## Bacterial Co-Infection in Pulmonary Tuberculosis

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**Abstract**

Patients diagnosed with tuberculosis are considered to be immunocompromised and as such they are more likely to be co-infected with other pathogens. Superimposed bacterial infection in a TB patients could also alter the disease prognosis and affect mortality rates. This study was carried out to determine the burden of bacterial co-infections and to identify associated factors in pulmonary TB patients. Bacteriologically confirmed adult pulmonary TB cases who were attending the TB clinics in North Okkalapa General Hospital, Insein General Hospital and Thingyun Sanpya Hospital were recruited for this study. Only TB cases within the first month of undergoing anti-TB therapy were selected. The socio-demographic and clinical characteristics of the patients were recorded and their sputum were cultured and microscopically examined using Gram stain and Ziehl-Neelsen stain. Among the 119 TB cases, 56% of them were found to have bacterial co-infections. The most common isolated pathogen was *Klebsiella pneumoniae* (61%). Pathogens that causes meiloidosis and nocardiosis were also isolated (2% in each group). Poor housing status, Low Body Mass index (BMI), Charlston's co-morbidity index more than 1 and cavitation in the lungs were found to be significantly associated with bacterial co-infection in TB patients. Due to the high frequency of bacterial co-infections seen in TB patients along with a wide spectrum of pathological organisms, sputum culture should be done in all pulmonary TB cases, particularly those with persistent symptoms, poor housing, co-morbidity and lung cavitation.

**Background**

Tuberculosis is a common disease in Myanmar with high mortality rates[1]. Tuberculosis is usually asymptomatic and it remains latent in the body as long as the person's immune system can contain the infection. Once clinical tuberculosis sets in it is an indicator that the immune system has failed and that the patient has become immuno-compromized. In addition, many patients remain symptomatic for many weeks after receiving anti-TB therapy. Such patients are likely to develop a superimposed infections caused by a variety of pathogenic bacteria present in the environment. In addition, most of the deaths from tuberculosis occurred in the early stages of anti-TB treatment. Nearly 40% of the TB related deaths are reported to have occurred in the first month of anti-TB

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treatment[2]. The causes may be multifactorial. However, one of the likely causes could be superimposed bacterial pneumonia. Bacterial pneumonia is a treatable condition and it is also one of the major causes of death.

**Method**

A hospital based observational study was carried out to determine the burden of bacterial co-infection in TB patients and to find out the factors associated. The study was conducted in the Public Public Mix - Directly Observed Treatment Short-Course (PPM-DOTS) Clinics of North Okkalapa General Hospital, Insein General Hospital and Thingyun Sanpya General Hospital. Adult TB patients who are currently taking anti-TB treatment and who are also during the first month of anti-TB treatment were included in the study. All TB cases included in the study were pulmonary TB cases confirmed by positive sputum microscopic examination or Gene Xpert tests. All the subjects included in the study were symptomatic at the time of the study. A total of 159 patients were recruited who fulfilled the study criteria. The cases were recruited into the study among those patients who attended the DOTS Clinics on Tuesday. The culture facility at Microbiology Department could be best performed only on Tuesday which was defined as study day. Patients who did not give consent and those who could not expectorate the required amount of sputum for the tests were excluded from the study. Forty cases were excluded due to not providing enough sputum for culture. The past history, clinical examinations, chest radiograph were recorded according to a fixed proforma. The sputum collected were sent to the microbiology laboratory of University of Medicine 2, Yangon for sputum culture and microscopy examination. Sputum culture was done using Mac Conkey's agar and blood agar. Sputum microscopy was done using Gram's stain and 1% Ziehl-Neelsen stain.

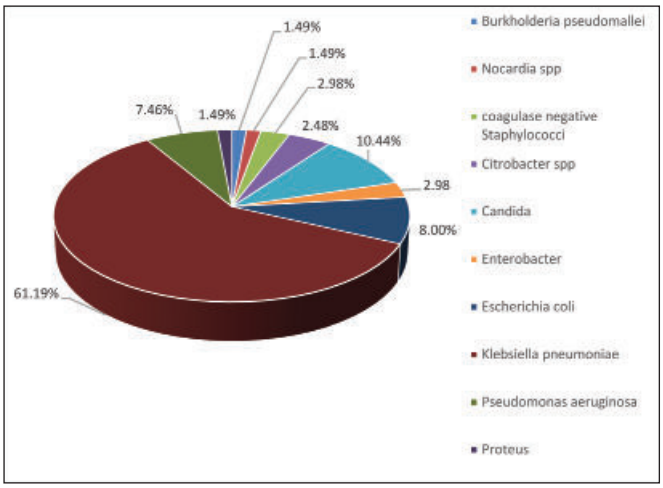
The socio-demographic data such as age, sex, literacy, residency (urban and rural) and poor housing conditions were collected. Poor housing status was defined as the presence of rodents and moulds, water leaks, dampness and poor ventilation in the patient's residence or its vicinity. The behavioral and clinical characteristics such as alcohol use, smoking, persistent cough, persistent fever, BMI, Charlston co-mobidity index (a clinical score which includes 8 life-threatening co-morbid conditions), chest X-ray and the type of TB treatment regimen given and sputum bacterial results were also collected and correlated. The study was approved by ethical review committee of University of Medicine 2, Yangon.

**Results**

A total of 119 pulmonary TB cases were studied. The mean age of the subjects was 50 years (range 18-89 years). Male to female ratio was 1. It was found that 76.47% (91/119) of the study population lived in urban areas. Smear positive pulmonary TB accounted for 31.93% (38/119 cases) in the study. Among them 82.35% (98/119 cases) were taking initial regimen of anti-TB and 17.65% (21/119 cases) were taking re-treatment anti-TB regimen. None of the cases in the study were taking multi-drug resistant TB regimen.

Figure 1 shows the distribution of pathogens isolated from sputum. Among the study population, pathogenic bacteria were isolated from the sputum in 56.30% of the patients (67/119 cases). The most common organism isolated was found to be *Klebsiella pneumoniae* accounting for 61.19% of all the isolated organisms. The mould, Candida spp were isolated in 10.44% of all isolated pathogens. Rare pathogens such as *Burkholderia pseudomallei* (1.49%) and *Nocardia spp* (1.49%) were also isolated. Other isolated organisms were *Pseudomonas aeruginosa* (7.46%), *Proteus spp* (1.49%), *Citrobacter spp* (2.48%), *Enterobactar spp* (2.98%), *Escherichia coli* (8.00%) and coagulase negative *staphylococci* (2.98%).

**Figure 1. Distribution of various pathogens isolated from sputum of TB patients**




Bacterial co-infection in TB patients were found to be not associated with either age, sex, smoking habits, alcohol use and place of residency (urban or rural). However, it was found to be significantly associated with poor housing status (33.0% vs 13.5%) (p = 0.01).

**Table 1. Socio-demographic characteristics of the study populations**

Table 2 shows the clinical characteristics of the TB patients in the study. Bacterial co-infection in TB patients was found to be not associated with persistence of symptoms

| Characteristics | TB with Bacterial Co-infection (N = 67) | TB without Bacterial Co-infection (N = 52) | p value |
|---|---|---|---|
| **Age (in years)**<br>**Mean age ± SD** | 51 ± 17 | 50 ± 17 | 0.68 |
| **Sex**<br>**Male to Female ratio** | 1 | 1 | > 0.99 |
| **Residence**<br>**Urban (Number and percent)**<br>**Rural (Number and percent)** | 52 (77.6)<br>15 (22.4) | 39 (75)<br>13 (25) | 0.74 |
| **Poor housing**<br>**(Number and percent)** | 22 (32.8) | 7 (13.5) | 0.01 |

of cough and fever, type of anti-TB treatment regimen and sputum smear status. But bacterial co-infection in TB patients was significantly associated with Charlson's co-morbidity index (1.33 vs 0.13; p = 0.0002), BMI (16.22 vs 17; p = 0.04) and cavitation diagnosed in chest radiograph (11.9% vs 1.9%; p = 0.04).

**Table 2. Clinical Characteristics of the Study Population**

| Characteristics | TB with Bacterial Co-infection (N = 67) | TB without Bacterial Co-infection (N = 52) | p value |
|---|---|---|---|
| Alcohol use (Number and Percent) | 22 (32.8) | 11 (21.2) | 0.16 |
| Smoker (Number and Percent) | 28 (41.8) | 26 (50) | 0.37 |
| Sputum smear Positive (Number and Percent) | 23 (34.3) | 15 (28.8) | 0.52 |
| Persistent cough (Number and Percent)* | 18 (26.8) | 15 (28.8) | 0.8 |
| Persistent fever (Number and Percent)* | 17 (25.4) | 15 (28.8) | 0.67 |
| BMI (Mean ± SD) | 16.22 ± 2.54 | 17 ± 2.42 | 0.04 |
| Charlson's comorbidity index (Mean ± SD) | 1.33 ± 2.2 | 0.13 ± 0.4 | 0.0002 |
| Chest radiograph<br>Lobar consolidation (Number and Percent)<br>Cavitation (Number and Percent) | <br>7 (10.4)<br>8 (11.9) | <br>4 (7.7)<br>1 (1.9) | <br>0.6<br>0.04 |
| TB Regimen<br>Initial Regimen (Number and Percent)<br>Retreatment Regimen (Number and Percent) | <br>54 (80.6)<br>13 (19.4) | <br>44 (84.6)<br>8 (15.4) | <br>0.57 |

*Persistent means symptoms > 4 weeks

The co-morbidity for Charlson's index found in the study population were HIV co-infection, COPD and diabetes mellitus.

## Discussion

The study showed that a significant proportion (56.30%) of TB patients were found be co-infected with pathogenic bacteria. A majority of isolated bacteria found in this study were Gram negative organisms (*Klebsiella pneumoniae*). In addition, rifampicin, a broad spectrum antibiotic used in the current anti-TB regimen was not effective for these pathogens. The dose of rifampicin that is used in the anti-TB regimen, moreover, is inadequate even for rifampicin sensitive pathogens. Therefore, anti-TB alone cannot be effective for these pathogens. The most frequently isolated respiratory pathogen in this study was a Gram negative bacteria, for which it would require an antibiotic sensitivity test to be properly treated. This study highlights the need for all TB patients to undergo sputum culture tests. The sputum culture results can alter the management of TB cases with co-infections. Appropriate antibiotic therapy is to be added according to drug sensitivity results.

However, it is still unclear if such add-on antibiotic treatment for bacterial co-infection can reduce TB mortality. Further studies will be necessary to answer this question. However, in a study done in Taiwan, 30% of tuberculosis cases were co-infected with other non-mycobacterial pathogens. In such co-infected cases, the mortality rate was found to be as high as 43%[3]. In this study, the mortality outcome was not studied and so nothing can be said about the treatment outcomes. The most common isolated organism in this study was *Klebsiella pneumoniae*. Similar results were found in Africa that showed 36% of bacterial co-infection in pulmonary TB cases was *Klebsiella pneumoniae*[4]. But in a large study in Philippines, the most commonly isolated organism was *Haemophilus influenzae*[5]. Therefore, local patterns could vary geographically. In addition, some of the isolated organisms were protean in variety ranging from the common pathogens to rare pathogens causing meiliodosis and nocardiosis. Empirical antibiotic use therefore is not going to be feasible for the treatment of bacterial co-inifection in TB patients. Sputum culture is the best way to detect the co-infected pathogen. The frequent isolation of Gram negative pathogens (such as *Klebsiella* and *Pseudomonas*) in sputum of TB patients could probably mean that the bacterial co-infection may be increasing the mortality risks. It was observed in a study carried out in Manila that 20% of bacterial co-infected pulmonary TB cases died within 2 weeks after diagnosis[5].

As age, sex and clinical symptoms were found to be not associated with bacterial co-infection in pulmonary TB cases, these factors could not be considered as risk factors for the presence of bacteria co-infections. In a similar study done in Cambodia, it was also revealed that the clinical characteristics of bacterial co-infected TB cases were similar to that of TB cases without bacterial co-infection[6]. However, the theory of TB as a marker of immunosuppression remains true[2]. In this study, the factors that could impair the host's immune system such as poor nutritional status (low BMI) and presence of immunosuppressing co-morbidities (like HIV infection, diabetes mellitus) were strong predictors of TB and bacteria co-infection. In a study conducted in Japan, it was found that hypo-albuminaemia (a strong marker of malnutrition) and the elderly people are more likely to be co-infected with bacterial infections and tuberculosis. In addition, it was also found that these groups had a high risk of mortality[7]. It was also seen that the presence of cavitation in chest X-rays was found to have a significant association with bacterial co-infection. Therefore, more focus needs to be given to do sputum culture in TB cases especially in cases with a chest radiographic feature of lobar consolidation. In the study carried out in Japan, high neutrophil count in the peripheral blood and elevated C-reactive protein were found to be significantly associated with bacterial co-infection[7]. However, these parameters were not assessed in this study.

The interesting point found in this study was the importance of environmental hygiene. It was found that poor housing status was significantly associated with bacterial co-infection in TB patients. These adverse environmental conditions are known to favour the persistence of *mycobacteria* and other saprophytic bacteria such as *Klebsiella*, *Pseudomonas* and *Nocardia* in the environment.

## Conclusion

The study highlighted the fact that a high frequency of bacterial co-infection was seen in pulmonary TB cases. It is recommended that sputum culture be performed in pulmonary TB cases, particularly in those with persistent symptoms after anti-TB therapy, those who live in poor housing, those with co-morbidity, and those with cavitation on chest radiograph.

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