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Research Article

Procalcitonin as a Guide of Antibiotics Administration in Lower Respiratory Tract Infection

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Abstract: *Background*: Pneumonia is one of the common infection-related death. Recently use of biomarkers in diagnostic and therapeutic approach to pneumonia has been considered. The aim of our study is to evaluate the length of antibiotic treatment, length of hospitalization and medical outcomes in procalcitonin-guided antibiotic therapy in patients with pneumonia. *Methods:* In a randomized controlled trial study with 134 hospitalized patients with the diagnosis of pneumonia were enrolled to the study and randomly divided into two groups, procalcitonin group (PCT-guided therapy) and control group (customary clinical guidelines). All patients had 14 days follow up. Data were analyzed with appropriate statistical analysis and using version 16 of SPSS statistical software. *Results:* Totally, the assessed patients were in the range of 18-94 years old and the mean of age in control group was 62.87 ± 19.20 years and mean age of PCT group was 58.34 ± 19.32 years. Length of antibiotic treatment in the PCT group was 3.17 days' vs 11.38 days in the control group ($P < 0.0001$). Length of hospitalization in the PCT group was 4.53 days' vs 6.75 days in the control group that was significantly reduced ($P < 0.0001$). In 14 days follow up all patients had not any complication and clinically improved. *Conclusions:* In conclusion, procalcitonin-guided antibiotic treatment in patients with acute respiratory infections effectively reduced antibiotic exposure and antibiotic side-effects while reducing the length of hospitalization and treatment duration and accordingly, decrease the expenditure of patients' treatment and avoid antibiotic resistance.
Keywords: Biomarker; Pneumonia; Procalcitonin.

INTRODUCTION

Despite advances in antimicrobial therapy, Lower respiratory tract infection (LRTI) is the most common cause of infection-related death [1]. Lower respiratory tract infection is defined as a severe infection of the pulmonary parenchyma that is connected to at least some symptoms of acute infection, with the presence of a serious infiltrate on a chest radiograph or auscultatory findings consistent with pneumonia such as localized rales and/or altered breath sounds [2]. Patients with severe LRTI have the mortality rate up to 50% worldwide [3].

Challenges of clinical diagnosis, etiologic determination of LRTI and although the different therapeutic approach to it is very important. The laboratory tests of blood or sputum cultures for diagnosis of pneumonia have not sensitivity and specificity to distinguish a large number of microorganisms [4]. Of course, it is not clear that initial antibiotic therapy should be based on a bacterial infection or nonbacterial infection or even non-infection and also, antibiotic treatment for bacterial infection varies from patient to patient [5].

Pneumonia is specified by recent symptoms of respiratory and infiltration in the chest x-ray (CXR). In pneumonia, respiratory symptoms can be vague and without fever especially in older people. However, distinguishing pneumonia patients with a bacterial

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infection from nonbacterial infection due to similar symptoms and radiographic findings is very difficult. In other words, the clinical challenge of LRTI involves difficulty in making a clinical and etiologic diagnosis, and the fact that no single antimicrobial regimen can cover all the possible causes. The Pattern of infiltration on CXR in patients with LRTI is usually not helpful in the diagnosis of a specific cause [6]. Treatment of patients with nonbacterial infection with antibiotics is not efficient and lead to prevail antibiotic resistance, increase health care cost, and create sidelong effects of medications such as toxicity together with allergic reaction risks [7]. The most common use of antibiotics in lower respiratory tract infection is acute bronchitis, acute exacerbation of Chronic Obstructive Pulmonary Disease (COPD) and pneumonia. About 75 percent of patients with lower respiratory tract infection in spite of viral etiology are treated with antibiotics [8].

Different biomarkers released by the infectious process which can help to diagnose and determine infection. One of the biomarkers for the diagnosis of bacterial Sepsis includes procalcitonin (PCT).

Procalcitonin as a glycoprotein with 116 amino acids is the pre-hormone of calcitonin. PCT is secreted by C cells of the thyroid gland in response to hypercalcemia under normal conditions [9]. In bacterial infections, the PCT level increases slightly and rarely reaches to higher than 1ng/ml, while the level of PCT increases about 20-200 ng/ml in severe bacterial infections [10]. PCT in bacterial infections increases and its release directly stimulated by bacterial toxins and indirectly by humoral factors (IL-β1, interleukin six and TNFα) or by the host cell response [11].

Therefore, PCT levels may be a predictor of the severity of LRTI and can be used as guidance for the use of antibiotics in hospitalized patients. The aim of our study is to evaluate the length of antibiotic treatment, length of hospitalization and medical outcomes in procalcitonin-guided antibiotic therapy in patients with pneumonia.

PATIENTS AND METHODS

Setting and Study Population

The sample size was calculated on the comparison of the proportion of antibiotic therapy based on a previous study [12] and considering the α level of 0.05 and power of 90%, the sample size was calculated as below:

$$N_1=N_2 = (Z_{\alpha/2}+Z_{\beta})^2 \text{ X } [p_1(1-p_1) + p_2(1-p_2)] / (p_1-p_2)^2 = 65$$

The sample size was calculated to be 65 for each group and taking into account 10% dropout, a total of 142 patients were enrolled in two groups of case and control. Patients were randomly assigned to either the PCT group or control group. The randomization was 1: 1 for the 2 groups and participants were assigned using computer-generated randomization. This study was authorized by the institutional review board of Arak University of Medical Sciences with approval number of ir.arakmu.rec.1394.23 in 11/05/2015 and registered by Iranian Registry of Clinical Trials (IRCT2017010331737N1). Written informed consent obtained from all patients to enter the study and all formal ethical rules were considered. Finally, 142 patients with diagnosis of LRTI hospitalized over a 10-month period from May 2015 through February 2016 to the Valiasr University Hospital (Arak, Iran). Five patients from the PCT group and three patients from the control group were excluded from the study (Figure 1). Inclusion criteria were patients to be at least 18 years; with a diagnosis of pneumonia or COPD exacerbation who admitted in Infectious ward of Arak Valiasr University Hospital. Exclusion criteria included patients' refusal to give informed consent, active intravenous drug abusers, severe immunosuppression, patients with hospital acquired pneumonia, Pregnancy, Cystic Fibrosis, Severe trauma or burn within previous 24 hour and patients requiring antibiotic therapy for infections other than LRTI.

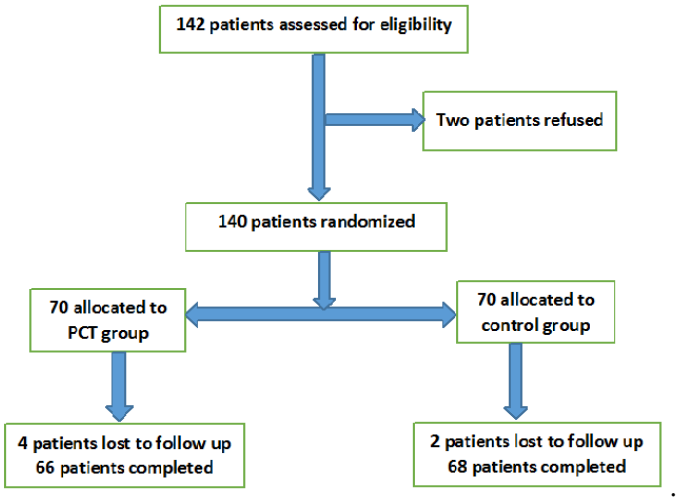

Fig-1: Flowchart of participants

Measurement of Serum Procalcitonin

Serum PCT was measured by B.R.A.H.M.S. PCT sensitive Kryptor® (B.R.A.H.M.S., Hennigsdorf, Germany), a rapid sensitive assay with a functional sensitivity of 0.06 µg/L and a lower detection limit of 0.02 µg/L with an assay time of fewer than 30 minutes in Valiasr hospital laboratory. Baseline assessment included clinical data and vital sign, comorbid conditions, chest x-ray (CXR), sputum smear and culture, complete blood count (CBC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and blood urea was performed for all patients.

Antibiotic Treatment

On admission, antibiotic therapy was initiated for all patients. In the PCT group, antibiotic therapy is guided by serum PCT. In this group, the patients are classified into four groups, according to the PCT algorithm that is validated in previous studies. A PCT level of less than 0.1 µg/L suggested the absence of bacterial infection and the initiation or continuation of antibiotics is strongly discouraged. A PCT level between 0.1 and 0.25 µg/L indicated that bacterial infection is unlikely, and the initiation or continuation of antibiotics is discouraged. A PCT level from 0.25 to 0.5 µg/L is considered to indicate a possible bacterial infection and the initiation or continuation of antibiotic therapy is encouraged. A PCT level greater than 0.5 µg/L strongly suggested the presence of bacterial infection and antibiotic treatment and continuation is strongly encouraged. Reassessment of PCT is done in PCT group at 3, 5, and 7 days if antibiotic therapy initiated and If the initial PCT level was >10 µg/L, discontinuation of antibiotic was "recommended" after an 80% decrease from the baseline level and "strongly recommended" after a 90% decrease from the initial value. In the procalcitonin group if antibiotic treatment was initially withheld, re-evaluation of the procalcitonin was obtained after 6 - 24 hrs. to insure that a rising level was not missed. In the control group, the antibiotic therapy is started and continued on the basis of usual practice guidelines (Table-1).

Table-1: Protocol of procalcitonin-guided antibiotic therapy for community-acquired pneumonia patients

Initial Procalcitonin Level			
< 0.1 µg/L	0.1 – 0.25 µg/L	0.26 – 0.5 µg/L	> 0.5 µg/L
Antibiotic therapy strongly discouraged	Antibiotic therapy discouraged	Antibiotic therapy encouraged	Antibiotic therapy strongly encouraged
Consider alternative diagnosis, no antibiotic therapy initiated and re-measure procalcitonin after 6-24 hours		Antibiotic therapy initiated	
Follow Up Procalcitonin Level			
< 0.1 µg/L or drop by >90%	0.1 – 0.25 µg/L or drop by >80%	0.26 – 0.5 µg/L	> 0.5 µg/L
Antibiotic cessation strongly encouraged	Antibiotic cessation encouraged	Antibiotic cessation discouraged	Antibiotic cessation strongly discouraged
Consider continuing if clinically unstable		If PCT rising or not adequately decreasing, consider possible treatment failure and clinical reassessment	

We consider antibiotic therapy in patients with hemodynamic instability, respiratory instability, need for intensive care unit admission, life-threatening co-morbidity, localized infection (Abscess, empyema, …), and concomitant infection requiring antibiotics regardless of PCT level and excluded from study.

Outcome Measures

The primary end-points were the duration of antibiotic therapy and length of hospital stay. Patients returned for a follow-up visit two weeks later and clinical outcomes were measured. Treatment success defined as reduction or resolution of clinical signs and symptoms of LRTI. Treatment failure included death, recurrence, or persistence of clinical signs and symptoms of LRTI. Complications included empyema, lung abscess, need for intubation, and ARDS. The secondary end-points were the clinical outcome. The final course of LRTI (success, failure or complication) determined two weeks after admission.

Statistical Methods

Stata statistical software, version 12, was used for data analysis. Fisher's exact test and chi-square were used to compare categorical variables and two-sample t-test or Mann–Whitney test using for compare of continuous variables. In the analytical part, differences between the treatment groups were compared by the chi-square or Fisher exact test for categorical variables and a two-sample t-test or Mann–Whitney test for continuous variables. Levels of significance was set at $P<0.05$ for two-tailed tests.

RESULTS

All clinical and laboratory data related to 134 patients were recorded and analyzed. In both groups, laboratory and clinical measures were similar at baseline. Totally, the assessed patients were in the range of 18-94 years old and the mean age was 60.66±19.46 (Mean ±SD). Generally, 51.5% of all patients were male, 79.85% patients were urban and 14.17% had a history of smoking. There were no significant differences regarding Demographics, Coexisting

illnesses, Clinical findings, Laboratory findings, between the two groups. Table-2 shows these results.

Table-2: Characteristics of patients of the control and PCT[*] groups

	Total (134)	PCT group (66)	Control group (68)	P-Value
Demographics				
Age, mean (SD[**])	60.66 (19.46)	58.34 (19.32)	62.87 (19.20)	0.176
Male, No. [†](%)	69 (51.49)	35 (53.03)	34 (50.00)	0.726
Urban Habitat, No (%)	107 (79.85)	50 (75.75)	57 (83.82)	0.246
History of smoking, No (%)	19 (14.17%)	8 (12.12)	11 (16.17)	0.503
Coexisting illnesses, No. (%)				
Hypertension	34 (25.37)	20 (30.30)	14 (20.58)	0.197
Diabetes Mellitus	24 (17.91)	12 (18.18)	12 (17.64)	0.935
Airway diseases	21 (15.67)	7 (10.60)	14 (20.58)	0.116
Hyperlipidemia	15 (11.19)	9 (13.63)	6 (8.82)	0.379
None	49 (36.56)	28 (42.42)	21 (30.88)	0.167
Clinical findings, No. (%)				
Cough	126 (94.02)	63 (95.45)	63 (92.64)	0.494
Sputum production	100 (74.62)	51 (77.27)	49 (72.05)	0.489
Fever	64 (47.76)	35 (53.03)	29 (42.64)	0.278
Chills	60 (44.77)	34 (51.51)	26 (38.23)	0.123
Dyspnea	36 (26.86)	16 (24.24)	20 (29.41)	0.501
Myalgia	31 (23.13)	16 (24.24)	15 (22.05)	0.764
Body temperature, (^{o}C[‡]) mean (SD)	37.64 (0.66)	37.83 (0.63)	37.86 (0.7)	0.794
Abnormal breath sounds	90 (67.2)	41 (62.1)	49 (72.1)	0.219
Abnormal Chest X-Ray, No. (%)	102 (76.1)	49 (74.2)	59 (86.7)	0.068
Laboratory findings				
WBC mean (SD)	8446 (2085)	8125 (2045)	8757 (2123)	0.082
ESR mean (SD)	29.11 (19.4)	31.30 (20.7)	26.98 (17.5)	0.194
PCT, No. (%)				
PCT<0.1µg/L	97(72.4)	48 (72.7)	49 (72.1)	0.938
0.1≤ PCT<0.25 µg/L	20 (14.9)	9 (13.6)	11(16.2)	0.673
0.25≤PCT<0.5 µg/L	4 (3)	2 (3)	2 (2.9)	0.972
PCT≥0.5 µg/L	13 (9.7)	7 (10.6)	6 (8.8)	0.725
Outcomes				
duration of antibiotic therapy, (d[¶]) mean (SD)	7.36 (3.12)	3.17 (1.7)	11.38 (4.49)	< 0.0001
Length of hospital stay, (days) means (SD)	5.65 (2.81)	4.53 (2.06)	6.75 (3.54)	< 0.0001
Treatment failure No. (%)	9 (6.7)	3 (4.5)	4 (5.8)	0.734
14-day mortality No. (%)	0	0	0	-
Adverse Effects From Antibiotic Therapy No.(%)	25 (18.7)	8 (12.1)	18 (26.5)	0.035

[*]Procalcitonin; [**]Standard Deviation; [†]Number(s); [‡]Centigrade; [¶]Day(s)

Procalcitonin guidance was associated with a reduction in length of hospital stay (mean 4.53 days' vs 6.75 days in the control group, $p < 0.0001$). and also total antibiotic exposure (mean 3.17 days' vs 11.38 days in the control group, $p < 0.0001$). Treatment failure in PCT group patients was numerically lower than control patients, but not significantly different (4.5% vs 5.8%; p=0.734). There was a significant reduction in antibiotic-related side-effects in procalcitonin-guided patients (12.1% vs 26.5%; P = 0.035). All patients were followed up to 30 days and there was no significant difference between the two groups in clinical outcomes (Treatment failure and 14-day mortality).

Therefore, PCT level measurement may help to reduce the length of hospital stay and treatment duration in patients and accordingly, decrease the costs of antibiotic therapy and antibiotic-related side-effects and of course avoid antibiotic resistance. Table-3 shows the duration of antibiotic treatment and length of hospital stay in different PCT levels in the PCT group and control group.

Table-3: Duration of antibiotic treatment and length of hospital stay in different PCT* levels in the PCT group and control group

PCT levels (µg/L)	PCT group, mean(SD**)	Control group, mean(SD)	P-Value
Treatment Duration			
PCT < 0.1	2.78(0.95)	11(1.87)	< 0.0001
0.1 ≤ PCT < 0.25	2.33(1.22)	11(1.90)	< 0.0001
0.25 ≤ PCT < 0.5	6(1.41)	14(2.11)	< 0.0001
0.5 ≤ PCT	6(2.64)	14.33(3.31)	< 0.0001
Duration of hospital stay			
PCT < 0.1	4.21(1.87)	7.16(3.27)	< 0.0001
0.1 ≤ PCT < 0.25	4.11(1.90)	6.09(2.66)	< 0.0001
0.25 ≤ PCT < 0.5	6(1.41)	3(1.21)	< 0.0001
0.5 ≤ PCT	6.85(2.26)	5.83(3.31)	0.039

*Procalcitonin; **Standard Deviation

DISCUSSION

This research showed that PCT guidance leads to a significant reduction in the duration of treatment and hospitalization in CAP patients without apparent harm. Clinical outcomes were similar in the PCT and control groups. Hence, the safety of PCT guidance for reducing antibiotic usage is confirmed which is consistent with the results of some previous studies [13-15].

To distinguish bacterial from the non-bacterial CAP is used clinical criteria include fever, purulent sputum, leukocyte counts, and CRP levels. Prompt initiation of antibiotic therapy for patients with a bacterial CAP is critical and in sometimes a delay at the administration of antibiotics increases mortality while antibiotic therapy used for patients with nonbacterial CAP creates the antibiotic resistance and adverse reactions. Therefore, using PCT levels can complete and improve clinical assessment to start an appropriate antimicrobial therapy. Besides, PCT levels show high diagnostic accuracy for assessing the severity of CAP and discriminating bacterial and nonbacterial CAP [16, 17].

Using of PCT guidance decreases the treatment duration from 11.38 days to 3.17 days and reduces the length of hospital stay from 6.75 days to 4.53 days This is consistent with findings in other studies [4, 10]. However, some studies did not show that PCT guidance reduces significantly the length of hospital stay in patients of procalcitonin group in comparison with control group (7.3 days versus 9.7 days P=0.097) [18]. Also in another studies, the length of hospital stay was similar in the procalcitonin and control groups [19, 20].

As mentioned, exploiting PCT guidance in CAP patients reduces the use of antibiotics and consequently, fewer use antibiotics potentially avoid resistant bacteria and decrease the risk of cross-contamination with these resistant microorganisms between patients.

As a result, in developing countries that the prescription rate of antibiotics is high, the measuring PCT levels and exploit its guidance may have important clinical implications.

There are several limitations to this study. This study has been implemented with a relatively small sample of patients in a single center. To confirm the obtained findings, it need to investigate a large sample of patients from multicenter. Besides, the study is limited to hospitalized patients and does not include outpatients and patients in ICU that causes limiting of study results. The study followed the patients for only 14 days while more time needs to determine clinical failure.

CONCLUSIONS

Our study demonstrates that implementation of PCT guidance, as part of a clinical decision making algorithm, represents a practical method to meaningfully and safely diminish antibiotic exposure in the management of adult patients admitted with uncomplicated pneumonia. PCT measurement may provide markedly reduced antibiotic exposure in patients with pneumonia without adversely affecting hospital readmissions.

Author's Contributions

AF and NA were involved in the conception and design, data acquisition, analysis and interpretation, and drafting and revising the manuscript. EG and FD were involved in the conception and design, data acquisition, drafting and revising the manuscript. All authors read and approved the final manuscript.

Conflict Of Interest

The authors declare that they have no conflicts of interest.

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