Non-Resolving Pneumonia study in a Tertiary Care Hospital

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Abstract:
Pneumonia is a common illness which causes significant morbidity and mortality all over the world, despite the availability of better and more potent antibiotics and improvement in supportive care. The problem increases with discrepancy in management despite the availability of guidelines for management. Pneumonia is often misdiagnosed and is commonly treated inadequately or over treated with misuse of potent antibiotics. This along with the increasing contact with health services is leading to an increase in infection with multi drug resistant (MDR) organisms which are of major concern. It is also important to consider the prevalence of specific organisms at that point of time. Non-resolving pneumonia is often an area of concern for physicians and pulmonologists. Fiber optic bronchoscopy (FOB) may have a special role in etiologic evaluation of non-resolving pneumonias. There is paucity of recent studies in this field. Both progressive and nonresolving pneumonia represent treatment failure as a result of inappropriate initial therapy, a noninfectious cause, or an overwhelming immune response. It is critical to be able to identify patients with nonresponding pneumonia and to identify patients at risk for progressive pneumonia to institute appropriate therapy.

Introduction:
Pneumonia is a common illness which causes significant morbidity and mortality all over the world. After starting appropriate antibiotic and other supportive therapy depending wholly on self clinical acumen, many times the physician is in dilemma; will this patient, will respond to my treatment or I am dealing with the non-resolving pneumonia. This is a day to day problem faced by every physician. [1]
Early definitions of non–resolving pneumonia were based principally on Physical examination findings. In 1975, Hendin defined slowly resolving as pulmonary consolidation persisting more than 21 days. [2] In 1991, Kirtland and Winterbauer [3] defined slowly resolving CAP in immunocompetent patients based upon radiographic criteria. Among patients who had improved clinically and defervesced with antibiotic therapy, slowly resolving was defined according to the rate and extent of clearing of chest radiographs--i.e., less than 50% clearing by 2 weeks or less than complete clearing at 4 weeks. In a 1987 review, Fein et al [4] defined nonresolving pneumonia as a clinical syndrome in which "focal infiltrates clearly begin with some clinical association of acute pulmonary infection (that is, fever, expectoration, malaise and / or dyspnea) and do not resolve in the expected time. " The expected time of radiographic resolution is influenced by both host factors and the culprit
pathogen .[5,6,7] Delay in diagnosis and treatment may lead to rise of mortality by 3-5% in both community – acquired pneumonia and nosocomial pneumonia . Incorrect diagnosis , inadequate antibiotic therapy, impaired host defence , atypical organisms , resistant pathogens , non-infectious causes , tuberculosis , endobronchial lesions , etc . are the common causes of nonresolving pneumonia or slowly resolving pneumonia. [8],[9],[10],[11] Slow or incomplete resolution of pneumonia, despite treatment, needs a more aggressive evaluation. 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 recovered from fever and symptomatically improved with antibiotic therapy.(12) 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.(13). Nonresolving pneumonia is defined as pneumonia with a slow resolution of radiographic infiltrates or clinical symptoms despite adequate antibiotics (10-14 days) treatment. In this study, we tried to find out the etiological diagnosis of nonresolving pneumonia or slowly resolving pneumonia and also to evaluate the efficacy of diagnostic investigations , like HRCT , and CT-guided FNAC and procedures especially bronchovascular lavage with F O B .

**Materials and Methods**

Patients admitted with pneumonia not showing adequate clinical and radiological improvement after 10-14 days of antibiotics from June 2013 to May 2014 were included in the study. The study was designed as a prospective observational study, performed in the department of Medicine at a Tertiary care Multi-speciality Hospital , Sainath Hospital , at Shirdi in Western Maharashtra . There were 90 consecutive cases of non-resolving or slowly resolving pneumonia of both sexes , and of more than 12 years of age as well as other criterias for including in the study attending the department of Medicine during the study period , were selected by adhering to the inclusion and exclusion criteria. Inclusion criterias were --Non-resolving or slowly resolving pneumonia was defined in this study by the presence of persistence of clinical symptoms and signs (cough, sputum production, with or without fever more than 100°F), failure of resolution of the radiographic features by 50% in 2 weeks or completely in 4 weeks on serial chest X-ray (indicated in at least 2 consecutive chest X-rays) in spite of antibiotic therapy for a minimum period of 10 days, and sputum for acid fast bacilli (AFB) smear negative for 2 consecutive days. 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 are followed up clinically & radiologically every 2 months for 6 months and clinical outcome was assessed based on extent of clinical and radiological improvement. After evaluation of all the relevant reports, determination of
etiology of non-resolving or slowly resolving pneumonia was attempted. Finally, efficacy of FOB and CT-guided FNAC as a diagnostic method for etiological analysis of non-resolving or slowly resolving pneumonia was assessed.

Observations and results:
Overall, mean age of the patients was 51.3 years, and most of the patients (83%) were above the age of 40 years; no significant difference was observed in age parameter between different etiological groups. Among the 90 patients, 62 (68.3%) were male and 28 (31.7%) female. Mean duration of illness was 4.5 weeks. Fifty-two patients (53.6%) were smoker, and smoking was distinctly more common in malignant etiology, compared to other groups [Table 1]; 29 patients (32.22%) were alcoholic. Nineteen patients (21.11%) had past history of treatment with anti-tuberculous medication.

Diabetes mellitus was the commonest comorbidity and was noted in 33 patients (36.66%) in the study population. Diabetes was significantly more associated with infective etiology, compared to malignancy [Table 1]. Klebsiella pneumoniae was the commonest organism isolated in patients with diabetes and was found in 12 out of 33 diabetics (36.36%), followed by Mycobacterium tuberculosis (24.2%, n = 8) and Staphylococcus aureus (18.18%, n = 6).

<table>
<thead>
<tr>
<th>Co-morbidities</th>
<th>No of cases</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough</td>
<td>90</td>
<td>100</td>
</tr>
<tr>
<td>Chest pain</td>
<td>36</td>
<td>40.2</td>
</tr>
<tr>
<td>Smoking</td>
<td>54</td>
<td>60</td>
</tr>
<tr>
<td>Alcohol abuse</td>
<td>45</td>
<td>50</td>
</tr>
<tr>
<td>COPD</td>
<td>32</td>
<td>35.7</td>
</tr>
<tr>
<td>Haemoptysis</td>
<td>28</td>
<td>30.6</td>
</tr>
<tr>
<td>Diabetes</td>
<td>43</td>
<td>47.8</td>
</tr>
<tr>
<td>Hypertension</td>
<td>45</td>
<td>50</td>
</tr>
<tr>
<td>immunosupression</td>
<td>4</td>
<td>4.44</td>
</tr>
</tbody>
</table>
Table no 2 : Etiological frequency in non-resolving pneumonias.

<table>
<thead>
<tr>
<th>Disease</th>
<th>No. of cases</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tuberculosis</td>
<td>38</td>
<td>42.22</td>
</tr>
<tr>
<td>Bacterial pneumonias</td>
<td>29</td>
<td>32.22</td>
</tr>
<tr>
<td>Malignancy</td>
<td>25</td>
<td>27.78</td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td>4</td>
<td>4.44</td>
</tr>
<tr>
<td>PCP</td>
<td>4</td>
<td>4.44</td>
</tr>
</tbody>
</table>

Among 38 cases of tuberculosis 22 had good clinical and radiological response, 12 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 12 deaths; 25 malignancy, 2 PCP pneumonias.

To summarise the outcome, there was good clinical and complete chest X-ray resolution in 45 cases (50%), good clinical response, but partial chest X-ray resolution in 24 cases (26.66%), poor clinical improvement and chest X-ray resolution in 9 case (10%), death in 12 cases (13.33%).

Discussion:
Nonresolving pneumonia is many times a diagnostic dilemma and these patients are usually subjected to inappropriate invasive and costly investigations for its evaluation. A knowledge regarding the spectrum of diseases which cause nonresolution in our setting and the frequency of their occurrence, so as to consider the investigative path will be of enormous value for the treating physician.

Non-resolving or slowly resolving pneumonia is a most frequent situation faced by many physicians after they have admitted a patient with provisional diagnosis of pneumonia and at the same time, can be a cause of concern in daily clinical practice.

Amberson was the first person to describe the term "unresolved organizing or protracted pneumonia" in 1943. [15] There is lack of uniformity regarding the definition for non-resolving pneumonia, but in many studies, the entity of "slow resolution" has been defined as failure of radiographic resolution by 50% in 2 weeks or failure of complete resolution by one month despite adequate antibiotic therapy. [16]

In our study, there were 56 male patients (62.22%) and 34 females (37.78%), thus giving a male:female ratio of 1.65:1, this shows male preponderance. This also correlates well with the study done by B.Jayaprakash et al. (19) where in the male:female ratio was 2.18:1.

In our study, 80% patients were over the age of 40 years and nearly 50% were over the age of 50 years. El Solh et al. stated that age alone has the most striking influence on resolution of pneumonia, and in their study, rate of resolution on chest X-ray was found to be 35.1% by 3 weeks and 60% by 6 weeks...
in patients above 70 years of age. [20] Fein has also shown in his study that only 30% of patients above 50 years of age show complete radiologic resolution by 4 weeks. [21]

In this study, after tuberculosis, bacterial pneumonias were found in 29 cases i.e. 32.22% and was the next leading cause for non-resolution of pneumonias. Among bacterial pneumonia, gram-negative bacilli were the predominant organisms isolated in 23 out of 25 cases of bacterial pneumonia (92%); Staphylococcus aureus accounted for 2 cases (8%). Klebsiella pneumoniae and Pseudomonas aeruginosa were the two most common gram-negative organisms, isolated. Eschericia coli and Acinetobacter spp were found in 1 case each.

Malignant lung disease was the next common cause found in 25 cases (27.78%) of nonresolution. A diagnosis of malignancy was made from tissue histopathology, sputum cytology, bronchoscopy, lung FNAC...etc. The incidence of malignancy was found to be very high as compared to western literature which shows malignancy in up to 11% of nonresolving cases. [22] Silver et al. found malignancy as a specific cause for non-resolving pneumonia in 11.4% cases in their series of 35 patients. [22]

Co-morbidities were present in majority of the patients. Smoking was the most common co-morbidity noted, seen in 54(60%) of the patients. Other major co-morbidities were alcohol abuse 45 (50%), diabetes mellitus 43(47.8%), COPD 32(35.7%) and hypertension 30 (33.3%). Jay.S reported the common conditions associated with delayed resolution are advanced age, COPD, and alcoholism. [23] Roson. B et al in their study analyzing the causes and factors associated with early resolution 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. [23]

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.

In the present study, CT-guided FNAC was done in 27 patients, and etiological diagnosis was established in 25 cases (diagnostic yield being 92.59%). Among these patients, malignancy was found in 17 cases (68%). In study conducted by Ferretti et al. in 23 patients of non-resolving pneumonia with negative FOB results, CT-guided core needle biopsy was done. Diagnostic yield of biopsy was 78%, 15 patients were diagnosed as malignancy, and 8 patients were diagnosed to have benign disease. The sensitivity and specificity for malignancy were 87% and 100%, respectively. [22]

Fiberoptic bronchoscopy (FOB) was done in 70 patients, and etiological diagnosis could be established in 61 cases (diagnostic yield 87.14%). BAL fluid was taken in all of these patients, and conclusive diagnosis achieved in 47 patients (77.05%); pyogenic infection was found to be the commonest etiology. In the study by Silver et al., FOB was diagnostic in 86% cases, and infections were the most common etiology obtained at FOB. [22] Balamugesh et al. have also found FOB a very useful tool in evaluating non-resolving pneumonia. [23] In our study, post-bronchoscopic sputum smear examination for AFB was done.
in all 70 patients, and 5 of them were AFB positive; 2 patients being exclusively positive for AFB by post-bronchoscopic sputum examination only. Therefore, overall diagnostic yield of FOB is very good, and it is a very useful tool for the evaluation of non-resolving pneumonia. The procedure is safe, and complications are very less if done properly.

**Conclusion:**
Both progressive and nonresolving pneumonia represent treatment failure as a result of inappropriate initial therapy, a noninfectious cause, or an overwhelming immune response. It is critical to be able to identify patients with nonresponding pneumonia and to identify patients at risk for progressive pneumonia to institute appropriate therapy at the earliest so as to decrease the morbidity and inherent mortality.

**References:**
5. Fein AM, Feinsilver SH: The approach to non-resolving pneumonia in the elderly. Semin Respir Infect 8:59-72, 1993