



Colonization of *Streptococcus pneumoniae* in Pneumonia Patients with Lung Cancer

Songwei Zhou,¹ and Qiuxia Zhao^{1*}

¹Department of Clinical Laboratory, Xinghua People's Hospital, Jiangsu, China

*Corresponding author: Qiuxia Zhao, Department of Clinical Laboratory, Xinghua People's Hospital, Jiangsu, China. Tel/Fax: +86-15152679513, E-mail: aclivehri@yahoo.com

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Abstract

Background: Lung cancer is the most common cancer and the leading cause of cancer deaths. *Streptococcus pneumoniae* is the most common pathogen found among lung cancer patients that has shown increased resistance towards various antibiotics. Reports on bacterial colonization especially *S. pneumoniae* colonization in patients with lung cancer are scarce.

Objectives: The study aimed to determine the prevalence and antibiotic resistance of *S. pneumoniae* isolated from lung cancer patients with pneumonia infection not undergoing any surgical procedure.

Methods: Bronchoalveolar lavage (BAL) and blood samples for blood culture and PCR were collected from 152 lung cancer patients with pneumonia. Blood culture and BAL specimens were cultured to isolate *S. pneumoniae* and antibiotic resistance was determined by minimum inhibitory concentration assay.

Results: Of the 152 blood samples, 85 (55.9%) samples from blood culture method and 97 (63.8%) samples from BAL specimens were positive for bacterial growth. *Streptococcus pneumoniae* was the predominant organism isolated from both blood culture (45.9%) and BAL (46.4%) specimens. Forty-seven (30.9%) samples were found to be positive for *S. pneumoniae* by PCR. The detection of *S. pneumoniae* in 60 patients by at least one of the 3 detection methods indicates that these patients harbored *S. pneumoniae* infection. Fifteen (9.9%) patients died due to the severity of pneumonia, rapid progression of lung cancer, multiple therapeutic failures, and unknown etiology. All our isolates were susceptible to penicillin; however, 48.7% and 60% of the isolates respectively from blood culture and BAL specimens were found to be resistant to erythromycin.

Conclusions: *Streptococcus pneumoniae* was the predominant organism colonized in lung cancer patients diagnosed to have pneumonia and showed higher resistance towards erythromycin. Our results emphasize the need for a continuous monitoring of *S. pneumoniae* colonization and resistance patterns, which needs to be considered during treatment of lung cancer patients with pneumonia.

Keywords: Colonization, Lung Cancer, Pneumonia, *Streptococcus pneumoniae*

1. Background

Lung cancer is the most common cancer and the leading cause of cancer deaths (1). A study has estimated 14 million new cancer cases worldwide and about 1,685,210 new cases of cancer in the United States in 2016 (2). Another study has estimated 4,292,000 new cancer cases and 2,814,000 cancer deaths in China in 2015 (1). In cancer patients, the lung is a common site of infection and the spectrum of pulmonary infection depends on the underlying immunologic deficit or deficits (3). The international agency for research on cancer has predicted 845,133 lung cancer patients in 2020 worldwide (4). The incidence of lung cancer and mortality due to lung cancer has been increased in the past decade and leads to a large socioeconomic burden in China (5, 6). The occurrence of frequent infection among lung cancer patients not only poses a big-

ger challenge in cancer treatment but also affects the overall survival rates (7, 8).

Pneumonia and bronchitis were the most common respiratory tract infections occurring mainly due to the colonization of potentially pathogenic and opportunistic microorganisms in the upper respiratory tract of the lung cancer patients (8-10). Pneumonia accounts for higher morbidity and mortality than any other infections in cancer patients (11-13). An estimated 10% of the hospital admissions for the treatment of cancer was complicated due to pneumonia and it exceeds up to 30% in patients with hematological malignancies (14-17). Cancer patients are highly susceptible to severe pneumococcal infections and *Streptococcus pneumoniae* was the most common pathogen found among them (18). Bronchial colonization can be found in lung cancer patients mainly caused by *S. pneu-*

moniae along with *Haemophilus influenza* and *Staphylococcus aureus* (19). *Streptococcus pneumoniae* has shown an increased resistance towards various antibiotics (20).

Early detection of *S. pneumoniae* and appropriate selection of antibiotics could improve the clinical outcomes of the patients and also helps in preventing drug resistance (21, 22). Fever is the constant and the only indicator of infection (19). Bacteremia can occur in more than 60% of pneumococcal pneumonia cases (22). For cancer patients, indices such as the pneumonia severity index and CURB-65 used for the general population to predict the severity and diagnosis of community-acquired pneumonia cannot be used to assess pneumonia (23). Thus, in our study, patients were categorized to have pneumonia when they have to infiltrate on chest radiograph and the presence of one or more conditions such as fever ($\geq 38^{\circ}\text{C}$) or hypothermia ($< 35^{\circ}\text{C}$), dyspnea, pleuritic chest pain, new cough with or without sputum production, and altered breath sounds on auscultation (18). Several studies reported the incidence of lung infection in patients with lung cancer after the surgical procedure (24-27). However, data regarding the bacterial colonization especially the *S. pneumoniae* colonization before a surgical procedure are scarce.

2. Objectives

In order to have a better patient management in this clinical setting, careful measurement of the incidence rate of *S. pneumoniae* and determination of its antibiotic susceptibility are highly warranted. Hence, this study aimed to determine the prevalence and antibiotic resistance of *S. pneumoniae* isolated from lung cancer patients with pneumonia infection before undergoing any surgical procedure.

3. Methods

3.1. Ethics Statement

The study was approved by the institutional review board of Xinghua People's hospital (No. YT3432321). After describing the nature of the study, written informed consents were obtained from all the patients or their legal representatives.

3.2. Study Population

A total of 152 patients with lung cancer, who were on chemotherapy and/or radiotherapy, diagnosed with pneumonia and not undergoing surgical treatment between June 2009 and June 2015 were included in this study. The patients were included in the study based on the histological evidence of lung cancer. Pneumonia was defined as described by Garcia-Vidal et al. (18).

3.3. Sample Collection and Processing

Three consecutive blood samples were collected at an hourly interval, aseptically inoculated into the blood culture bottles, incubated in the BACTEC 9120 blood culture system (Becton Dickinson diagnostic instrument systems), and evaluated for 7 days. Positive blood culture bottles were subjected to Gram's staining, cultured on sheep blood agar, chocolate agar, and MacConkey agar (Biobasic, Canada), and incubated at 37°C with 5% CO_2 (except for MacConkey agar) for 7 days. During the blood culture sampling, 2 mL of blood samples were collected into a separate heparinized vacutainer and stored at -40°C until use for DNA extraction. Bronchoalveolar lavage (BAL) specimens were collected from each patient as described earlier (28). Briefly, using sterile bronchoscope fixed in the lobar bronchus of tumor location, 100 mL of sterile normal saline in fractionated doses was injected and then BAL was removed by suction and collected in a sterile suction device. Specimens were mixed and cultured on sheep blood agar, chocolate agar, and MacConkey agar (Biobasic, Canada) at 37°C for 48 hours in presence of 5% - 10% CO_2 (except for MacConkey agar). Bacterial isolates were identified using conventional biochemical methods. The isolates were characterized using conventional tests including the production of acetoin, fermentation of mannitol and sorbitol, and hydrolysis of arginine, aesculin, and urea (29).

3.4. Real-Time Qualitative PCR

A real-time qualitative PCR was performed to detect *S. pneumoniae* using *S. pneumoniae*-specific capsular polysaccharide biosynthesis (*cpsA*) gene primers (30). The REDExtract-N-AmpTM Tissue PCR Kit (Sigma, USA) was used to extract DNA from the blood specimens. Briefly, 100 μL of the extraction solution was added to 50 μL of each blood sample and incubated at room temperature for 10 minutes. Then, the sample was incubated at 95°C for 3 minutes. After incubation, 100 μL of neutralization solution B was added to the sample and mixed by vortexing. The sample was stored at 4°C until use for PCR. The stored sample containing DNA was subjected to real-time PCR using the following primer *cpsA*-348F: 5'-GCTGTTTTAGCAGATAGTGAGATCGA-3' and *cpsA*-415R: 5'-TCCCAGTCGGTGCTGTCA-3'. The QuantStudioTM 7 Flex Real-Time PCR System (Applied Biosystems) was used to amplify the DNA. PCR cycling conditions were as follows: initial denaturation at 95°C for 10 minutes, followed by 40 cycles of 95°C for 15 seconds and 60°C for 1 minute. The inbuilt intuitive software of the system was used to analyze the amplification data. Non-specific amplifications were detected by Melt-curve analysis. If two of the three triplicates yielded a positive result within the < 40 -cycle cut-off, the sample

was considered as positive. The PCR results were compared with the culture results obtained from blood culture and BAL specimens.

3.5. Minimum Inhibitory Concentration

Minimum inhibitory concentration (MIC) of various antibiotics such as penicillin, amoxicillin, cefotaxime, cefepime, erythromycin, levofloxacin, and clindamycin (Sigma-Aldrich, USA) was determined against *S. pneumoniae*. The inoculum was prepared by direct suspension of colonies grown overnight on sheep blood agar in 0.85% saline and the turbidity was adjusted to 0.5 McFarland's standard for inoculation. MIC assay at a concentration ranging from 0.03 µg/mL to 128 µg/mL was performed by micro broth dilution method using Muller-Hinton broth (MHB) supplemented with 5% lysed horse blood as described in the Clinical Laboratory Standard Institute (CLSI) guidelines (31). Briefly, 10 µL of culture was inoculated into various concentrations of MHB supplemented 5% lysed horse blood and incubated at 37°C for 24 hours. After incubation, 5 µL of culture from the MIC tube was inoculated onto the Muller-Hinton agar supplemented with 5% sheep blood, incubated at 37°C for 24 hours, and observed for the presence of growth.

3.6. Statistical Analysis

Continuous variables were represented as mean and ranges and categorical variables were expressed as numbers and percentages. A student t-test and Chi-Square test were performed to determine the statistical significance and a regression analysis was performed to determine the relationship between variables using SPSS software package (SPSS, version 13.5; SPSS Inc., Chicago, Illinois). A P value < 0.05 was considered statistically significant.

4. Results

All the 152 lung cancer patients who were included in the study were presented with fever or hypothermia and diagnosed to have pneumonia. All patients were in chemotherapy, radiotherapy, or a combination of both treatments. There were 86 (56.6%) males and 66 (43.4%) females. Majority of the patients belonged to the age group of 51-60 years (52, 34.2%) followed by 41-50 years (41, 27.0%), 31-40 years (29, 19.1%), 22-30 (16, 10.5%), and 61-73 years (14, 9.2%). Of the included patients, 50.0% had right lung cancer. Demographic and clinical characteristics of the patients are summarized in Table 1.

Of the 152 blood samples tested, 85 (55.9%) samples from blood culture and 97 (63.8%) samples from BAL aspirations were found to be positive for bacterial growth. *S.*

Table 1. Characteristics of the Patient Population

Demographic Characteristics	No. of Patients (%)
Age, y (Median and range)	62 (22-73)
Male	86 (56.6)
Female	66 (43.4)
Smoker	92 (60.5)
Non-smoker	60 (39.5)
Types of Lung cancer (histology)	
Squamous cell carcinoma	49 (32.2)
Adenocarcinoma	35 (23.0)
Large cell carcinoma	28 (18.4)
Small cell carcinoma	20 (13.2)
Anaplastic small cell carcinoma	12 (7.9)
Carcinoid	8 (5.3)
Location of tumor	
Right lung	76 (50.0)
Left Lung	67 (44.1)
Both	9 (5.9)
Stage of lung cancer	
IV	79 (52.0)
IIIB	48 (31.6)
rIV	25 (16.4)

pneumoniae was the predominant organism isolated from blood cultures (45.9%) and BAL aspirations (46.4%). The presence of *S. pneumoniae* was found to be significantly higher ($P < 0.05$) among the isolates in both the groups (Table 2). There were 15 episodes of polymicrobial colonization, of which 4 patients were isolated with more than 2 microorganisms. *Streptococcus pneumoniae* along with *K. pneumoniae* was the predominant combination followed by the combination of *S. pneumoniae* and *Pseudomonas aeruginosa* (Table 3). There was no significant association between the presence of bacterial colonization (from both specimens) and sex, smoking habit, and location of the tumor ($P > 0.05$). Among the blood samples subjected to PCR, 47 (30.9%) samples were found to be positive for *S. pneumoniae*. There was no significant difference in the presence of *S. pneumoniae* between different samples analyzed by the three methods ($P > 0.05$).

Comparing the blood culture, BAL aspiration, and PCR methods, 24 samples were found to be positive for *S. pneumoniae* by all the three methods, 11 were positive by blood culture and BAL culture, 8 were positive by BAL culture and PCR, and 4 were positive by blood culture and PCR (Table

Table 2. Prevalence of Bacterial Colonization from Blood Culture and BAL Specimens

Bacterial Species	No. of Isolates from Blood Culture (%) (N = 85)	No. of Isolates from BAL (%) (N = 97)
<i>S. pneumoniae</i>	39 (45.9)	45 (46.4)
<i>K. pneumoniae</i>	21 (24.7)	21 (21.6)
<i>P. aeruginosa</i>	11 (12.9)	8 (8.2)
Viridans group streptococci	7 (8.2)	17 (17.5)
<i>Staphylococcus sp.</i>	5 (5.9)	4 (4.1)
<i>E. coli</i>	2 (2.4)	2 (2.1)

Table 3. Patterns of Mixed Culture of Patients with Poly-Microbial Infection

No of Patients	Patterns of Mixed Culture
1	<i>S. pneumoniae, S. aureus, E. coli</i>
2	<i>S. pneumoniae, S. aureus, P. aeruginosa</i>
1	<i>S. pneumoniae, K. pneumoniae, P. aeruginosa</i>
7	<i>S. pneumoniae, K. pneumoniae</i>
4	<i>S. pneumoniae, P. aeruginosa</i>

4). The Pearson correlation test showed an excellent correlation ($r^2 = 0.997$) between blood culture and BAL culture methods. Although the PCR method showed a positive correlation with blood culture ($r^2 = 0.797$) and BAL culture ($r^2 = 0.823$) methods, it was not statistically significant ($P > 0.05$). A total of 60 patient samples were positive for *S. pneumoniae* by at least one of the 3 detection methods.

Table 4. Comparison of *S. pneumoniae* Detection Methods

No. of Isolates	Blood Culture	BAL Culture	PCR
24	+	+	+
11	+	+	-
11	-	-	+
8	-	+	+
4	+	-	+
2	-	+	-
Total	39	45	47

All the *S. pneumoniae* isolates from both blood culture and BAL specimens were susceptible to penicillin using non-meningeal breakpoint. Majority of the blood culture isolates (48.7%) and BAL aspiration isolates (60.0%) were found to be resistant to erythromycin. Cefepime resistance was the second most common resistance exhibited by the

blood culture (23.1%) and BAL specimen (33.1%) isolates (Table 5). The presence of erythromycin resistance was significantly higher ($P < 0.05$) among the isolates in both blood culture and BAL specimen groups.

All the 152 patients were treated with empirical antibiotics. The most commonly administered antibiotics were amoxicillin, cefepime, ceftriaxone, and levofloxacin. Nineteen patients were admitted to the intensive care unit due to the severity of disease and 8 patients were on mechanical respiratory support. A total of 15 patients died during the course of study and the mortality rate was 9.9%. Of the 15 deaths, 8 patients died due to the severity of pneumonia. All these 8 patients were under mechanical respiratory support and subsequently developed severe pneumonitis and died. The remaining 6 patients died due to rapid progression of lung cancer ($n = 3$), multiple therapeutic failures ($n = 2$), and unknown etiology ($n = 1$).

5. Discussion

The advent of newer antimicrobial agents and advanced treatment strategies has improved the management of cancer treatment; however, respiratory infections are common among cancer patients (32). Pneumonia is considered to be one of the major complications in lung cancer patients, occurring mainly due to the failure of clearance system in peripheral bronchial obstruction sites or stenosis brought by cancer therapy or cancer itself (33). Bacterial colonization especially *S. pneumoniae* and *H. influenzae* colonization is more common among lung cancer patients with impaired clearance system (19). In our study, the blood culture specimens and the BAL specimens yielded both Gram-positive and Gram-negative microorganisms. Among our significantly higher ($P < 0.05$) number of culture-positive specimens, *S. pneumoniae* grew from both blood culture (45.9%) and BAL (46.4%) specimens, compared to other isolates. However, there was no significant difference in the presence of *S. pneumoniae* between the blood culture and BAL specimens ($P > 0.05$).

Streptococcus pneumoniae was the predominant isolate in our study, which was similar to that reported elsewhere (28, 34). Our result corroborates with a recent study from China reporting that *S. pneumoniae* (68.1%) was the predominant isolate from cancer patients with pneumonia (34). Similarly, Garcia-Vidal et al. (18) from Spain and Dancewicz et al. (28) from Poland reported *S. pneumoniae* as the predominant isolate found among cancer patients. In our study, *Klebsiella pneumoniae* was the second most predominant bacterial species isolated from blood culture (24.7%) and BAL (21.6%) specimens. In contrast to our results, Meena and Shreevidya from India reported that *P.*

Table 5. Antibiotic Resistance and MIC of *S. pneumoniae* Isolates^a

Variables	Blood Culture Isolates (N= 39)						BAL Specimen Isolates (N= 45)					
	S	I	R	MIC50, µg/mL	MIC90, µg/mL	Range, µg/mL	S	I	R	MIC50, µg/mL	MIC90, µg/mL	Range, µg/mL
Penicillin	39	0	0	≤ 0.03	1	≤ 0.03 - 2	39	6	0	≤ 0.03	4	≤ 0.03 - 4
Amoxicillin	25	9	5	1	16	0.06 - 64	29	7	9	0.5	16	0.06 - 64
Cefotaxime	31	6	2	0.5	4	0.12 - 16	17	18	10	0.12	16	0.12 - 32
Cefepime	24	5	10	0.5	8	0.06 - 8	13	12	20	0.5	8	0.06 - 16
Erythromycin	12	8	19	1	64	≤ 0.03 - > 128	8	10	27	1	64	≤ 0.03 - > 128
Levofloxacin	22	8	9	2	4	0.5 - 16	25	5	15	1	8	0.5 - 64
Clindamycin	34	5	0	0.12	0.5	0.06 - 0.5	23	17	5	0.12	2	0.06 - 4

^aNon-meningeal CLSI breakpoint was used.

aeruginosa was the predominant etiological agent of pneumonia among cancer patients, and *S. aureus* and *K. pneumoniae* were the next predominant organisms isolated in this study (32).

Vento et al. from Italy reported *P. aeruginosa* and *S. aureus* as the predominant organisms isolated from cancer patients after chemotherapy, followed by *Escherichia coli* (35). The primary objective of our study was to determine the prevalence of *S. pneumoniae* showing that *S. pneumoniae* was the predominant isolate identified. However, the contrasting evidence of other studies with our result of *S. pneumoniae* predominance indicates that there are regional variations in presence of microbial colonization among cancer patients. The poly-microbial pneumonia was commonly associated with *P. aeruginosa* and *K. pneumoniae* that increase the morbidity and mortality of the patients. Of the 16 patients who had poly-microbial infections, 4 patients died due to severe infection. The overall mortality rate in our study was 9.9%.

Rapid diagnosis and appropriate treatment play a vital role in life and death. In general, lung cancer patients are highly susceptible to infection due to the rapid spread of tumor cells, which can deteriorate the clinical condition. Thus, a rapid detection of infectious agents will help in the successful management of the disease. PCR identified a higher number of *S. pneumoniae* (37.5%) than blood culture (25.7%) and BAL aspiration (29.6%). However, the detection of *S. pneumoniae* was not significantly different ($P > 0.05$) between the detection methods used. The detection of *S. pneumoniae* in 60 patients by at least one of the 3 detection methods indicated that these patients harbored *S. pneumoniae* infection.

The treatment of lung cancer patients with pneumonia often is complicated by infectious agents, which can easily disseminate into the bloodstream and other parts of the body leading to bad prognosis. These infectious organisms are increasingly becoming resistant to various antibiotics posing an additional challenge in the treatment of

pneumonia. *S. pneumoniae*, as one of the major etiological agents of pneumonia, was reported to have increased resistance towards various antibiotics such as cephalosporins, macrolides, penicillin, and fluoroquinolones (9, 36). In the United States, *S. pneumoniae* resistance to penicillin ranged from 8% - 15%, while in Asian countries it ranged from 50% to an overwhelming 70% (37-39). *Streptococcus pneumoniae* is reported to have an increased resistance towards penicillin while none of our isolates was found to be resistant to penicillin. This could be attributed to the limited use of penicillin as an empirical antibiotic in our region, which in turn reduces the exposure to oral bacteria such as *S. pneumoniae*.

It is a well-established fact that the more the exposure to an antibiotic, the more the bacterial resistance. Similar to our results, two studies from Spain and China reported that none of the *S. pneumoniae* isolates from cancer patients showed resistance to penicillin (18, 34). Although none of our isolates was resistant to penicillin, 12.8% and 20% of our isolates respectively from blood culture and BAL specimens were found to be resistant to amoxicillin. We report that 48.7% and 60% of our isolates respectively from blood culture and BAL specimens were found to be resistant to erythromycin, which were higher than that reported (28%) elsewhere (40-42). The MIC₅₀ and MIC₉₀ of erythromycin against *S. pneumoniae* isolated from both blood culture and BAL specimens were 1 µg/mL and 64 µg/mL (range: ≤ 0.03 to > 128 µg/mL), respectively.

Erythromycin-resistant *S. pneumoniae* complicates the choice of antibiotic treatment since other macrolides such as clarithromycin and azithromycin might not be ideal choices where the prevalence of resistant pneumococci is high (38-42). We report an overall mortality of 9.9%, which is lower than that reported (30%) from France (43). Irfan et al. reported that the local prevalence and bacterial resistance patterns determine the choice of first-line empiric therapy (44). Hence, the varied susceptibility pattern reported in our study indicates the importance of appropri-

ate selection of antibiotics based on the local prevalence of microorganisms for the treatment of pneumonia infections. The key limitations of our study included the single-center study design that may not represent the wide geographical area of the Greater China, small study population, and specific selection of lung cancer patients with pneumonia.

6. Conclusion

Lung cancer patients who were diagnosed to have pneumonia were predominantly colonized by *S. pneumoniae*. Although all our isolates were susceptible to penicillin, they showed an increased resistance towards erythromycin. Our results emphasize the need for a continuous monitoring of *S. pneumoniae* colonization and resistance patterns that need to be considered during treatment of lung cancer patients with pneumonia. Studies with larger populations involving wide geographical locations are highly warranted to understand the geographical variation in terms of *S. pneumoniae* colonization and resistance patterns in lung cancer patients.

Footnotes

Authors' Contribution: The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

Conflict of Interests: The authors declare that there is no conflict of interest to disclose.

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