

## A PROSPECTIVE STUDY ON CLINICAL AND RADIOLOGICAL RESOLUTION OF COMMUNITY-ACQUIRED PNEUMONIA

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### ABSTRACT

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#### BACKGROUND

Despite exhaustive literature on community-acquired pneumonia (CAP), studies assessing the rates of clinical and radiographic resolution among these patients are limited.

#### AIM

To study the duration for clinical and radiological resolution of community-acquired pneumonia and the factors leading on to delay in resolution.

#### METHODS

A prospective observational clinical study conducted in the Department of Pulmonary Medicine during the period of one year from August 2009. The severity of symptoms in patients with CAP were recorded through structured questionnaires at 0, 3, 7, and 14 days of treatment and the scores tabulated. Serial chest radiographs were taken at baseline and on days 7, 14, and 28. Radiographs were reviewed in sequence and the pattern and extent of opacities evaluated. Extent of opacity in the followup x-rays were compared with the baseline film. Kappa statistics used to measure interobserver agreement on radiological clearance. Chi square test was used to analyse qualitative variables. Quantitative variables between groups were compared using ANOVA and t test.

#### RESULTS

Of the total 51 patients, 46 (90%) were males. Clinical resolution occurred in 75% of patients at two weeks. Radiological resolution occurred in 43% by the end of 4 weeks and 78% at the end of 8 weeks. Females and those aged more than 60 years showed delay in resolution. Longer duration of symptoms prior to diagnosis and those with multilobar involvement showed delay in resolution.

#### CONCLUSION

Majority (75%) showed clinical resolution within a period of two weeks. Radiological resolution occurred in 43% at four weeks and in 78% at 8 weeks. Female sex, advanced age, longer duration of symptoms prior to diagnosis and multilobar involvement were associated with delay in resolution. Once clinical resolution has occurred, radiological resolution will eventually follow and a delay beyond 4 weeks doesn't require concern especially in resource limited settings.

#### KEYWORDS

Community-Acquired Pneumonia (CAP), Resolution.

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**INTRODUCTION:** Community-acquired pneumonia (CAP) is the commonest cause of infection related mortality in the world. It is responsible for an average of 5.6 million cases annually of which 20% result in hospitalisation. Overall incidence of CAP is reported to be 170 cases per 100,000 persons and the mortality rate is 1% in the outpatient setting which may increase up to 25% in those requiring hospital admissions.<sup>1</sup>

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Pneumonia refers to a syndrome caused by acute infection, usually bacterial, characterized by clinical and/or radiographic signs of consolidation of a part or parts of one or both lungs. It is characterised pathologically by inflammation both within and around the alveolar spaces of the lung leading to consolidation.<sup>2</sup> Pneumonia that develops outside the hospital setting is considered community-acquired pneumonia. The IDSA (Infectious Disease Society of America) defines CAP as "an acute infection of the pulmonary parenchyma that is associated with at least some symptoms of acute infection, accompanied by the presence of an acute infiltrate on a chest radiograph or auscultatory findings consistent with pneumonia (such as altered breath sounds and/or localised rales), in a patient

not hospitalised or residing in a long term care facility for more than 14 days before onset of symptoms."<sup>3</sup>

Plain chest radiography is used in clinical practice, to confirm the diagnosis of CAP, to characterise the extent and severity of disease, and to search for complications. It also serves as a tool to monitor the response to therapy and for detection of possible alternative or additional diagnosis. Despite exhaustive literature on CAP, the published data on the rate of resolution of symptoms in patients with pneumonia are limited and there is a paucity of studies assessing rates of clinical and radiological resolution. A proper understanding of the expected duration for clinical as well as radiological resolution of CAP will guide physicians for the timely intervention and judicious utilisation of further diagnostic studies in managing patients with delayed resolution. This study was conducted with an objective to assess the duration for clinical and radiological resolution of community-acquired pneumonia and to identify the factors leading on to delay in resolution.

**MATERIALS AND METHODS:** A prospective observational clinical study was conducted in a tertiary care setting during the period from September 2009 to August 2010. All patients diagnosed as community-acquired pneumonia as per IDSA criteria were included. Treatment was started as per ATS guidelines. All patients were started on empirical antibiotic regimen as per the guidelines. No change in antibiotics were made on the basis of sputum reports unless they fail to show symptomatic improvement within 72 hours. Those with hospital acquired pneumonia or pulmonary tuberculosis were excluded. During the baseline visit, detailed history obtained and a careful clinical examination done.

The presence and severity of pneumonia related symptoms like cough, sputum, fever, pleuritic chest pain and shortness of breath were recorded using questionnaire (see Appendix) at the time of initial presentation and again during followup visits on 3<sup>rd</sup>, 7<sup>th</sup> and 14<sup>th</sup> day of treatment. Scores were assigned for each symptom and the individual symptom scores at each time point were tabulated.

Chest x-rays were taken at baseline visit and on days 7, 14, and 28. The site, extent and radiological pattern of opacities recorded. Two pulmonologists blinded to the patient's clinical status independently evaluated all the chest radiographs in sequence. The pattern and extent of opacities in the followup x-rays were compared with the baseline film and rate of clearance recorded as percentage (i.e. no clearance or static; worsening; <50% clearance; 50-75% clearance; 75-100% clearance).

Statistical analysis was done using SPSS software version 16. Chi-square test was used to analyse qualitative variables. Quantitative variables were analysed using t test or ANOVA; p value of < 0.05 was considered as significant. Measurement of interobserver agreement on radiological clearance was done using kappa statistics.

**OBSERVATIONS:** A total number of 59 patients were enrolled in the study out of which six patients were lost to followup and two were excluded as their sputum AFB smear result was positive. Remaining 51 patients completed the study. Out of the total 51 patients, 41% were above the age of 60 years and 31% were between 46 to 60 years (Table 1). The mean age of the study population was 53.49 + 15.35. Majority of the patients were (90%) males. Fever and cough were present in all the patients at the time of presentation. Dyspnoea was the next common symptom present in 73% of the patients. Pleuritic chest pain was present in 67% and wheezing in 7% of patients (Table 2).

Age(yrs.)	18-30	31-45	46-60	61-75	Total
Number	4	10	16	21	51
Percentage (%)	8%	20%	31%	41%	100%

**Table 1: Age distribution**

Symptoms	n (%)
Fever	51(100)
Cough	51(100)
Dyspnoea	37(73)
Chest pain	34(67)
Wheezing	7(14)

**Table 2: Symptoms**

Duration of symptoms	<10 days	10-20 days	>20 days	Total
Number	30	17	4	51
Percentage (%)	59%	33%	8%	100%

**Table 3: Symptom Duration prior to Diagnosis**

The duration of symptoms prior to diagnosis was, 10 days in 59% of patients; between 10 to 20 days in 33% and more than 20 days in 8% of patients (Table 3).

Comorbid conditions noticed in the patients are shown in Table 4.

Co-morbid condition	n (%)
Diabetes Mellitus	26 (51)
Hypertension	10 (20)
COPD	12 (47)
Smoking	27 (53)
Alcoholism	10 (20)

**Table 4: Comorbidities**

The mean symptom score at the time of diagnosis and during followup visits are shown in Table 5.

	Day 0	Day 3	Day 7	Day 14
Mean symptom score	16.67	12.41	9.14	4.37
Std. deviation	2.92	4.78	5.76	7.43

**Table 5: Symptom score at each Visit**

Complete clinical resolution occurred in 73% of patients at the end of two weeks (Table 6).

	Complete	Partial	Total
Number	37	14	51
Percentage	73%	27%	100%

**Table 6: Clinical Resolution at day 14**

The patterns of radiological abnormality noted at the time of diagnosis were consolidation (70%), acinar infiltrates (20%), interstitial infiltrates (4%) and mixed pattern (6%) (Table 7). The opacities were on the right

side in 53% patients and on the left side in 35% patients. In the remaining 12%, the shadows were bilateral.

Radiological pattern	Consolidation	Acinar infiltrate	Interstitial infiltrate	Mixed	Total
Number	36	10	2	3	51
Percentage	70%	20%	4%	6%	100%

**Table 7: Radiological Patterns**

At the end of first week compared to the baseline film, progression of opacities noted in 14% of patients whereas in 41%, the opacities remained stationary. In 33%, a clearance of less than 50% compared to the baseline were observed while 12% of patients showed a clearance rate between 50% to 75%. None of the patients showed more than 75% clearance at the end of first week (Table 8).

Rate of clearance	Progression	Static	<50% clearance	50-75% clearance	>75% clearance	Total
Number	7	21	17	6	0	51
Percentage (%)	14%	41%	33%	12%	0%	100%

**Table 8: Chest X-ray at Day 7**

At the end of second week 51% of patients showed radiological clearance in the range of 50 to 75% and 4% showed a clearance rate more than 75% (Table 9).

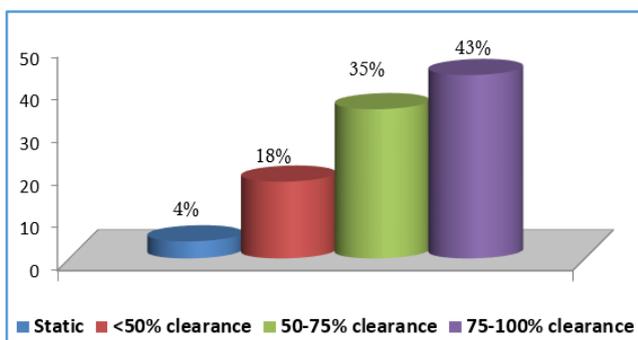
Rate of Clearance	Static	<50% Clearance	50-75% Clearance	>75% Clearance	Total
Number	7	16	26	2	51
Percentage (%)	14%	31%	51%	4%	100%

**Table 9: Chest X-ray at Day 14**

By the end of fourth week, 43% of patients showed radiological clearance of more than 75% (Table 10, Fig. 1).

Rate of clearance	Static	<50% clearance	50-75% clearance	>75% clearance	Total
Number	2	9	18	22	51
Percentage (%)	4%	18%	35%	43%	100%

**Table 10: Chest X-ray at Day 28**



**Figure 1: Chest X-ray at Day 28**

**Radiological Resolution:** A clearance of more than 75% was seen in only 4% of patients by the end of second week whereas this occurred in 43% of patients by the end of four weeks (Table 11, Fig. 2).

Rate of clearance	<25% clearance	25-50% clearance	50-75% clearance	>75% clearance	Total
Day 7	28 (55%)	17 (33%)	6 (12%)	0 (0%)	51 (100%)
Day 14	7 (14%)	16 (31%)	26 (51%)	2 (4%)	51 (100%)
Day 28	2 (4%)	9 (18%)	18 (35%)	22 (43%)	51 (100%)

**Table 11: Radiological Resolution**

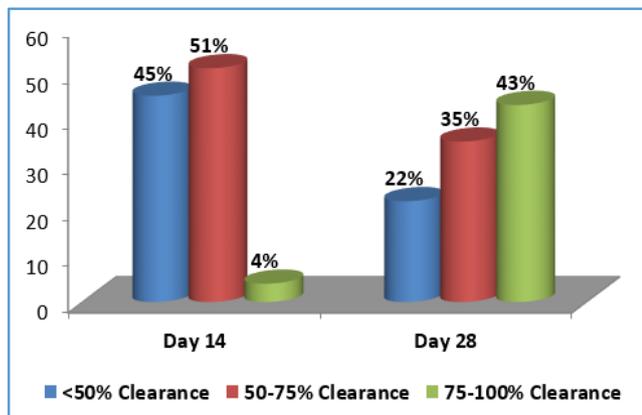


Figure 2: Radiological Resolution

**Age and Resolution:** Majority of patients (75%) in the age group of 18 to 30 years showed a radiological clearance of more than 75% whereas only 19% of patients in the age group of 60 to 75 years showed a similar clearance rate (Table 12). The rate of clearance was significantly higher in those patients in the younger age group (p value<0.01).

Age group (yrs.)	<50% clearance n(%)	50-75% clearance n(%)	>75% clearance n(%)	Total n(%)
18-30	1(25)	0(0)	3(75)	4(100)
31-45	1(10)	2(20)	7(70)	19(100)
46-60	3(20)	5(30)	8(50)	16(100)
61-75	10(48)	7(33)	4(19)	21(100)

Table 12: Resolution according to Age

Gender	<75% clearance n(%)	>75% clearance n(%)	Total n(%)	p value
Male	10(22)	36(78)	51(100)	0.045
Female	3(60)	2(40)		

Table 13: Resolution according to Gender

Male patients showed a significantly higher rate of resolution compared to females (p value<0.05).

The resolution was significantly delayed in those patients presented with prolonged duration of symptoms prior to diagnosis. (Table 14)

Duration	Rate of clearance			Total n(%)	p value
	<50% clearance n(%)	50-75% clearance n(%)	>75% clearance n(%)		
<10 days	6 (20)	8 (27)	16 (53)	30 (59)	0.05
10-20 days	4 (24)	9 (52)	4 (24)	17 (33)	
>20 days	3 (75)	1 (25)	0 (0)	4 (8)	

Table 14: Duration of Symptoms Vs. Resolution

**Extent of Disease and Resolution:** Radiological resolution was significantly delayed in those patients with multilobar involvement at the time of presentation (p value 0.05) (Table 15).

	<50% Clearance	50-75% Clearance	>75% Clearance
Unilobar	9(22%)	14(33%)	19(45%)
Multilobar	4(44%)	4(44%)	1(12%)

Table 15: Radiological Extent Vs. Resolution

The factors associated with delayed resolution were shown in Table 16.

Factor	P value
Age>50	<0.01
Duration of symptoms>20 days	<0.01
Female sex	0.045
Smoking	0.027
Alcoholism	<0.01
COPD	0.05
Multilobar disease	<0.01

Table 16: Factors associated with Delayed Resolution

**Outcome assessment at 8<sup>th</sup> Week:** In the final outcome assessment at the end of 8<sup>th</sup> week, it was found that resolution of CAP had occurred in 78% of the patients. The final diagnosis arrived at the end of workup in the remaining 22% of patients were as follows: malignancy in 8%; tuberculosis in 6%; cryptogenic organising pneumonia in 4% and bronchiectasis in 4%.

**DISCUSSION:** Pneumonia is the most common cause of infection related mortality in the world. Classically, the rate of resolution of pneumonia has been defined in terms of clearance of radiographic abnormalities associated with the illness. The terms non-resolving and slowly resolving pneumonia have been used interchangeably to refer to persistence of radiographic abnormalities beyond the expected time course. However, the precise criteria regarding the expected time course for resolution is lacking. In this background, our objectives were to study the duration for clinical and radiological resolution of community-acquired pneumonia, to ascertain the percentage of patients in whom the resolution is delayed and to identify the factors leading on to delay in resolution.

Majority of the patients in the present study were males. Various other studies also have reported a higher incidence of community-acquired pneumonia in males than females <sup>4,5</sup>

The predominant age group affected was those above 60 yrs. reflecting the fact that advanced age is a risk factor for development of CAP. This may be due to alterations in host defence mechanisms ranging from mechanical changes such as loss of lung elasticity or impaired cough reflex to immunological senescence in elderly patients, so

that they have weaker immune responses and higher chance of oropharyngeal colonisation.<sup>6</sup>

The most common symptoms in the patients at the time of presentation were fever and cough. Jennifer et al in a prospective study also had reported fever and cough as the commonest symptoms in patients with CAP.<sup>6</sup> The mean symptom score showed a consistent reduction during treatment and complete clinical resolution occurred in majority of patients by two weeks even though radiological resolution was lagging. Consolidation was the predominant radiological pattern which was found in 70% of the patients.

At the end of first week, 14% of the patients showed worsening of radiological shadows and 40% remained static. It is reported that chest radiographic improvement typically lags behind clinical improvement and the radiological abnormalities may even get worse initially following treatment.<sup>7</sup> Within the first few days, persistence or even progression of infiltrates on chest radiographs is not unusual.<sup>8</sup>

Complete clinical resolution occurred in 73% of the patients by two weeks whereas radiological resolution occurred only in 4% of patients by this time. By the end of 4 weeks, 43% of the patients showed radiological resolution. In a study by Jay et al, radiological resolution occurred in 41% of patients by four weeks which is almost similar to our findings.<sup>8</sup> In another study, Israel et al reported radiological resolution in 87% of patients by four weeks but majority of the patients in their study population were in the younger age group compared to the present study.<sup>9</sup>

In the present study, the resolution of CAP was significantly delayed in those patients above the age of 60 years. Israel et al reported that patients aged 50 and older showed delayed resolution two to four times as often as young patients. Several studies have demonstrated that age itself is an independent factor for delayed resolution.<sup>9</sup>

Compared to males, female patients showed a delay in resolution which may be due to the delay in seeking medical care ignoring mild symptoms. The resolution is significantly delayed in those patients presented with prolonged duration of symptoms. The other factors associated with a delay in resolution were presence of comorbidities and multilobar involvement. Various other studies reported similar findings. Jay et al reported that alcoholism, COPD, and age greater than 50 years as independent factors associated with delayed resolution.<sup>9</sup>

The majority (53%) were smokers and 47% had COPD. Tobacco smoking is the most important risk factor for the development of COPD which in turn is recognised as a risk factor for respiratory infections including CAP. Both of these are predisposing factors for CAP.<sup>10</sup> Smoking is recognized as the most important causative factor for

COPD. Smokers have a 50% probability of developing COPD during their lifetime.<sup>11</sup> Cigarette smoke contains an extremely high concentration of oxidants. The reactive oxidant substances generated by smoking induce inflammation in the lung and its airway.<sup>12</sup> Tobacco smoking causes an inflammatory process in the airways and lung parenchyma, which is present even in smokers with normal lung function. Smoking is a well-known and important risk factor for CAP through alterations in mechanisms of the host defence system that favour the entrance, establishment, and multiplication of pathogenic organisms.<sup>13</sup> Studies showed that patients with chronic respiratory diseases, including COPD had a twofold to fourfold increase in the risk of CAP.<sup>14</sup>

Alcoholism was present in 20% of the patients. Alcohol adversely affects pulmonary antibacterial defences and facilitates bacterial colonization of oropharynx. It impairs cough reflexes, alters swallowing and mucociliary transport and also impairs the function of lymphocytes, neutrophils, monocytes and alveolar macrophages.<sup>15</sup>

Diabetes mellitus is one of the most prevalent co-existing diseases in patients with CAP. This is attributable to alterations in the immune system. Polymorphonuclear functions like leukocyte adherence, chemotaxis, and phagocytosis are depressed in patients with diabetes.<sup>16</sup>

The outcome assessment at the end of eight weeks revealed that resolution has resulted in 78% of the patients. This highlights the fact that once clinical resolution has occurred, radiological resolution will eventually occur in majority of the patients at least by a period of eight weeks.

In patients with CAP, clinical response to therapy is the most important determinant for further invasive diagnostic studies. Resolution of symptoms suggests favourable response to therapy even when radiographic abnormalities fail to clear. Interventions or invasive diagnostic techniques can be deferred until a reasonable observation period of at least eight weeks in patients who are clinically stable or improving, even though the radiological clearance is delayed.

**CONCLUSION:** Clinical resolution of community-acquired pneumonia occurred in 73% of patients within a period of two weeks. Radiological resolution occurred in 43% at the end of four weeks and 78% at the end of eight weeks. For those patients in whom clinical resolution has occurred, a delay in radiological resolution beyond a period of four weeks has not much clinical significance as the radiological resolution will follow eventually. Advanced age, female sex, prolonged duration of symptoms prior to diagnosis, multilobar involvement and co-existing diseases are associated with delay in resolution of community-acquired pneumonia.

**Appendix:**

Questionnaire for symptom scoring						
Name:	Age:	Sex	Date:	Day 0 / 3 / 7 / 14		
Please answer with reference to what happened in the last 24 hours(Put 'X' mark in the appropriate column)						
	0	1	2	3	4	Score
Cough?	No	Only in the morning when getting up	Occasionally throughout the day	Frequently, throughout the day	Frequently, throughout day&night	
Sputum?	No	Less than 2spoons	More than 2 spoons(<1/2 cup)	1/2 cup or more		
Colour of sputum?	No	Thin, watery	Mucoid, thick white	Yellow, green, or brown		
Fever?	No	Occasionally throughout the day	Frequently, throughout the day	Frequently, throughout day & night		
Chest pain?	No	Mild	Moderate	Severe		
Shortness of breath?	No	Breathless when walking up a slight hill	Has to stop when walking at own pace on level ground	Has to stop on walking 100mtr on level ground	Breathless on dressing or undressing	
					Total score	

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