



# Etiology and Clinical Outcome of Non-Resolving Pneumonia in a Tertiary Care Centre

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## Abstract

**Background:** A patient diagnosed to have pneumonia and put on empirical antibiotics but did not show the expected resolution is a common problem faced by the clinician.

**Aim of Study** (1) To find out the etiology and clinical outcome of nonresolving pneumonia in a tertiary care centre, (2) To find out the co-morbid conditions associated with nonresolution.

**Materials and methods:** 70 patients who did not show expected resolution after two weeks of adequate antibiotics were investigated systematically to find out the possible cause for non resolution and the associated co-morbid conditions.

**Results:** Tuberculosis was the commonest cause of nonresolving pneumonia (35.7%), followed by malignancy (27.1%), Bronchiectasis (8.6%), Pneumocystis pneumonia (7.1%), BOOP (5.7%) and Resistance to antibiotics (14.3%). Co-morbidities like COPD, diabetes, alcoholism, smoking and immunosuppression are significant factors causing nonresolution.

**Conclusion:** This study stresses the need for a systematic approach to find out the etiology and properly manage nonresolving pneumonias.

## Introduction

Pneumonia which resolves slowly after appropriate antibiotic therapy can be problematic. Richard Winterbauer et al had empirically defined slowly resolving pneumonia in immunocompetent patients as either less than 50% clearing at 2 weeks or less than complete clearance at 4 weeks in a patient who has defeveresced and symptomatically improved with antibiotic therapy.<sup>1</sup> Normal resolution of pneumonia is not easily defined. It can vary depending on the infecting organism and the host immune status. Patients typically note subjective improvement within 3-5 days of initiation of treatment.<sup>2</sup> Nonresolving pneumonia is defined as pneumonia with a slow resolution of radiographic infiltrates or clinical symptoms despite adequate antibiotics (10-14 days) treatment. This can be due to defects in local or systemic immune defense mechanisms, presence of unusual organism, resistant bacteria or diseases that mimic pneumonia. Knowledge about factors causing nonresolution, noninfectious causes & time taken for radiological resolution of pneumonias will help to avoid unnecessary invasive diagnostic procedures

## Materials and Methods

Patients admitted with pneumonia not showing adequate clinical and radiological improvement after 10-14 days of antibiotics from January 2008 to December 2008 were included in the study. The study was designed as a prospective observational study. A total of 821 patients were admitted with provisional diagnosis of pneumonia, out of which 70 patients (8.5%), 48 males and 22 females, who showed less than 50% radiological clearance, were selected. Patients below 12 years,

sputum positive pulmonary tuberculosis, diagnosed cases of bronchiectasis, congenital lung diseases, lung abscess, empyema and hospital acquired pneumonia were excluded from the study.

All patients with pneumonia admitted were interviewed with a structured Questionnaire (symptoms, co-morbidities, past history, treatment history, physical findings, and investigations). Baseline Chest X-ray is taken and patients were started on empirical broad spectrum antibiotics based on IDSA guidelines<sup>(3)</sup> (changed later according to culture & sensitivity results). Repeat Chest X-ray was taken after 2 weeks of treatment. Those patients showing <50% resolution after 2 weeks of antibiotics were included in the study and investigated with Mantoux, sputum gram stain, sputum culture and sensitivity, sputum fungal culture, sputum cytology, sputum mycobacterial culture, HIV-ELISA, FOB etc. CT scan, FNAC/ biopsy was done in indicated cases. Diagnosed cases after these investigations- malignancy, BOOP, PCP etc. were managed accordingly. Patients who have no other diagnosis even after these investigations, chest X-ray lesion suggestive of tuberculosis and Mantoux >10mm were started on empirical CAT I ATT based on a departmental consensus. All patients are followed up clinically & radiologically every 2 months for 6 months and clinical outcome was assessed based on extent of clinical and radiological improvement. Data were analyzed using computer software, Statistical Package for Social Sciences (SPSS) version 10. Data is expressed in its frequency and percentage. To elucidate the associations and comparisons between different parameters, Chi square ( $\chi^2$ ) test was used as nonparametric test. For all statistical evaluations, a two-tailed probability of value, <0.05 was considered significant.

## Observations and Results

A total of 70 patients were included in the study, male 48 (68.6%) and female 22 (31.4%) with a male: female ratio 2.18:1. 84.6% patients were above the age of 40 years. Commonly affected

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**Table 1 : Co-morbidities**

Co-morbidities	Frequency	Percentage	X <sup>2</sup>	P value
Smoking	42	60	4.447	<0.05
Alcohol abuse	34	48.6	6.6186	<0.05
COPD	25	35.7	12.217	<0.001
Hypertension	15	21.4	22.195	<0.001
Diabetes	32	45.7	7.650	<0.01
CAD	13	18.6	24.844	<0.001
Immunosuppression	5	7.1	38.487	<0.01

**Table 2 : Etiology**

	Number	Percentage
Tuberculosis	11	15.71%
Probable tuberculosis	14	20%
Malignancy	19	27.1%
Bronchiectasis	6	8.6%
PCP	5	7.1%
BOOP	4	5.7%
Resistance to empirical antibiotics	10	14.3%
Others	1	1.4%

age group was 51-60 years. Fever (80%) and cough (87.1%) were the most common symptoms. 70% of patients had symptom duration over 4 weeks. Smoking 42(60%) was the most common co-morbidity noted. Other statistically significant co-morbidities were alcohol abuse 34 (48.6%), diabetes mellitus 32 (45.7%), COPD 25 (35.7%) and hypertension 15(21.4%). 5(7.1%) patients were HIV positive (Table 1). 40% of the smokers had a smoking index above 500. Chest X-ray lesions were unilateral in 82.9% of the patients, lower zone predominance in 65.7%. Out of the 19 cases of malignancy diagnosed, 8(42.10%) were adenocarcinoma (Figure 1), 5(26.3%) squamous cell carcinoma, 3(15.79%) small cell carcinoma and 1(5.26%) large cell carcinoma. Positive culture was obtained in 15 patients, out of which 10 cases showed resistance to empirical antibiotics. Klebsiella accounted for 7(60%) (Figure 2), followed by Pseudomonas 3(20%), E. coli and Acinetobacter 10% each. Fiberoptic bronchoscopy was done in 52 patients. Malignant cells were detected in 9 cases from FOB brushing/washing/biopsy. Sputum cytology yielded malignant cells in 8 cases. Mycobacterium tuberculosis culture was positive in 6 cases. Out of 70 cases Mantoux test was >10mm in 36(51.4%). Most common cause of nonresolution of pneumonia in this study was tuberculosis 25(35.7%) followed by malignancy 19 (27.1%). Other causes were drug resistant organisms 10(14.3%), bronchiectasis 6(8.6%), PCP pneumonia 5(7.1%) and BOOP 4(5.7%) (Table 2). Among 25 cases of tuberculosis 14 had good clinical and radiological response, 8 had good clinical response but partial radiological clearance. All cases of pneumonia due to organisms resistant to empirical antibiotics, responded favorably to the treatment after modification of specific antibiotics. There were total of 11 deaths; 8 malignancy, 2 PCP pneumonia and 1 BOOP (due to myocardial infarction).

Summing up the outcome, there was good clinical and complete chest X-ray resolution in 40%, good clinical response, but partial chest X-ray resolution in 25.7%, poor clinical improvement and chest X-ray resolution in 10%, death in 15.7%, non compliance to treatment in 2.9% and lost follow up in 5.7%.

## Discussion

Nonresolving pneumonia is a diagnostic dilemma and those patients are usually subjected to inappropriate invasive and costly investigations for its evaluation. A knowledge regarding

**Fig. 1 : Left upper lobe consolidation with drug resistant Klebsiella****Fig. 2 : Broncho alveolar Carcinoma**

the spectrum of diseases which cause nonresolution in our setting will be valuable for the physician. As there are no such studies available in our setting, a study about the etiology and clinical outcome of nonresolving pneumonia is highly relevant in proper evaluation and management. A total of 821 patients were admitted with diagnosis of pneumonia during the study period out of which 70 patients who satisfied the criteria of nonresolving pneumonia were included in the study. Patients aged 50 years and more constituted 64.3% of the total study population. Lowered immune status due to smoking, diabetes etc; and malignancies may be responsible for this distribution. General debilitation and poor social support in the elderly may be the contributing factor for tuberculosis in these patients. 70% of patients had duration of symptoms more for than 4 weeks and represent the chronic nature of illness in most of the cases. On analysis of the data, tuberculosis 25(35.7%) was the most common cause of non resolving pneumonia in our study. Sputum negative pulmonary tuberculosis presenting as consolidation (lobar, segmental or bronchopneumonia) were probably treated in the periphery as



**Fig. 3 : Sputum negative pulmonary tuberculosis before treatment**

bacterial pneumonia because they lacked the typical chest X-ray lesions of tuberculosis, especially cavitation. The diagnosis of tuberculosis was made in our study after excluding all other causes of non resolution, careful interpretation of chest X-ray, Mantoux test, sputum cultures, lung FNAC and CT examination. CATI anti tuberculous treatment was initiated for smear positive patients and for smear negative patients based on a departmental consensus (Figures 3 and 4).

Malignant lung disease was the next common cause 19(27%) of nonresolution. A diagnosis of malignancy was made from tissue histopathology, sputum cytology, bronchoscopy, lung FNAC...etc. The incidence of malignancy is very high compared to western literature which shows malignancy in up to 11% of nonresolving cases.<sup>4</sup> BOOP 4(5.7%) was diagnosed on the basis of positive history, chest X-ray, HRCT findings and the response to steroids. Pneumocystis carini (jiroveci) pneumonia 5(7.1%) was diagnosed by the typical radiological findings, arterial PaO<sub>2</sub> <70mmHg in patients who are HIV positive and the response to therapy.

Co-morbidities were present in majority of the patients. Smoking was the most common co-morbidity noted, seen in 42(60%) of the patients. Other major co morbidities were alcohol abuse 34(48.6%), diabetes mellitus 32(45.7%), COPD 25(35.7%) and hypertension 15 (35.7%). Jay.S reported the common conditions associated with delayed resolution are advanced age, COPD, and alcoholism.<sup>5</sup> Roson. B et al in their study analyzing the causes and factors associated with early failure in hospitalized patients with community acquired pneumonia found that independent factors associated with early failure were old age, multilobar pneumonia, pneumonia severity index greater than 90, Legionella pneumonia, gram negative pneumonia and discordant anti microbial therapy.<sup>6</sup> Positive results for bacteria were low (Gram stain 31.43% and culture 21.43%), may be due to prior course of antibiotics before admission or conditions mimicking bacterial pneumonia. Sputum mycobacterial culture was positive in 6 cases. Evaluation of chest X-ray gave valuable clues to the diagnosis. Bilateral disease was common in tuberculosis, but for malignancy,



**Fig. 4 : Pulmonary tuberculosis after treatment**

reverse was the case. CT scan especially HRCT was a useful aid in reaching a diagnosis. Six cases of occult bronchiectasis were diagnosed from HRCT. In tuberculosis, a bilateral acinar pattern with cavitation (especially cavities not made out in the chest X-ray), and bronchiolitis with tree in bud appearance were helpful in diagnosis. Carcinoma lung was suspected when mass lesions, hilar adenopathy, collapse with consolidation and chest wall involvement were present. Lower zone lesions, mosaic perfusion on HRCT in expiratory films and nodules suggestive of bronchiolitis were present in BOOP. Bronchoscopic evaluation was done using fiberoptic bronchoscope in 52 patients. Malignant cells were detected in 9 cases by FOB guided biopsy, brushing or washing cytology. All bronchial washing samples were negative for AFB and bacterial culture. Feinsilver SH et al reported that approximately 15% of consultations and 8% of bronchoscopies were done specially to evaluate patients with nonresolving pneumonia.<sup>5</sup> Percutaneous FNAC was used to get tissue in 33 cases. (CT guided in 21 and blind FNAC in 12). Malignancy was the most common result obtained and exact type of carcinoma could be diagnosed in 13 cases, followed by tuberculosis.<sup>5</sup> After 6 months of follow up, it was found that death occurred in 11 patients (15.7%). 8 due to malignancy, 2 PCP pneumonia and 1 death in BOOP (due to myocardial infarction). Western literature shows a mortality of 27%-49% in nonresolving pneumonia.<sup>8,9</sup>

After six months of follow up there was good clinical improvement and complete chest X-ray resolution in 28(40%), good clinical improvement, but partial chest X-ray resolution in 18(25.7%), poor clinical improvement and chest X-ray resolution in 7(10%), non compliance to treatment in 2(2.9%) and lost to follow up in 4(5.7%). In an earlier study done in our department of Respiratory Medicine, after 2 months follow up, there was good clinical improvement and complete chest X-ray resolution in 37.91%, good clinical improvement, but partial chest X-ray resolution in 13.79%, poor clinical improvement and chest X-ray resolution in 27.58%, non compliance to treatment in 6.89% and lost follow up in 13.79% (Unpublished data).

## Conclusions

Patients aged 40 years and above are at risk for non resolving pneumonia. Comorbidities like COPD, diabetes, alcoholism, smoking and immunosuppression are significant factors causing nonresolution. Tuberculosis is the commonest cause of non resolving pneumonia in our setting. This possibility has to be kept in mind during evaluation, since it is a curable cause. Malignancy is the next common cause of non resolving pneumonia, so a high index of suspicion is needed. Invasive procedures are needed more frequently to reach a diagnosis. We have to consider unusual or resistant pathogens and non infectious etiologies while evaluating a case of non resolving pneumonia. This study stresses the need for a systematic approach to manage non resolving pneumonia properly.

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