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REVIEW ARTICLE

NON- RESOLVING PNEUMONIA – A BRIEF ETIOLOGICAL AND DIAGNOSTIC REVIEW

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Abstract

A delayed resolution or non-resolving pneumonia (NRP) is a common clinical problem both in community-acquired pneumonia and hospital acquired pneumonia. Causes of non-resolving pneumonia include Nontargeted or Inadequate dose of antibiotic therapy, multidrug resistant pathogens, pneumonia complications or incorrect approach to diagnosis. Comorbidities like COPD, diabetes, alcoholism, smoking, Bronchiectasis and Immunosuppression are significant factors causing non-resolution. NRP is associated with increased morbidity and mortality. If non-resolving pneumonia is recognised, then patients should undergo a full re-evaluation, including microbiological testing with culture/sensitivity, repeat chest X-ray, Contrast enhanced CT scan and consideration of transbronchial lung biopsy(TBLB) or CT guided biopsy from specific disease site. A wide range of non-infectious disorders can present as non-resolving pneumonia, including Eosinophillic pneumonia, sarcoidosis, pulmonary embolism, malignancy, collagen vascular disease, alveolar haemorrhage, and vasculitis. There is no specific guidelines for diagnosis of patients with Non-resolving Pneumonia. This article reviews the causes, investigation and specific approach for diagnosis of nonresolving pneumonia.

Key Words : Non-resolving pneumonia(NRP), Fibreoptic Bronchoscopy, CT guided FNAC

INTRODUCTION

Kirtland and Winterbauer defined slowly resolving community acquired pneumonia in immunocompetent patients among patients who had improved clinically and defervesced with antibiotic therapy less than 50% clearing by 2 weeks or less than complete clearing at 4 weeks.[1] Fein et al 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”.[2] The expected time of radiographic resolution is influenced by both host factors and the culprit pathogen. In a later review Fein and Feinsilver modified their definition to require “a minimum of 10 days of antibiotic therapy and a radiographic infiltrate that has not resolved in an ‘expected’ period of time based on the presumed diagnosis”.[3] Approximately 90 percent of patients younger than 50 years of age show radiographic resolution by four weeks, compared with only 30 percent of patients older than 50 even in the absence of concurrent disease.[4] Causes of non resolution pneumonia are co-morbid illnesses like diabetes, alcoholism, COPD and bronchiectasis, age greater than 50 year, cytotoxic/ immunosuppressive therapy, bacteremia, multilobar pneumonia,

presence of drug resistant organisms, presence of unusual organisms and diseases mimicking pneumonia.[5]

Patients will have resolution of pneumonia at different rates and the most of pneumonia will resolve symptomatically and radiologically with median time of 3-7 days. If the patient has delayed or non resolution of pneumonia beyond 10 days, re-evaluation of patient is needed. The most important predictors of Nonresolution are age, comorbidities, unusual pathogen and disease severity.

Disease severity can be calculated by PSI scoring and CURB-65 scoring. Although the PSI and CURB-65 criteria are valuable aids in avoiding inappropriate admissions of low-mortality-risk patients, another important role of these criteria may be to help identify patients at high risk who would benefit from hospitalization. The committee preferred the CURB-65 criteria because of ease of use and because they were designed to measure illness severity more than the likelihood of mortality. Patients with a CURB-65 score>2 are not only at increased risk of death but also are likely to have clinically important physiologic derangements requiring active intervention.[6]

The Infectious Diseases Society of America/ American Thoracic Society (IDSA/ATS) 2007 guidelines recommend the use of Halm's [7] criteria for determining the presence of clinical stability, and therefore, treatment response. These criteria consist of temperature ≤37.8 °C, heart rate ≤100 beats/minute, respiratory rate ≤24 breaths/minute, systolic blood pressure ≥90 mmHg, O2 saturation ≥90%, or arterial O2 tension ≥60 mmHg, normal mental status, and normal oral intake.$_7$ Akram et al [8] compared four strategies for determining treatment response: Halm's criteria, the simplified ATS criteria, reduction in the CURB65 score, and CRP reduction. This study found that Halm's criteria was the most effective to define treatment response (0.5% mortality, 0.3% risk of requiring mechanical ventilation or vasopressor support, and 0.7% risk of developing complicated parapneumonic effusion or empyema), although a reduction in CRP was also found to give excellent prediction.

Non-resolving pneumonia : Etiology

Host factors are important risk factor for non resolution of pneumonia. Two Indian study Jayprakash et al[9] and Jain et al[5] has observed that Smoking, Alcohol and Diabetes are significant risk factor for Non resolving pneumonia. Jayprakash et al [9] and Jain et al [5] has also observed that Tuberculosis is one of leading cause of nonresolving pneumonia in india. Jayprakash et al has also shown that multidrug resistant orgainism is also important cause of non resolving pneumonia.

TABLE 1 NON RESOLVING PNEUMONIA ETIOLOGY

Comorbidities	**Age>60 year, COPD, bronchiectasis, Alcohol abuse, Smoking, Diabetes Mellitus,**
Multidrug resistant orgainism	**P. aeruginosa, K. pneumonia, Acinetobacter, Tuberculosis, Anaerobes, MRSA**
Unusual pathogen	**Viral, Endemic Fungi, Parasitic Infection, Pneumocystic carnii pneumonia**
Complication or wrong diagnosis	**Lung Abscess, Pyothorax, Intrathoracic Lymphadenopathy, Cavitation, Recurrent aspiration pneumonia**
Immunosuppression	**HIV, Congenital or Acquired Immunoglobin and T cell deficiency**
Non infectious cause	**Collagen vascular disease (CVD), Pulmonary Embolism, Drug induced Lung Disease, Eosinophillic pneumonia, Sarcoidosis, Malignancy, Chronic renal Impairment, Myocardial infarction**

Tuberculosis and multidrug resistant orgainism like pseudomonas, staphylococcus aureus should always be ruled out by culture sensitivity of infectious orgainism because antibiotics not targeted to particular orgainism can also lead to nonresolving pneumonia. The unusual pathogen like PCP, virus or cryptococcus can be subjected for Bronchoscopic BAL culture or PCR specific for orgainism. Non resolution may also result due complication of pneumonia like pyothorax, recurrent aspiration pneumonia or Lung abscess. Another important etiology of nonresolving pneumonic is immunosuppression either acquired infection (AIDS) or congenital T or B cell deficiency.

Malignancy of lung is one of important noninfectious cause of nonresolving pneumonia.[5,9,10] Pulmonary embolism, collagen vascular disease and eosinophilic pneumonia are some of rare non infectious cause of non resolving pneumonia.

TABLE 2 ETIOLOGY OF NON RESOLVING PNEUMONIA IN DIFFERENT STUDIES

	Jayprakash et al [9] Total 70 patient	**Chaudhuri et al [10] Total 60 patients**	**Jain et al [5] Total 65 patient**	**M. Avijgan et al [11] Total 50 patient**
Bacterial pneumonia	**NR**	**32(53.3%)**	**24(37%)**	**NR**
Tuberculosis	**25(35.7%)**	**10(16.6%)**	**19 (29.2%)**	**23 (46%)**
Malignancy	**19(27.1%)**	**16(26.6%)**	**15 (23%)**	**13 (26%)**
Other diagnosis	**Resistant bacterial pneumonia 10(14%)**	**1 (1.67%) Wegners granulomatosis**	**Foreign Body 2 (3%)**	**Bronchitis 8 (16%)**

Non - Resolving Pneumonia : Diagnosis

Tuberculosis, Multidrug resistant bacterial pneumonia, Unusual pathogen and malignancy are important cause of Non-resolving pneumonia in different studies.[5,9,10,11] Non resolving pneumonia is a difficult to diagnose and challenging state to pulmonologists. A detailed history of travel, occupational exposure and knowledge of endemic disease in particular region is very important for diagnosis of non resolving pneumonia. Repeat physical examination with special consideration for extrapulmonary involvement should be considered for systemic disease like sarcoidosis and collagen vascular disease. Results of microbiological testing should be reviewed

and culture-sensitivity performed on admission should be evaluated in detail. Risk factors for unusual or resistant pathogens should be considered and the appropriate initial broad spectrum antibiotic therapy is considered in the context of the clinical findings and clinical response. Repeat microbiological testing should be considered, particularly when patient is febrile or WBC count is gradually increasing specially by procuring sterile BAL fluid for culture-sensitivity. Depending on the radiological and clinical profile, additional testing for unusual pathogen like Mycobacteria, fungi, or PCP may be considered.

Use of bronchoscopy and bronchoalveolar lavage is recommended in cases of clinical deterioration or failure to improve where non-invasive microbiological sampling has not been helpful, where opportunistic or unusual pathogens are suspected, and where certain pneumonia mimics are considered, such as endobronchial lung cancer, pulmonary alveolar haemorrhage, and acute eosinophilic pneumonia.[12]

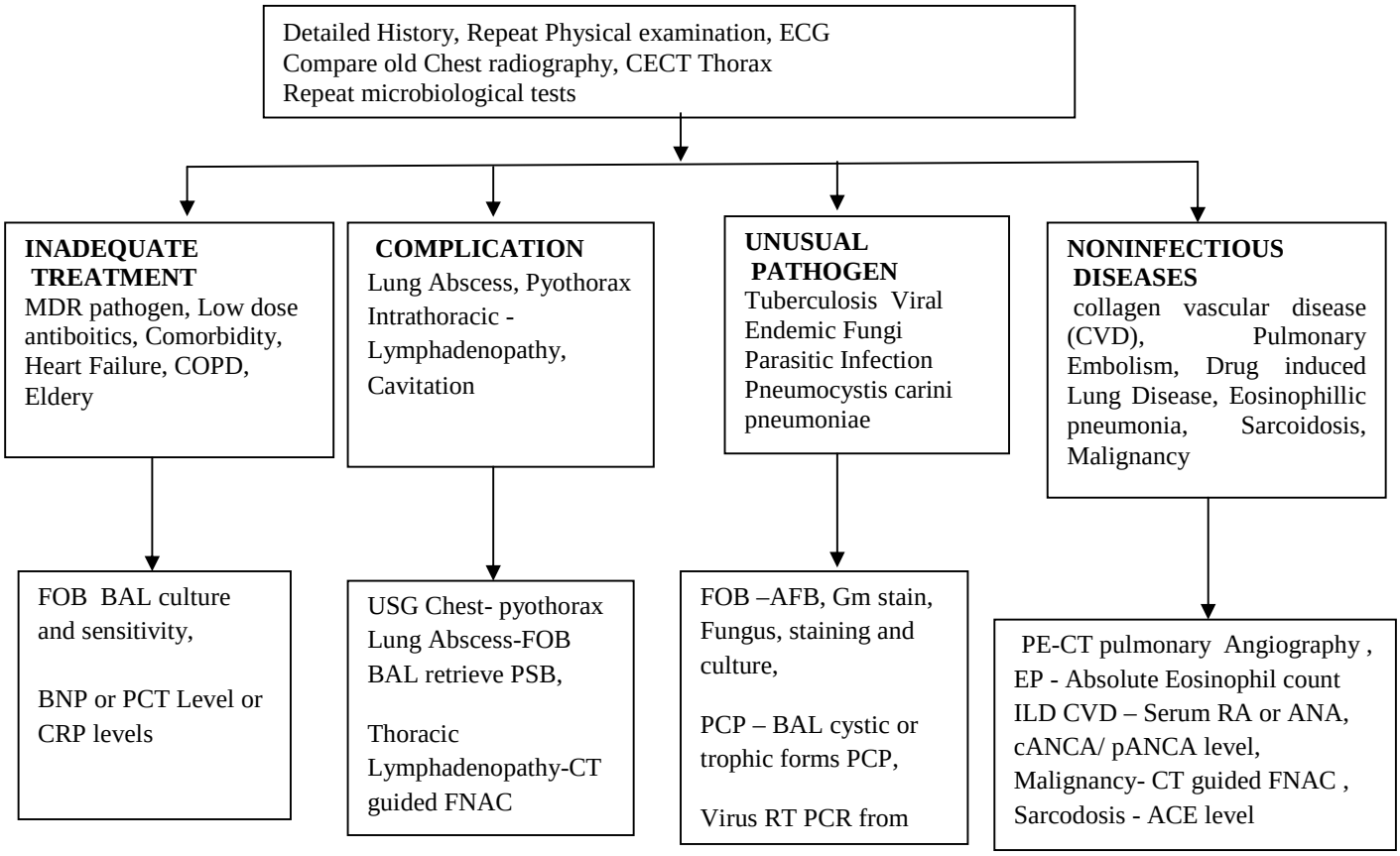

Figure 1 Non -Resolving pneumonia Diagnosis

PE- pulmonary Emblism, EP- Eosinophillic Pneumonia, ILD CVD -Interstitial Lung Disease-collagen vascular disease, PCP – Pneumocystis carini pneumonia ,BNP- Brain natriureic peptide, PCT –Procalcitonin, CRP- C Reactive protein

Biomarkers appear promising as a guide to treatment response to antibiotics. A combination of Halm's criteria and CRP <30 mg/L was 100% specific and had a positive predictive value of 100%, indicating no patients reaching these criteria had complications.[13] Procalcitonin reduction certainly appears to be useful to guide treatment response, as clinical trials have indicated that antibiotic therapy can be stopped once procalcitonin falls below a threshold level (the threshold used is often different depending on the assay or disease under study), without an increase in clinical failure or mortality.[14,15]

Serological tests or biopsies of extrapulmonary sites are helpful for diagnosis in some case like sarcoidosis and collagen vascular disease. CT pulmonary angiography is specific investigation when pulmonary embolism is strong suspect for Non-resolving pneumonia.

Objective data suggest that fibreoptic bronchoscopy with bronchoalveolar lavage and transbronchial biopsy can successfully diagnose approximately 90% of patients who eventually have a specific diagnosis established. It is most likely to be useful in younger, nonsmoking patients with multilobar involvement and prolonged disease, whereas elderly patients, smokers, and those with immunodeficiency are more likely to have a non diagnostic bronchoscopy and to have a slowly resolving pneumonia.[16] When endobronchial anatomy is normal and there is no purulence to suggest infection TBBs should be done to exclude noninfectious causes or infections attributable to mycobacteria or fungi.[17] Jain et al[5] series has also shown that TBLB was helpful in diagnosis of two case of tubercular pneumonia, one case of candida pneumonia and two cases of bronchogenic carcinoma.[5]

Choudhari et al [10] shown that yield of CT-guided FNAC (91%) was slightly better as compared to yield of FOB (85.7%) in non resolving pneumonia but CT-guided FNAC was done only in selected cases in their study. Jain et al study [5] has shown that diagnostic yield of FOB was (81.25%) which is slightly less than other studies because FOB is more helpful in diagnosis of centrally situated non resolving pneumonia and for peripheral situated lesion like adenocarcinoma and large cell bronchogenic carcinoma, CT guided FNAC is better option. The diagnostic efficacy of FOB was 81% and diagnostic efficacy of CT guided Biopsy was 91% for non resolving pneumonia. Both procedure are safe and no mortality was reported.

Non resolving pneumonia accounts for 10% - 15% of nosocomial pneumonias and is estimated to be responsible for approximately 15% of inpatient pulmonary consultation and 8% of bronchoscopies.[18] The most important findings of Menendez et al[19] study is that the incidence of empirical treatment failure was 15% in community acquired pneumonia and the independent risk factors associated were multilobar CAP, cavitation on chest radiograph, pleural effusion, liver disease, leucopenia, and high PSI.

CT-guided FNAC is a good procedure for peripherally situated lesions when FOB result is inconclusive. Its diagnostic yield is significantly high in particularly selected cases. Last resort for confirmatory diagnosis is surgical (open or VATS) biopsy to diagnose refractory or Non - resolving pneumonias.[5]

CONCLUSION :

Non-resolving pneumonia is common and difficult to diagnose condition and the cause may vary from a benign infectious cause to malignancy. A systematic approach to investigation is needed with consideration of infectious, non-infectious and malignant causes.

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