antibiotic sensitivity testing was determined by the Kirby-Bauer disk diffusion method as per the standard guidelines Clinical and Laboratory Standards Institute (CLSI, 2018) using the commercially available antibiotic disks from Hi-Media (Mumbai, India). Extended spectrum beta-lactamases (ESBL) production and methicillin resistant *Staphylococcus aureus* (MRSA) were tested as per standard CLSI protocol. ATCC reference strains, *Escherichia coli* ATCC 25922, *Staphylococcus aureus* ATCC 25923 and *P. aeruginosa* ATCC 25873 were included as control strains.

In this study, we evaluate the following variables: (1) patients' demographic features; (2) pleural fluid cytochemistry such as: total protein (TP), lactate dehydrogenase (LDH), glucose, albumin, total number of nucleated cells and total and differential leukocyte count and (3) pleural fluid microbiology such as Gram-stain and aerobic and anaerobic bacterial cultures of both pleural fluid and insertion site.

### Statistical analysis

We used the Mann-Whitney test for non-categorical data and the chi-square test for categorical data, by means of the Statistical Package for the Social Sciences (SPSS) software (version 11.0, Chicago, United States) to evaluate the differences between the two groups. The results were presented as means ± standard deviations, unless otherwise indicated. Significant Differences were considered if P value < 0.05.

## Results

A total of 690 patients {males: 430 (62.3%), females: 258 (37.7%)} with uncomplicated tuberculous effusion were included in this study (Figure 1). Patients who had evidence of drain infection (group A) were 220 patients (31.9%), of these, 140 (64.1%) were males and 79 (35.9%) were females. Patients who had no evidence of drain infection (group B) were 470 patients, of these, 290 (62%) were males and 179 (38%) were females. There was no statistically significant difference in relation to sex and age distribution between groups A and B. However, there was predominance of males in both groups (Table 1).

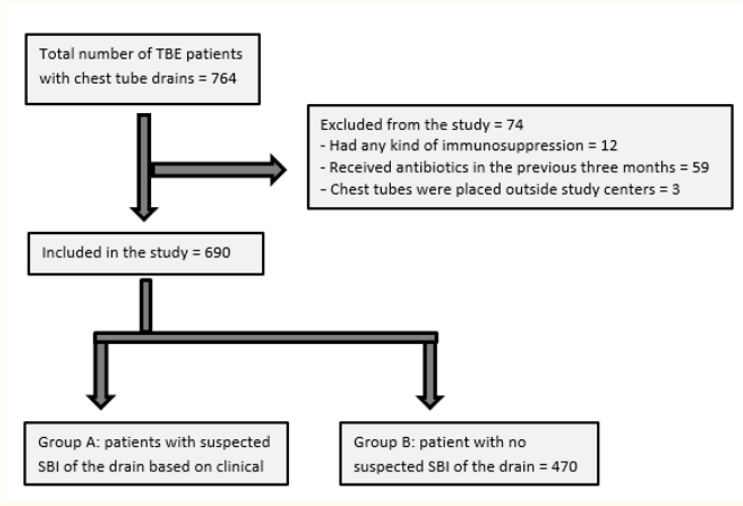


***Figure 1:*** *Study flow diagram.*
*TPE: Tuberculous Pleural Effusion; SBI: Secondary Bacterial Infection*

| | Group A suspected SBI (n = 220) | Group B no suspected SBI (n = 470) | P value |
|---|---|---|---|
| Age (mean ± SD) | 58.2 ± 13.1 | 57.9 ± 14.4 | 0.912 |
| Sex | | | |
| Male | 140 | 290 | 0.748 |
| Female | 79 | 179 | |

***Table 1:*** *Demographic features of study patients.*

*SBI: Secondary bacterial infection, Statistical tests: Mann-Whitney or chi-square; significant if P < 0.05.*

In biochemical analysis of pleural fluid samples, there were statistically significant differences between groups A and B regarding the levels of LDH (1466.9 ± 6169.4 U/l versus 255.2 ± 445.4 U/l; P < 0.001) which was significantly higher in group A. In the other hand, glucose was significantly higher in group B (109.4 ± 82.2 mg/dl versus 131.6 ± 76.4 mg/dl; P < 0.001). In Cytological analysis, the percentages of total nucleated cells, leukocytes, neutrophils were significantly higher in group A, while the percentages of lymphocytes, monocytes and macrophages were significantly higher in group B (Table 2). In microbiological analysis, Gram staining was performed on 137 samples (62.2%) in group A and on 283 samples (60.2%) in group B, which yielded rates of positive findings of 12.4% and 1.0%, respectively. Because of its low sensitivity in pleural fluid, Gram staining, is not always requested in pleural fluid samples and this explain why it was not requested for 39% of our study patients. Pleural fluid cultures were done on 185 samples (84%) in group A, and they were positive in 34% of samples. In the other hand, pleural fluid cultures were done on 396 samples (84.2%) in group B, and they were positive in only 6% of samples (Table 3). Among group A, 26 samples (14%) have positive insertion site culture results. While in group B, 17 samples (4.2%) were positive. The positive and negative predictive values of chest tubes drain culture for insertion site infection (ISI) for group A were 36.5% and 97.5% respectively. In group B, the positive and negative predictive values were in the same range, 37.5% and 97.8% respectively (Table 4). The most prevalent bacterial isolates from both groups A and B were gram positive bacteria which account for 74% and 48% respectively. *Staphylococcus aureus* species were the predominant bacteria in both groups A and B, 63% and 42.8% respectively (Figure 2). In the other hand, gram negative bacteria were more prevalent in group B and account for 42% of total isolates with *Pseudomonas* species were the most common gram-negative bacteria (21%). In group A, gram negative bacterial constitute 19% of total isolates and *Pseudomonas* species were the predominant gram-negative bacteria (9%). Anaerobic bacteria were isolated from group A and group B in 2.2% and 3.9% of samples, respectively. The antimicrobial susceptibility profile of all positive bacterial isolates is shown (Table 5).

| | Group A suspected SBI (n = 220) | Group B no suspected SBI (n = 470) | P value |
|---|---|---|---|
| Total Protein (g/dl) | 2.2 ± 1.6 | 1.9 ± 1.4 | 0.089 |
| LDH (U/I) | 1466.9 ± 6169.4 | 255.2 ± 445.4 | < 0.001 |
| Glucose (mg/dl) | 109.4 ± 82.2 | 131.6 ± 76.4 | < 0.001 |
| Albumin (g/dl) | 1.1 ± 0.9 | 1.3 ± 6.2 | 0.146 |
| Total nucleated cells/$mm^3$ | 10082.4 ± 35181.2 | 300.5 ± 559.6 | < 0.001 |
| Leukocytes (%) | 68.4 ± 25.2 | 43.3 ± 25.5 | < 0.001 |
| Neutrophils (%) | 79.9 ± 20.2 | 24.4 ± 25.3 | < 0.001 |
| Eosinophils (%) | 0.7 ± 0.8 | 1.1 ± 3.8 | 0.419 |
| Basophils (%) | 0.1 ± 0.1 | 0.1 ± 0.2 | 0.101 |
| Lymphocytes (%) | 16.8 ± 19.1 | 69.5 ± 26.6 | < 0.001 |
| Monocytes (%) | 2.6 ± 2.8 | 4.7 ± 6.1 | < 0.001 |
| Macrophages (%) | 28.1 ± 23.6 | 52.1 ± 25.8 | < 0.001 |
| Mesothelial cells (%) | 3.5 ± 7.7 | 3.7 ± 7.1 | 0.908 |

***Table 2:*** *Cytochemical characteristics of pleural fluid.*

*SBI: Secondary Bacterial Infection, LDH: Lactate Dehydrogenase, Statistical tests: Mann-Whitney or chi-square; significant if P < 0.05.*

| | | Group A suspected SBI (n = 220) | Group B no suspected SBI (n = 470) | P value |
|---|---|---|---|---|
| Gram Stain | | | | |
| Positive | | 17 | 3 | < 0.001 |
| Negative | | 120 | 280 | 0.225 |
| Not done | | 83 | 187 | 0.694 |
| Pleural fluid Culture | | | | |
| Positive | | 63 | 24 | < 0.001 |
| Negative | | 122 | 372 | < 0.001 |
| Not done | | 35 | 74 | 0.871 |
| Insertion site Culture | | | | |
| Positive | With positive pleural fluid Culture | 23 | 9 | |
| | With negative pleural fluid Culture | 3 | 8 | |
| Negative | With positive pleural fluid Culture | 40 | 15 | |
| | With negative pleural fluid Culture | 119 | 364 | |
| Not done | | 35 | 74 | |

***Table 3:*** *Microbiological characteristics of pleural fluid and ISI.*
*SBI: Secondary Bacterial Infection; ISI: Insertion Site Infection; Statistical tests: Mann-Whitney or chi-square; significant if P < 0.05.*

| | Group A suspected SBI (n = 220) | Group B no suspected SBI (n = 470) |
|---|---|---|
| **Prediction of ISIs** | **Percentile** | |
| Sensitivity | 88.5 | 52.9 |
| Specificity | 74.8 | 96.0 |
| PPV | 36.5 | 37.5 |
| NPV | 97.5 | 97.8 |

***Table 4:*** *Predictive power of positive chest drains cultures for ISI.*
*SBI: Secondary Bacterial Infection; ISI: Insertion Site Infection; PPV: Positive Predictive Value; NPV: Negative Predictive Value.*

| Antibiotic | Gram positive bacteria (n = 67) | | | | | |
|---|---|---|---|---|---|---|
| | ***Staph aureus*** **(n = 35)** | **CONS (n = 16)** | ***Corynebacterium*** **sp. (n = 13)** | **MRSA (n = 3)** | | |
| Amoxicillin | - | - | - | - | | |
| Ofloxacin | 19 (55) | 0 (0) | 1 (8) | 0 (0) | | |
| Azithromycin | - | - | - | - | | |
| Erythromycin | 17 (49) | 0 (0) | 2 (15) | 0 (0) | | |
| Amikacin | 21 (60) | 0 (0) | 0 (0) | 0 (0) | | |
| Gentamicin | 20 (57) | 0 (0) | 1 (8) | 0 (0) | | |
| Cefaclor | 14 (40) | 0 (0) | 0 (0) | 0 (0) | | |
| Cefazolin | 19 (55) | 4 (25) | 1 (8) | 0 (0) | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Oxacillin | 18 (52) | 4 (25) | 0 (0) | 0 (0) | | |
| Vancomycin | 34 (97) | 15 (94) | - | 3 (100) | | |
| Linezolid | - | - | - | 3 (100) | | |
| **Antibiotic** | **Gram negative bacteria (n = 27)** | | | | | |
| | ***E. coli* (n = 7)** | ***Citrobacter* sp. (n = 3)** | ***Klebsiella* sp. (n = 2)** | ***Proteus* sp. (n = 1)** | ***Acinetobacter* sp. (n = 1)** | ***Pseudomonas* sp. (n = 13)** |
| Amikacin | 3 (42) | 1 (30) | 1 (50) | 0 (0) | 0 (0) | 8 (62) |
| Gentamicin | 2 (28) | 1 (30) | 1 (50) | 0 (0) | 1 (100) | - |
| Tobramycin | - | - | - | - | - | 8 (62) |
| Cefepime | 1 (14) | 1 (30) | 0 (0) | 0 (0) | 0 (0) | - |
| Cefixime | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | - |
| Ceftriaxone | 1 (14) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | - |
| Ofloxacin | 5 (72) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | - |
| Ceftazidime | - | - | - | - | - | 4 (31) |
| Piperacillin | - | - | - | - | - | 5 (38) |
| Piperacillin+tazobactam | - | - | - | - | - | 7 (54) |
| Imipenem | - | - | - | - | - | - |
| Levofloxacin | - | - | - | - | - | 6 (46) |

***Table 5:*** *Antimicrobial sensitivity pattern of all positive bacterial isolates*.*

**: Total no of all positive cultures is 98 (gram positive bacteria = 67, gram negative bacteria = 27, anaerobic bacteria = 4).*

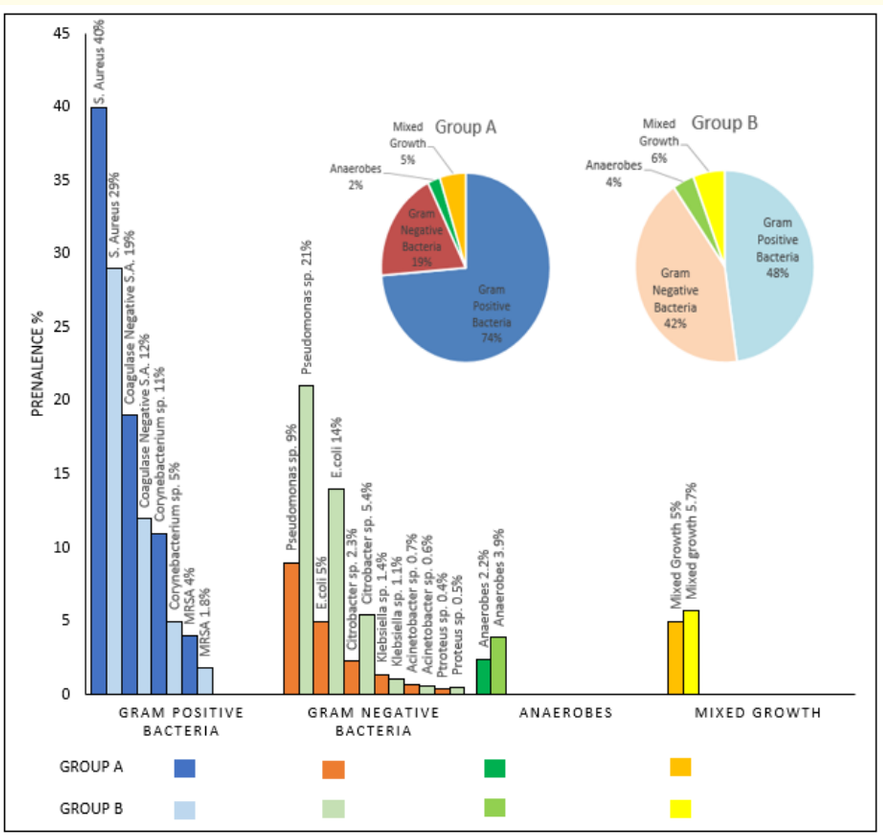


***Figure 2:*** *Prevalence of bacterial isolates from group A and group B.*

## Discussion

Tuberculous pleural effusion (TPE) is one of the most common complications of Tuberculosis infection, it could complicate pulmonary tuberculosis infection, or it could present as a separate entity without evidence of pulmonary involvement. Patients with TPE usually presents with fever, pleuritic chest pain and shortness of breath with or without cough. The pleural fluid in TPE is an exudative and predominantly lymphocytic fluid. The definitive diagnosis of TPE depends on the detection of *Mycobacterium tuberculosis* in the pleural fluid, or pleural biopsy specimens or the histological demonstration of caseating granulomas in the pleura along with acid fast bacilli [8]. We were strict to confirm the diagnosis of TPE during patient's selection to this study, thus we had selected only those patients who have definitive diagnosis of TPE. TPE is a self-limited disease, and most of cases resolve spontaneously within 1 - 2 months if left untreated. However, treatment of TPE is warranted in most cases to relieve symptoms, to prevent recurrence of active TB and to prevent future complications such as fibrothorax [9]. The primary treatment of uncomplicated, non-drug resistant TPE is the same as that used for pulmonary tuberculosis, anti-tuberculosis chemotherapy which includes isoniazid, rifampin, pyrazinamide, and ethambutol for 2 months followed by 4 months of two drugs, isoniazid and rifampin [3]. In some cases, drainage of pleural space is necessary especially when the amount of pleural fluid is large or when future local complications are expected in the presence of septations and loculations [4,5]. Closed chest tube drainage is considered as "clean contaminated" procedure and the estimated risk of infection is low. Indeed, secondary bacterial infection of chest drain, or insertion site still happened even with the implementation of aseptic measures [6]. Pleural SBIs and empyema that sometimes complicate chest tube drainage rates 1% - 25% and the rate is higher when pleural effusion was present before chest tube placement [6]. Clinically, patients with these secondary bacterial pleural infections developed signs or symptoms of drain infections such as, new onset fever, redness, tenderness, or pus around drain insertion site or in the drain tube [7]. In fact, these clinical features of drain infection were expected and were reported with chest tubes placed for other different reasons. However, in our study we found that these clinical features of drain infection have not changed by the presence of pre-existing pleural mycobacterial infection or by the ongoing antituberculosis treatment. The acute bacterial infection (and inflammation) of the drain or the insertion site was not clearly altered by the chronic lymphocytic infection caused by the mycobacterium or its treatment [10]. In addition, even with the presence of the mycobacterial infection and the antituberculosis treatment, these clinical features continued to be an important guide to think about possible pleural SBIs and subsequently to diagnose it by performing pleural fluid or drain insertion site cultures. In our study we found that 34% of patients who had clinical features of drain infection (i.e. had SBI) had their fluid culture positive, while only 6% of those who had no clinical features had positive pleural fluid cultures. It is known that mycobacterial infection of pleural space led to an exudative fluid with high LDH level [11], However, we found that pleural fluid samples from patients with pleural SBI have a statistically significant higher level of LDH compared to those without evidence of SBI and this could be attributed to that the bacterial superinfection led to this increase in LDH level. Surprisingly, LDH levels were low in samples without the evidence of SBI in spite of the presence of mycobacterial infection, and this simply could be explained by the action of the ongoing antituberculosis treatment that decrease the mycobacterial load in pleural space, hence, the LDH levels and to the fact that LDH levels decrease with time in exudative effusions. TPE produce lymphocytic predominant fluid due to either delayed hypersensitivity reaction or chronic granulomatous mycobacterial infection of the pleural layers [12]. In some cases, although little, TPE was associated with neutrophil-rich fluid and usually patients have more prominent clinical features than those with lymphocyte-rich fluid [13]. In this study, we found that the percentages of total nucleated cells (mainly neutrophils) were significantly higher in samples with SBI which is caused by the acute inflammatory process generated by the invading bacteria. This increase in neutrophil overcome and mask the high level of the preexisting lymphocytes. In the other hand, percentages of lymphocytes were significantly higher in samples without the evidence of the SBI which is simply related to the preexisting mycobacterial infection as described above. Both community acquired and hospital acquired pleural bacterial infections has been described widely in the literature and several bacterial morphological profiles were reported [14,15]. Several bacterial groups were identified to be associated with hospital acquired pleural SBIs including *Staphylococcus aureus*, gram negative bacilli and anaerobes, with *Staphylococcus aureus* Species were the most common cultured organism. Our study also showed that *Staphylococcus aureus* species were the predominant bacteria in both study groups and it was clear that the presence of mycobacterial infection has not significantly changed this bacterial profile. However, we no-

ticed that gram negative bacteria especially *Pseudomonas* species were more prevalent in samples without evidence of SBI. From our side, we think that treatment of these SBI (in addition to the treatment for mycobacterial infection) is important and would decrease the duration and the morbidity of the disease. Dr. C N Meyer and his colleagues in their retrospective study found no difference in observed mortality, underlying disease severity, outcome, or treatment parameter when they compared patients with microbiology negative pleural infection and known bacterial etiology of pleural infection [16]. Co-infection of mycobacteria with other bacteria has been described before in the setting of lung infection [17,18]. However, pleural co-infection (with or without drains) has not been described before, thus our study is the first study to highlight this co-infection in detail. Furthermore, pleuropulmonary co-infection of mycobacteria and HIV (with or without opportunistic infection) had been described widely in the literature, however, we excluded this kind of patients from our study to prevent the effect of this confounding factor on our results [19,20]. All first line anti-TB drugs except Rifampicin are active only against Mycobacterial infections, thus, we would not expect any influence in the prevalence, clinical feature or in the bacterial profile of the pleural SBIs that we have reported. Rifampicin has activity against many bacteria including *Staphylococcus aureus*, gram negative bacilli and many other bacterial groups [21]. All of our patients in both groups had received Rifampicin as part of the given anti-TB treatment and the effect of Rifampicin (on both groups) would explain the decrease in the rate of Gram negative SBI in this study. However, gram negative bacilli especially *Pseudomonas* species were more prevalent in samples without evidence of SBI. Nevertheless, and to a lesser extent, *Pseudomonas* species were also the most common cultured organism in the other group. Other treatment interventions for TPE such as steroid, intrapleural fibrinolytics and surgery were mentioned in the literature with variable outcomes [22,23], however, we limit our treatment to the first line anti-TB drugs and chest tube drainage aiming to minimize the cofounding affect. Our study has many strength points such as the large number of study population, the strict inclusion-exclusion criteria we used, the many variables we evaluated and that it is the first study that address the pleural SBIs in patients with preexisting TPE being treated with anti-TB drugs and chest tube drain. In the other hand, it has some weak points such as that it is a retrospective study and also some variables which could be important or have cofounding affect were not addressed. Of course, larger, and randomized studies are needed to figure this out.

## Conclusion

Our study showed that the presence of clinical features and high pleural LDH levels is a good evidence for the presence of superimposed bacterial infection of pleural space and chest tube drain in patients being treated for TPE and this was confirmed by bacterial cultures, and hence, can be relied on. It also highlighted that, in spite of the presence of ongoing pleural mycobacterial infection and anti-TB drug treatment, the causative bacterial organisms are not different from what has been reported for other cases (without mycobacterial coinfection), with *Staphylococcus aureus* and *Pseudomonas* species being the more prevalent organisms.

## Acknowledgements

Authors acknowledge the Chairs of the Institutional Ethics committees in the involved Hospitals for granting permission and support.

### Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

## Ethical Statement

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Written informed consent and approval for collection of the relevant information of this study were obtained from Institutional Ethics committees. A copy of this written consent is available for review by the Editor-in-Chief of this journal.

## Conflicts of Interest

The authors have no conflicts of interest to declare.

## Funding Statement

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