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C-reactive protein as a prognostic marker and guidance for use of antibiotic therapy in patients presenting with lower respiratory tract manifestations in intensive care unit in tertiary care centre

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ABSTRACT

Introduction: C-reactive protein is a acute phase reactant protein synthesized in the liver and in response to various stimuli. It is a simple blood test to distinguish between viral and bacterial pneumonia. It is a cheap and easily available useful adjunctive test to limit the use of antibiotics in patients presenting with lower respiratory tract manifestations.

Materials and Methods: It is a prospective study of 60 patients admitted with lower respiratory signs and symptoms in Intensive Care Unit of Mallareddy institute of medical sciences, Hyderabad, Telangana. Serum CRP level measured by latex agglutination method and other markers of infection like Complete blood count, Sputum microscopy culture and sensitivity and chest X-ray were done on presentation. CRP concentration of more than 20mg/l taken as positive. Number of CRP positive patients were correlated with patients of increased WBC count and positive sputum routine culture and sensitivity and results were compared using chi -square test.

Result: Total 60 patients were taken for study out of which 38 were male and 22 were female. Out of which 24(40%) were diagnosed with pneumonia, 6(10%) with pulmonary Koch's, 7(11.6%) with acute exacerbation of asthma, 11(18.3%) were COPD,4(6%) with congestive cardiac failure, 5(8.3%) with autoimmune disorder and 3(5%) with interstitial lung disease. Among them 29(48.3%) patients were found to have CRP value of more than 20mg/dl which is considered as positive, out of these 29 patients, 16(55.17%) were having pneumonia which was confirmed on imaging and sputum culture and sensitivity. Out of these 29 patients with CRP positive 21(72.4%) were found to have sputum culture and sensitivity as positive for bacteria in which 4(19%) were diagnosed as autoimmune disorder,2(9%) with bronchial asthma, 10(47.6%) with pneumonia, 3(14.2%) with COPD, 2(9.5%) with pulmonary Koch's. Among 29 patients with positive CRP, 18(62%) patients have the WBC count of >11,000cells/mm3. Patients with CRP positivity having positive culture sensitivity {21patients (72.4%)} were started on antibiotic therapy. Out of total 24 pneumonia cases, 10(41.6%) were sputum culture positive as well as CRP positive pneumonia. As according to the result of our study the patient of pneumonia had higher CRP in comparison with patients with COPD, bronchial asthma, Congestive cardiac failure, Autoimmune disorders, interstitial lung disease. Correlation of number of raised CRP positivity, sputum positivity and raised WBC count were statistically significant with p value of <0.005 by using chi -square test. No significant difference of CRP found in the age and sex distribution of the patients and no significant mortality found. Patients with positive CRP, positive sputum culture and sensitivity were started on specific antibiotic therapy.

Conclusion: Serum CRP levels is a useful marker for establishing the diagnosis of Community Acquired Pneumonia in adult patients presenting with lower respiratory tract manifestations. Higher CRP values are suggestive of severity of the disease which may help in deciding the appropriateness of use of antibiotics in the line of management.

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1. Introduction

C-reactive protein is a acute phase plasma protein of the pentraxin family, is produced and released by hepatocytes and adipocytes, playing distinct roles in innate and adaptive immunity with inflammatory effects.[1,2] CRP has been reported to function by binding to the phosphocholine moieties that are located on some damaged cells and certain bacteria, and to have a crucial part in complement activation through strengthening phagocytosis, which may clear dead cells and bacteria.[3,4] Interleukin-6 (IL-6) and other cytokines such as Tumour necrosis factor(TNF), Interleukin-1(IL-1) and Transforming growth factor (TGF) are also involved in CRP production.[5,6] A number of conditions stimulate CRP synthesis including pulmonary infarction, vasculitis, liver disease, inflammation, neoplasia, bacterial infections are most potent stimuli leading to marked elevation of serum CRP with in few hours. Pneumonia elicits a powerful inflammatory response both locally and systematically with chemotactic cytokine release into peripheral circulation. CRP has also being used as an index of response to treatment in rheumatic fever and certain other conditions.[7] CRP is tested either by capillary precipitation of patient sera with anti-sera prepared in rabbits against purified CRP or by passive agglutination using latex particles coated with anti-CRP antibodies.[8] It is a simple blood test to distinguish between viral and bacterial pneumonia.

Raised CRP value in viral infection during first week may mislead the clinician in the decision to prescribe antibiotics and may also explain why the CRP has shown a higher specificity in predicting pneumonia after one week then in first week of respiratory tract infections.[9]

2. Aim and Objectives of the Study

1. To evaluate the CRP level in the patients admitted with acute respiratory symptoms.
2. To evaluate the diagnostic value of serum CRP in differentiating pneumonia from other respiratory conditions.
3. To evaluate the severity of pneumonia with serum CRP level.
4. To evaluate the need of antibiotic usage in patients with acute respiratory symptoms.
5. To evaluate the prognostic value of CRP in comparison with WBC count.

3. Materials and Methods

It is a prospective study of 60 patients admitting with the acute respiratory signs and symptoms in Intensive Care Unit of Mallareddy institute of medical sciences, Hyderabad, Telangana. Serum sample was preserved at the time of presentation and CRP was measured in undiluted sera and in dilution of 1/10, 1/20, 1/30, 1/40, 1/60, 1/80, 1/100 using a commercially available latex agglutination test (Humatex CRP). Value of CRP was calculated by multiplying the denominator of dilution by 6 to get value in mg/l. Mid-value of positive and negative titre was used in calculation. CRP concentration of > 20mg/l is taken as positive according to our lab. CRP level mean, median were calculated and CRP level positivity in patients is correlated with no of patients with raised WBC count and sputum culture positivity by using chi-square test and p value <0.005 is considered significant.

3.1. Inclusion criteria

1. Age >18 years old admitted to our hospital,
2. Respiratory symptoms like cough, sputum production, dyspnoea, tachypnoea, pleuritic pain as main complaint with or without fever.

3.2. Exclusion criteria

1. Final diagnosis of pulmonary embolism, lung malignancy, upper respiratory tract infection like acute pharyngitis, rhinitis and sinusitis
2. Patient with severe immunosuppression like HIV and haematological disease or who receive immuno-suppressive therapy like prednisolone.
3. Non-hospitalization patients.
4. Liver disease and vasculitis.

3.3. Hospitalisation criteria for the patients

1. Patients who need respiratory support (SPO_2 less than 90, Respiratory acidosis, Ph<7.3.
2. Patients with hypotension who require vasopressor drugs.
3. Patiets with confusion or unconsciousness.
4. Patients with respiratory rate >30.

3.4. Measurements

Patients with known response to initial adequate treatment in emergency department.

At the initial visit to emergency department patients demographic data and basic clinical information was collected and in addition to it markers of infection like Complete blood count, Serum CRP level measured by latex agglutination method, sputum for gram staining, AFB, culture sensitivity, blood culture and sensitivity, chest X-ray, HRCT and 2 Decho were done. To stratify the severity CURB 65 score (confusion, serum urea, respiratory rate and systolic blood pressure of patient) were used to decide the severity of pneumonia patients. LRTI was defined by the presence of atleast one respiratory symptom (cough, sputum production, dyspnoea, tachypnoea, i.e. crepitations

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or wheeze or one sign of infection like temp>38 °C, shivering, leucocyte count <4000 or For pneumonia a new infiltrate, haziness, consolidation, effusion on chest X-ray.initiative for chronic obstructive lung disease(gold guidelines) as FEV1/FEC ratio <70%. Acute bronchitis defined as LRTI in the absence of underlying lung disease or COPD or infiltrates on chest X-ray.grounds(history, physical examination, chest high resolution computerised tomography, electrocardiogram, echocardiogram).

4. Results

Total 60 patients admitting into Mallareddy institute of medical sciences, Hyderabad, Telangana has been included in these prospective study. CRP was measured in undiluted sera and in various dilution at the time of presentation as already described and value calculated. The parenchymal involvement of lung in various diseases was confirmed on chest X ray and high resolution CT scan of chest and cardiac involvement was proved on echocardiography. Total 60 patients were taken for study out of which 38 were male and 22 were female(Table 1). Out of which 24(40%) were diagnosed with pneumonia,6(10%) with pulmonary koch's, 7(11.6%) with acute exacerbation of asthma, 11(18.3%) were COPD, 4(6%) with congestive cardiac failure, 5(8.3%) with autoimmune disorder and 3(5%) with Interstitial lung disease (Table 2). Among them 29(48.3%) patients were found to have CRP value of more than 20mg/l which is considered as positive as shown in Table 3 out of these 29 patients, 15(51.7%) were having pneumonia which was confirmed on imaging and sputum culture and sensitivity (Table 7). for bacteria in which 4(19%) were diagnosed as autoimmune disorder,2(9%) with bronchial asthma, 10(47.6%) with pneumonia, 3(14.2%) with COPD, 2(9.5%) with pulmonary Koch's(Table 7). T8 suggest positive pneumonia patients.

Among 29 patients with positive CRP, 18(62%) patients have the WBC count of >11,000cells/mm^3. Out of 24 Patients with pneumonia have increase WBC count in 10 patients, 2 patients in COPD, 3 patient in autoimmune disorders, in 2 patients of bronchial asthma no patient with Congestive cardiac failure no patient with tuberculosis and interstitial disease as shown in (Table 9). Patients with CRP positivity who were having positive culture sensitivity {21 patients(72.4%)} were started on antibiotic therapy. Out of total 24 pneumonia cases,10(41.6%) were sputum culture positive as well as CRP positive pneumonia. Out of 15 patients with CRP positive in pneumonia 10 cases(66.6%), were found to have raised WBC count. All these 10 cases have sputum positive on culture sensitivity (Table 9) patient with pneumonia (24) 10 patient have sputum culture as positive and were started on antibiotics, 5 patients with autoimmune disorders 4 were sputum positive, in 11 COPD patients 3 patients were sputum positive and started on antibiotics, out of 6 patients with Tuberculosis 2 were sputum positive were started on antibiotics and out of 7 patients in bronchial asthma 2 were sputum positive and started on antibiotics, whereas in congestive cardiac failure (4) and interstitial lung disease (3) were not having any sputum positivity so no antibiotic therapy was given(Table 9).

In our study the correlation of raised WBC count in no of patients is done with no of CRP positive individuals is done using chi -square test as shown in Table 10. 18 patients with CRP positive were having raised WBC count which is 62.1% which is found statistically significant.

In our study the correlation of CRP level positivity is done with antibiotic use in patient as shown in Table 11 that antibiotic given in 21 CRP positive patients out of 29 which is 72.4% patients which is statistically significant as p value <0.005 using chi-square test. The correlation of antibiotic usage with raised WBC count is also found out as shown in Table 12 that 14 patients with raised WBC count were given antibiotics which is 77.8% which is statistically significant by chi-square test with p value of <0.005.

As according to the result of our study the patients of pneumonia and autoimmune disorders had higher CRP in comparison with patients with COPD, bronchial asthma, Congestive cardiac failure and Interstitial lung disease. Patient with high CRP have raised WBC count. No significant difference of CRP found in the sex distribution of the patients. Patients with positive CRP, Positive sputum culture and sensitivity with increased WBC counts were started on specific antibiotic therapy. A CRP value of more than 20mg/l is considered positive.

5. Discussion

In healthy adults, the normal concentrations of CRP varies between 0.8 mg/L to 3.0 mg/L. However, some healthy adults show elevated CRP at 10 mg/L. CRP concentrations also increase with age, possibly due to subclinical conditions. There is also no seasonal variations of CRP concentrations. Gene polymorphism of interleukin 1 family, interleukin 6, and polymorphic GT repeat of the CRP gene do affect the usual CRP concentrations when a person does not have any medical illnesses.[10] CRP is used mainly as an inflammation marker. Apart from liver failure, there are few known factors that interfere with CRP production.[10] Interferon alpha inhibits CRP production from liver cells which may explain the relatively low levels of CRP found during viral infections compared to bacterial infections.[11] The plasma half-life of CRP is 19 hours, and is constant in all medical conditions. When there is a stimulus, the CRP level can increase 10,000-fold from less than 50 μg/l to more than 500 mg/L. Its concentration can increase to 5 mg/L by 6 hours and peak at 48 hours. Therefore, the only factor that affects the blood CRP concentration is its production rate, which increases

Table 1: Sex distribution among patients

Sex	Frequency	Percent	Valid	Cumulative
Female	22	36.7	36.7	36.7
Male	38	63.3	63.3	100.0
Total	60	100.0	100.0	

Table 2: Distribution of patients on basis of diagnosis

Diagnosis	Frequency	Percent	Valid	Cumulative
Autoimmune	5	8.3	8.3	8.3
Bronchial asthma	7	11.7	11.7	20.0
CCF	4	6.7	6.7	26.7
COPD	11	18.3	18.3	45.0
Interstitial lung	3	5.0	5.0	50.0
Pneumonia	24	40.0	40.0	90.0
Pulmonary TB	6	10.0	10.0	100.0
Total	60	100.0	100.0	

Table 3: CRP level among patients

CRP	Frequency	Percent	Valid	Cumulative
Normal	31	51.7	51.7	51.7
positive	29	48.3	48.3	100.0
Total	60	100.0	100.0	

Table 4: WBC count among patients

WBC	Frequency	Percent	Valid	Cumulative
Normal	42	70.0	70.0	70.0
Raised	18	30.0	30.0	100.0
Total	60	100.0	100.0	

Table 5: Use of antibiotic among patients

Antibiotic	Frequency	Percent	Valid	Cumulative
Given	21	35.0	35.0	35.0
Not given	39	65.0	65.0	100.0
Total	60	100.0	100.0	

Table 6: Correlation of CRP in patients with different diagnosis

Diagnosis	Frequency and percentage	CRP-Normal	CRP- Positive	Total
Autoimmune	frequency	1	4	5
	% in CRP	3.2%	13.8%	8.3%
Bronchial asthma	frequency	5	2	7
	% in CRP	16.1%	6.9%	11.7%
CCF	frequency	4	0	4
	% in CRP	12.9%	0.0%	6.7%
COPD	frequency	8	3	11
	% in CRP	25.8%	10.3%	18.3%
Interstitial lung disease	frequency	0	3	3
	% in CRP	0.0%	10.3%	5.0%
Pneumonia	frequency	9	15	24
	% in CRP	29.0%	51.7%	40.0%
Pulmonary TB	frequency	4	2	6
	% in CRP	12.9%	6.9%	10.0%
Total	frequency	31	29	60
	% of CRP	51.66%	48.33%	100%

	value	df	Asymp .sig
Pearson Chi-Square	14.475	6	0.025
Likelihood ratio	17.447	6	0.008
N of valid cases	60		
Chi-Square Test			

Table 7: Sputum culture positivity among patients

Diagnosis	Number of patients with sputum culture positive	Percent
pneumonia	10	48%
Tuberculosis	2	9%
COPD	3	14%
Bronchial asthma	2	10%
Congestive cardiac failure	0	0%
Autoimmune disorders	4	19%
Interstitial lung disease	0	0%
Total	21	100%

Table 8: Correlation of CRP level with causative organism among patients

Causative organism		CRP normal	CRP positive	Total
Fungal Growth	frequency	0	2	2
	% in CRP	0.0%	6.9%	3.3%
E.coli	frequency	0	1	1
	% in CRP	0.0%	3.4%	1.7%
Klebsiella	frequency	0	4	4
	% in CRP	0.0%	13.8%	6.7%
Proteus	frequency	0	3	3
	% in CRP	0.0%	10.4%	5%
Pseudomonas	frequency	0	1	1
	% in CRP	0.0%	3.4%	1.7%
Staphylococcus aureus	frequency	0	2	2
	% in CRP	0.0%	6.9%	3.3%
Sterile	frequency	31	8	39
	% in CRP	100.0%	27.6%	65.0%
Streptococcus pneumonia	frequency	0	8	8
	% in CRP	0.0%	27.6%	13.3%
Total	frequency	31	29	60
	% in CRP	100.0%	100.0%	100.0%

	Value	df	Asymp.sig
Pearson Chi-Square	34.536[a]	9	.000
Chi-Square Test			

Table 9: Frequency table showing CRP positivity, sputum positivity, raised WBC count and antibiotic usage in patients

S.No	Diagnosis	No. of cases	Cases with CRP positive	Sputum positive	WBC count	Antibiotic given
1	Pneumonia	24	15	10	10	10
2	COPD	11	3	3	2	3
3	Tuberculosis	6	2	2	0	2
4	Autoimmune disorder	5	4	4	3	4
5	Congestive cardiac failure	4	0	0	0	0
6	Bronchial asthma	7	2	2	2	2
7	Interstitial lung disease	3	3	0	0	0
8	total	60	29	21	18	21

Table 10: Correlation of WBC count with CRP level

WBC	Frequency and percent	CRP normal	CRP positive	Total
Normal	frequency	31	11	42
	% in CRP	100.0%	37.9%	70.0%
Raised	frequency	0	18	18
	% in CRP	0.0%	62.1%	30.0%
Total	frequency	31	29	60
	% in CRP	100.0%	100.0%	100.0%

	Value	df	Asymp.Sig.
Pearson Chi-Square	27.488[a]	1	.000
Chi-Square Test			

Table 11: Correlation of CRP level with antibiotic usage in patients

Antibiotic	Frequency and percent	CRP normal	CRP positive	Total
Given	frequency	0	21	21
	% in CRP	0.0%	72.4%	35.0%
Not given	frequency	31	8	39
	% in CRP	100.0%	27.6%	65.0%
Total	frequency	31	29	60
	% in CRP	100.0%	100.0%	100.0%

	Value	df	Asymp.Sig.
Pearson Chi-Square	34.536[a]	1	.000
Chi-Square Test			

Table 12: Correlation table of antibiotic usage in patients with raised WBC count

Antibiotic	Frequency and percent	WBC normal	WBC raised	Total
Given	frequency	7	14	21
	% in CRP	16.7%	77.8%	35.0%
Not given	frequency	35	4	39
	% in CRP	83.3%	22.2%	65.0%
Total	frequency	42	18	60
	% in CRP	100.0%	100.0%	100.0%

	Value	df	Asymp.Sig.
Pearson Chi-Square	20.684[a]	1	.000
Chi-Square Test			

Table 13: Mean CRP level among patients with various patients

Diagnosis	N	Mean	Std deviation	Std error	95%CI lower	95%CI upper	Minimum	Maximum
autoimmune	5	86.20	77.338	34.587	-9.83	182.23	17	180
Bronchial asthma	7	22.86	17.430	6.588	6.74	38.98	8	48
CCF	4	12.00	3.162	1.581	6.97	17.03	8	15
COPD	11	20.00	14.738	4.444	10.10	29.90	5	60
Interstitial lung disease	3	42.33	5.859	3.383	27.78	56.89	38	49
Pneumonia	24	153.25	152.936	31.218	88.67	217.83	12	480
Pulmonary TB	6	27.50	18.876	7.706	7.69	47.31	15	64
Total	60	80.48	116.332	15.018	50.43	110.54	5	480

	Sum of squares	df	Mean square	F	Sig
Between groups	230698.660	6	38449.777	3.589	0.005
Within groups	567758.324	53	10712.421		
Total	798456.983	59			
ANOVA					

Table 14: Median CRP value in patients with various diagnosis

S.No	Diagnosis	Median CRP value
1	Pneumonia	95
2	Autoimmune disorder	42
3	Interstitial lung disease	40
4	Tuberculosis	18.5
5	Bronchial asthma	14
6	COPD	17
7	Congestive cardiac failure	12.5

with inflammation, infection, trauma, necrosis, malignancy, and allergic reactions. Other inflammatory mediators that can increase CRP are TGF beta 1, and tumour necrosis factor alpha.

In acute inflammation, CRP can increase as much as 50 to 100 mg/L within 4 to 6 hours in mild to moderate inflammation or an insult such as skin infection, cystitis, or bronchitis. It can double every 8 hours and reaches its peak at 36 to 50 hours following injury or inflammation.CRP between 100 and 500 mg/L is considered highly predictive of inflammation due to bacterial infection. Once inflammation subsides, CRP level falls quickly because of its relatively short half-life.[12] CRP concentrations between 2 and 10 mg/L are considered as metabolic inflammation: metabolic pathways that cause arteriosclerosis and type II diabetes mellitus. Normal levels increase with aging.[13] Higher levels are found in late pregnant women, mild inflammation and viral infections (10–40 mg/L), active inflammation, bacterial infection (40–200 mg/L), severe bacterial infections and burns (>200 mg/L).[14] In our study we took CRP > 20 mg/l as positive according to our laboratory values. And our study shows that CRP value in case of pneumonia patients with sputum positivity has higher value than in sputum negative pneumonia. According to the table no-the153.25,86.20Interstitial lung disease is 42.3, Tuberculosis is 27.50, Bronchial asthma is 22.86.

According to table no- 14 the median values of Pneumonia is 95, Autoimmune is 42, ILD is 40, Bronchial asthma is 14, COPD is 17, CCF is 12.5 and TB is 18.5. The British Thoracic Society stated that the measurement of serum CRP on admission may be helpful in distinguishing pneumonia from other lower respiratory tract infestations with moderate weight being placed on this recommendation.[15]

6. Conclusion

Serum CRP levels is a useful marker for establishing the diagnosis of Higher CRP values are suggestive of severity of the disease which may help in deciding the appropriateness of use of antibiotic in the line of management with lower infections.

7. Limitations

No relationship found in our study between CRP level and parenchymal and endobronchial involvement in lung and parenchymal involvement and causative organism.

8. Source of Funding

None.

9. Conflict of Interest

None declared.

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