

INTRODUCTION

Non resolving pneumonia is a common problem faced by physicians. This is responsible for 15% of pulmonary consultations needing hospitalization and 8% of bronchoscopies. 10% of community acquired pneumonia (CAP) and 60% of hospital acquired pneumonia (HAP) show inadequate responses to empirical therapy initiated.

DEFINITION

The term NRP has been used to refer to “Persistence of radiological abnormalities beyond expected time of course”. The expected time course for resolution is controversial. In 1975 Hendin defined slow resolving pneumonia (SRP) as pulmonary consolidation persisting for more than 21 days. In 1991 Kirtland & winterbauer defined SRP in immune competent patients based upon radiological criteria ; Less than 50% clearings by 2 weeks or less than complete clearing 4 weeks.

Non resolving Pneumonia (NRP) is a clinical syndrome in which focal infiltrates begin with some clinical association of acute pulmonary infection and despite a minimum of 10 days of antibiotic therapy patients either don't improve or worsen or radiographic opacities fail to resolve within 12 weeks.

NORMAL RESOLUTION OF PNEUMONIA

Normal resolution of pneumonia is not easy to define. It depends upon the underline causes. Subjective improvement starts 3-5 days after initiated treatment.

Figure 1 showing rate of resolution of clinical, Laboratory and Radiological abnormalities.

Pneumonia resolution depends upon many key factors. Rapid resolution of pneumonia occurs when

Abnormalities	Duration
Fever	2 – 4 days
Cough	4 – 9 days
Tachycardia	2 days
Hypotension	2 days
Tachypnea	3 days
Crackles	3 – 6 days
Leukocytosis	3 – 4 days
C-reactive protein	1 – 3 days
Chest X-Ray (CXR) abnormality	4 – 12 weeks

Fig. 1: Resolution of Pneumonia

1. Host is young, nonsmoker and non hospitalized.
2. CAP is of mild severity.
3. Causative microorganisms are mycoplasma pneumoniae or Chlamydia pneumoniae.

CAUSES OF NON RESOLVING PNEUMONIA

There are numerous causes which can delay normal resolution of pneumonia. They can be broadly categorized into two groups.

Infectious Causes

40% of the causes are attributable to infections which may be primary, persistent or nosocomial infections. Streptococcus pneumoniae, Legionella, Staphylococcus aureus and Pseudomonas aeruginosa are common organisms responsible for non resolution. Methicillin-resistant S aureus (MRSA) [33%], enteric- Gram negative bacilli (24%) and P aeruginosa (14%) have been found in elderly patients with nosocomial infections.

S pneumonia resistance is less common if the treatment is appropriate and according to the guideline. The unusual microorganisms like tuberculosis and fungal infections are usually the cause of NRP.

Non Infectious Causes

In one study in an ICU Jacobs et al found 19% of noninfectious causes of NRP. They include drug induced pneumonitis, ARDS, PTE (Pulmonary thrombo-embolism, carcinomatous lymphangitis, and cardiogenic pulmonary edema.

This group of non infectious causes is also called pneumonia mimics. Pulmonary neoplasm is estimated to account for 1-8% in most series. Bronchoalveolar cell carcinoma, lymphoma bronchogenic carcinoma, carcinoid and pulmonary metastasis may present like pneumonia.

History

In order to resolve the mystery of non resolving pneumonia comprehensive history taking is very essential. Fever and productive cough indicates infectious cause but many patients may have no symptom, only radiological findings. A history of pulmonary infections which are notorious to cause delayed radiological resolution can be a harbinger of NRP.

Past history of comorbid conditions like COPD, renal failure and alcoholism should also be sought as they delay radiological clearance. If we don't find any clue of

Table 1: Showing Causes of non-resolving pneumonia (Infectious)

Complications	<ul style="list-style-type: none"> • Empyema, abscess • Metastatic infection (e.g. infective endocarditis)
Host factors	<ul style="list-style-type: none"> • Age > 60 years (radiographic clearance of pneumonic infiltrate on completion of antibiotic therapy decreases by 20% per decade after the age of 20 Years) • C-morbid illnesses like COPD, congestive heart failure, diabetes mellitus, renal failure, alcoholism) • Smoking • Defects in defense (immunosuppressive/cytotoxic therapy, use of feeding tube, endotracheal tube, tracheostomy or sedating drugs) • Malnutrition.
Presence of resistant organisms	<p>Drug-resistant Streptococcus pneumoniae suspected if :</p> <ul style="list-style-type: none"> • Treated with beta lactams within 6 months • Close exposure to young children • Pneumonia in last 1 year • HAP in last 2 months <p>Methicillin- resistant Staphylococcus aureus (MRSA) suspected if :</p> <ul style="list-style-type: none"> • Advanced age • Prior antibiotic coverage, indwelling IV catheters, tertiary care centre, dialysis • Burns, surgical wounds <p>CAP : especially S pneumoniae, S aureus</p> <p>Nosocomial pneumonia : especially MRSA, pseudomonas aeruginosa, Acinetobacter</p>
Presence of unusual organisms	<ul style="list-style-type: none"> • Tuberculosis, atypical mycobacteria • Nocardis, Actinomyces • Pneumocystis jirovecii • Fungi ; Aspergillus, Cryptococcus, Histoplasma, coccidioidomycosis • Exposure to animals: Coxiella burnetii, Chlamydia, psitaci
Delayed radiological recovery	<ul style="list-style-type: none"> • Extent of disease : multilobar or bilateral pneumonia, pleural effusion, bacteraemia • Casual micro-organism

Table 2: Showing Causes of non-resolving pneumonia (Non Infectious)

Neoplasia	Bronchoalveolar cell carcinoma, Lymphoma, Lymphangitis carcinomatosa
Inflammatory disorders	Systemic Vasculitis, CTD (Connective Tissue Diseases), Diffuse alveolar hemorrhage, BOOP (Bronchiolitis Obliterans Organizing Pneumonia), Sarcoidosis
Drugs	Nitrofurantoin, Amiodarone, Methotrexate, Bleomycin
Cardiac causes	PTE, CHF

Table 3: Causative Agent and Clearance of Pneumonia

Causative agent	Time to clearance	Residual radiographical abnormalities
Pneumococcus		
Bacteremic	3 to 5 months	25% to 35%
Non bacteremic	1 to 3 months	Rare
Haemophilus influenzae	1 to 5 months	Occasional
Legionella	2 to 6 months	10% to 25%
Mycoplasma	2 weeks to 2 months	Rare
Chlamydia sp	1 to 3 months	10% to 20%
Staphylococcus aureus	3 to 5 months	Common
Gram negative	3 to 5 months	10% to 20%
Moraxella catarrhalis	1 to 3 months	Rare

infection a search for non infectious etiology should be thoroughly made.

Common chronic infections like mycobacterium tuberculosis, fungal and parasitic diseases should also be evaluated.

A history of angina and dyspnea may indicate cardiac cause of radiological opacity. A patient with history of heavy smoking, hemoptysis, cachexia or weight loss with non resolving opacities points to malignant etiology. Hematuria may indicate DAH whereas joint pain or rashes indicate CTD.

Asthma and persistent migratory opacities are suggestive of ABPA. Drugs history is important cause of pulmonary infiltrate. Similarly occupational history is also significant for NRP.

PHYSICAL EXAMINATION

Although the traditional finding of consolidation like dullness on percussion over the chest, tubular bronchial breathing may not be present in spite of persistent finding of radiological opacity, the examination of a patient with NRP should proceed in the comprehensive manner.

In HIV patients skin manifestation of a pulmonary

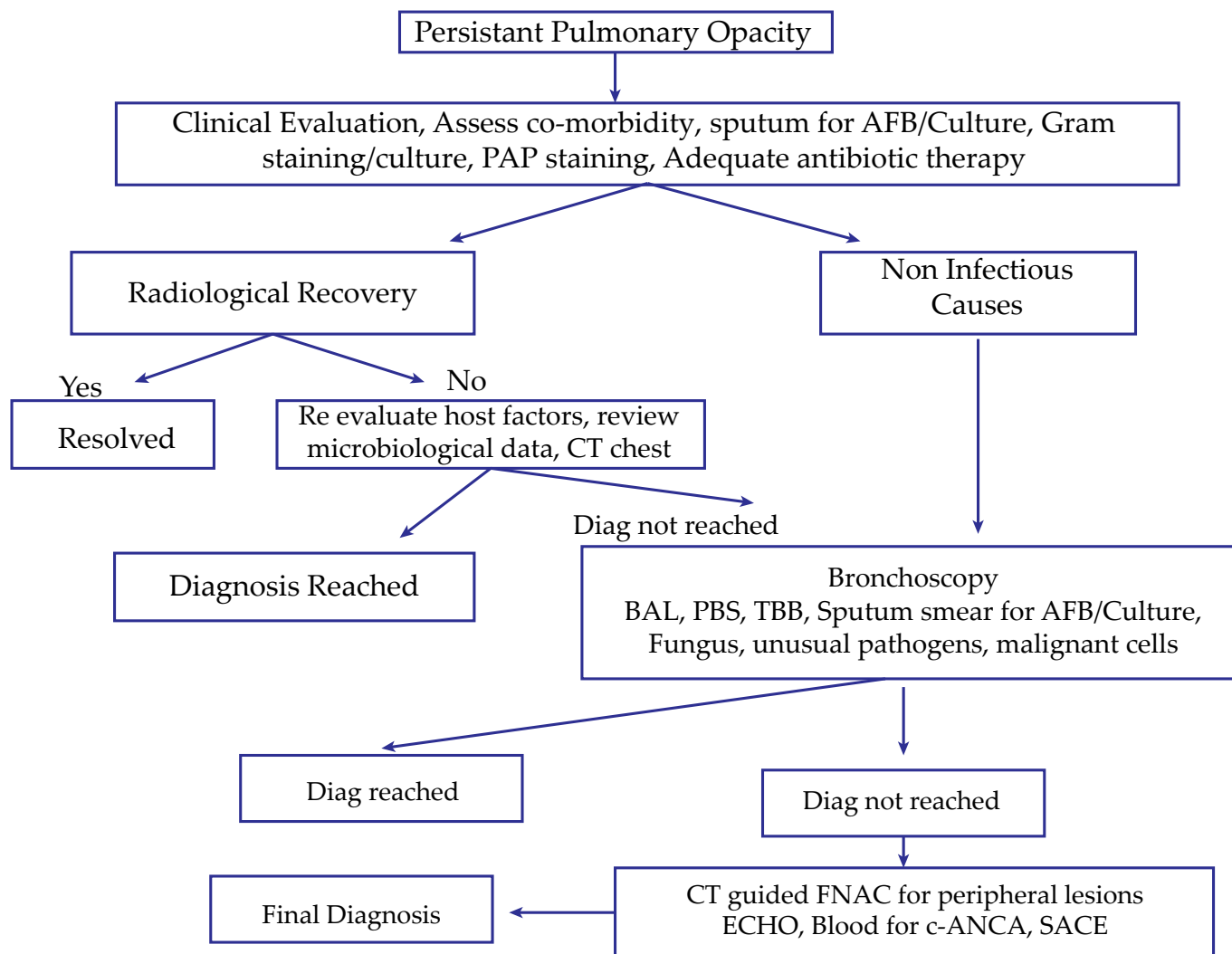


Fig. 2: Flow Chart of NRP

associated bacterial, fungal, viral or neoplastic disorder (Kaposi's sarcoma). Pedal edema, raised JVP and basal crackles are signs of heart failure while clubbing of fingers and toes may indicate idiopathic pulmonary fibrosis, asbestosis and malignancy.

Involvement of eyes, joints, skin, kidneys, heart and salivary glands may suggest sarcoidosis.

LABORATORY EXAMINATION

In patients with non resolving pneumonia microbiological examinations are mandatory to confirm or deny the diagnosis of CAP because many microorganisms like Legionella are known for delayed resolution (Table 3). In a patient of pneumonia if reduction of leukocytosis and CRP strongly supports response to antibiotic therapy no further evaluation is necessary for NRP even if chest opacity is persistent.

Microbiological investigations are as follows:-

Sputum for gram staining, sputum for culture sensitivity
Sputum for AFB, CBNAAT, LPA and Culture and Sensitivities if tuberculosis is suspected.

Staining for fungi in respiratory samples

Blood Culture

Direct immunofluorescence for legionella

Urinary Legionella antigen and streptococcus pneumonia antigen assays

Stains and culture for bacteria and anaerobes in plural fluid in case of pleural effusion.

D-dimer testing for PPE

Rheumatoid factor, ANA & ANCA should also be ordered in CTD and vasculitis

Serum angiotensin converting enzyme (SACE) in sarcoidosis.

IMAGING

Serial Chest X-Ray is an important investigation which confirms the persistence of radiological opacity. Chest CT is the most helpful in resolving NRP, which can detect plural diseases, empyema or abscess & mediastinal masses. CT is also very useful in non infectious causes of NRP. Active interstitial pneumonitis may be suggested by

204 ground glass opacity on HRCT. CT angiography is also indicated if PTE is suspected.

BRONCHOSCOPY

After laboratory and radiological evaluation if the diagnosis of NRP is not certain, fiber-optic bronchoscopy (FOB) is diagnostic in more than half of the cases of persistent pulmonary opacity.

Bronchoscopy allows direct visualization of affected area and the direct obtaining of samples. Protected brush specimen (PBS), broncho alveolar lavage (BAL) and trans bronchial biopsy (TBB) can be used to take the sample tissues. Microbiological studies of BAL and PBS may include staining in culture of usual bacteria, specific staining for AFB and culture, legionella, fungi, virus and direct immunofluorescence for legionella.

If FOB is not successful or doesn't yield a definitive diagnosis transthoracic needle aspiration or open lung biopsy may be done.

TREATMENT

In the management of NRP choose appropriate antibiotics considering etiology, antibiotic resistance & compliance. Treatment should include antipseudomonal B-lactams and IV fluoroquinolones. Complications and underline causes are treated. Treatment is changed if other diagnosis is confirmed. If NRP is not resolved respiratory experts should be consulted.

Figure 2 shows the Algorithm in approach to NRP.

REFERENCES

1. Rosario Menendez, Antoni Torres. Treatment failure in community-acquired pneumonia. *Chest* 2007; 132:1348-1355.
2. Kirtland SH, Winterbauer RH. Slowly resolving, chronic, and recurrent pneumonia. *Clin Chest Med* 1991;12:303-18