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Use of antibiotic in the guidance of Procalcitonin at the Lower Respiratory Tract Infections

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Abstract

Introduction: Lower respiratory tract infections (LRTI) are common type of diseases among children. It is difficult to differentiate bacterial pneumonia from viral pneumonia using clinical, radiological and laboratory findings. We aimed to evaluate the relationship in the diagnosis and prognosis of cut-off value procalcitonin used as a tool in the antibiotic therapy, applied for the children with the LRTI. Above mentioned children were hospitalized or were outpatient. **Methods:** This study included 195 patients diagnosed with LRTI. Files were retrospectively evaluated. Due to the data in the file, patients with high cut-off value (0.5 ng / ml) were treated with antibiotics and were included in A group. Patients with a low cut-off value were treated with antibiotics and added to the B group. Patients which had a low cut-off value were treated without using antibiotics and were included to the C group. The relationship between clinical status, recovery days during physical examinations and procalcitonin (PCT), C-reactive protein values have been evaluated. In addition,in order to determine all the agents before the treatment, PCR results have been evaluated. **Results:** 88 female (45.1 %) and 107 male (54.9%) patients, totally 195 patients, aged from 1 to 180 months were included in this study. About 86.2% of patients were under 5 years. Like it is mentioned in the literature, most patients applied to the hospital in spring time. C group patients despite of having less rale (p=0,005) in comparison with A and B group patients, were more often to have sibilant rhonchus (p=0,001). When the increase of aeration was high among C group patients (% 48,2) lobar involvement was more seen among A group patients (62,5%). In total, agents have been determined in 114 (58,4%) patients. In all groups, the viral etiology was predomınant. While determining viral or bacterial agents, no significant findings have been detected. This means that separation of viral and bacterial agents in PCT in LRTI is not statistically affective (p: 0,33 - p: 0,37-0,51). It was determined that 62 (32%) patients of 133 (68%) patients didn't take antibiotics. **Conclusion:** In your study we found out that the rate of bacteria in patients with the high Procalcitonin wasn't higher than in those with the lower PCT. It is critically important to explain pediatricians at every meeting about the significance of popularizing the diagnosis of LRTI and the use of treatment guides algorithms in LRTI. In addition, there is a need in a well-randomized prospective study about PCT values.

Keywords: Lower respiratory tract infections, Procalcitonin, Antibiotic

INTRODUCTION

Especially in developing countries, Lower Respiratory Tract Infections (LRTI) all over the world is the most important cause of morbidity and mortality [1]. According to the World Health Organization' s 2005 report, LRTI is the main cause of 19% of 10.5 mln child deaths per year under the age of 5 [2-6]. In our country pneumonia is responsible for the %48.4 of infant's death, aged under 1 year and for the 42,1% of 1-4 years aged child deaths [7]. Again, according to Turkey data, %29 of children under 5 years was diagnosed with a LRTI [8]. This data shows that pneumonia and LRTI are the important public health problem, that leads to the high level of mortality and morbidity

especially among children aged under 5 years. It is pretty difficult to identify the causative pathogens especially among children with lower respiratory tract infections. Starting antibiotic treatment against bacteria in such a case mustn't be delayed, but unfortunately antibiotics can be frequently used in unnecessary cases. Procalcitonin (PCT) levels, a calcitonin propeptide, have been reported to be elevated in such an invasive bacterial infection as bacterial meningitis, but stayed low at viral infections [9]. Various methods have shown that in only 24 – 85 % of cases etiologic agents have been determined [10]. The aim of this study is to evaluate the relationship between diagnosis and prognosis of LRTI by using procalcitonin as a tool in antibiotic treatment.

METHODOLOGY

Patients who were diagnosed with LRTI, outpatients with the same diagnose or patients who came for control during 2011-2014 to Zonguldak Bülent Ecevit University Pediatric Clinic have been included to this study. The LRTI diagnose has been put according to the Diagnose and Treatment Guideline of the Turkish Thoracic Society. All the files of 195 patients older than 1 month and younger than 16 months have been examined. Also, their demographic characteristics, symptoms and findings at the admission stage, vital parameters, laboratory tests, other diseases, treatment options and duration of hospitalization have been recorded. Nasal PCR and peripheral blood culture have also been obtained. Patients with chronic diseases, pleural effusion and empyema, patients with severe pneumonia that need intensive care, those with severe immunosuppression haven't been included in this study. Patients whose procalcitonin level was higher than cut off value (0,5 ng / ml), were treated with antibiotic therapy and added to A group. Patients whose procalcitonin cut off level was low, but still due to various reasons these patients were given antibiotics were added to group B. Patients with a low cut off value and without using antibiotics were classified as C group. All patients that came for the control were again examined. Serum PCT levels were measured at BRAHMS KRYPTOR device, using BRAHMS sensitive kryptor kit (BRAHMS Diagnostica, Berlin, Germany) and TRACE (Time Resolved Amplified Cryptate Emission) technology device, that is based on the immunoassay method and no radiative energy. Necessary approve have been obtained from families in order to make this study and what's more, an approval have been received from Bülent Ecevit University Ethical Committee. (BEU2013-99-03/99). SPSS 18,00 program was used to analyze statistical data. Mann-Whitney U, Pearson Chi-Square and Fisher's Exact tests helped to compare various data. P value as <0.5 was considered as a significant result.

RESULT

Age of patients ranged from 1 to 180 months. Total number of patients was 195, that included 88 (45,1%) female and 107 (54,9%) male. Group A had 60 (30,8%) patients, group B 73 (37,4%) patients, and group C consisted of 62(31,8%) patients. Male and female rates in group are given in the table 1. If we look at the table and analyze age and gender distribution, we can see that the difference among groups is not significant. (in order of p=0,074, p=0,299). (Table 1). If we look at the ages of patients, it is clearly seen that % 86,2 of patients have applied to hospital in the first 5 years of life (table 2). As it is given in the literature, patients visited hospital in spring time.

Table 1: Gender distribution among groups

GENDER	A group (n: 60)	B group (n: 73)	C group (n : 62)
Female n: 88 (45,1%)	29 (48,3%)	31 (42,5%)	28 (45,2%)
Male n: 107 (54,9%)	31 (51,7%)	42 (57,5%)	34(54,8%)
Average age (month)	38 ±3,5	27 ±1,5	27 ±3,1

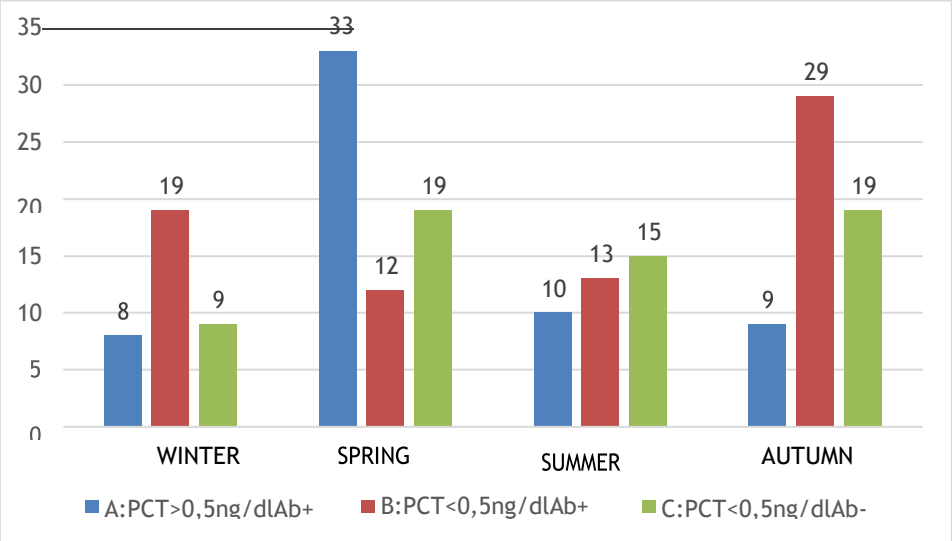
Table 2: Age distribution among groups on the moment of visiting a doctor

Age	A group	B group	C group	Total n:195
First 5 years	48 (28,5%)*	64 (38%)*	56 (33,3%) *	168 (86,2%)
6-10 years	6 (35,2%)**	6 (35,2%) **	5 (29,4%) **	17 (8,7%)
>10 years	6 (60%)***	3 (30%) ***	1 (10%) ***	10 (5,1%)

*percentage of patients in the first 5 years **percentage of patients aged from 6 to 10 years
***percentage of patients older than 10 years

Twenty-nine (14,9%) patients were premature and 19 (65,5%) of these patients were in the B group (p=0,003). It has been detected that 177 (90,8%) patients consumed breast milk, while 54 (27,7%) patients under 1-year-old started to drink cow milk. However statistically significant difference among groups haven't been determined (p=0,90, p=0,58). In all groups, 11(5,6%) patients had deficiencies in routine child vaccines. Significant statically difference of vaccines between groups haven't been detected. We look at physical examination findings of patients from all groups, that 129 patients had crepitant rale and 118 patients suffered from sibilant rhonchus. If we take a look at all groups, we can find that despite patients of C group had less rale (p=0,005) than patients from A and B group, patients from C group had more sibilant rhonchu (p=0,001). Radiologic chart findings have been compered statistically among groups. While the increase of aeration is high (48,2%) among C group patients, lobar involvement is more seen (62,5%) among A group patients. 62.5% of patients in group A;

In group B and C, 37.5% of patients had lobar involvement (p: 0.001) (Table 3).



Graph 1: Seasonal distribution of groups

Table 3: Respiratory system pathologic physical examination and chest x-ray findings

Finding / all groups	A group	B group	C group	p value
Rale (n : 129)	44 (34,1%)	54 (41,9%)	31 (24%)	**0,005**
Rhonchus (n : 118)	25 (21,2%)	44 (37,3%)	49 (41,5%)	**0,001**
Increase of aeration	14 (25%)	15 (26,8%)	27(48, % 2)	**0,007**
Lobar involvement	15 (62,5%)	8 (33,3%)	1(4,2%)	**0,001**

Table 4: Distribution of viral and bacterial agents in nasal PCR among groups

	With no factor	Bacteria	Virus	Viral + bacteria
A group	28 (46,7%)	8 (13,3%)	17 (28,3%)	7 (11,7%)
B group	24 (32,9%)	11 (15,1%)	24 (32,9%)	14 (22,6%)
C group	29 (46,8%)	5 (8,1%)	14 (22,6%)	14 (22,6%)
Total	81 (41,5 %)	24 (12,3 %)	55 (28,2 %)	35 (17,9 %)

Table 5: Viral and bacterial agents' distribution in nasal PCR among groups

Virus		A group	B group	C group
	Total n (%)	n (%)	n (%)	n (%)
RSV a	41 (21)*	10 (24,4) **	17 (41,5) **	14 (34,1) **
RSV b	21 (10,8)*	3 (14,3) **	11 (52,4) **	7 (33,3) **
Influenza	1 (0,5)*	1 (100) **	0 (0) **	0 (0) **
Rhino V	31 (15,9)*	7 (22,6) **	16 51,6) **	8 (25,8) **
Parainfluenza V	9 (4,6)*	1 (11,1) **	4 (44,4) **	4 (44,4) **
Corono V	3 (1,5) *	1 (33,3) **	2 (66,7) **	0 (0) **
AdenoV	7 (3,6) *	2 (28,6) **	2 (28,6) **	3 (42,9) **
hMP V	2 (1) *	2 (100) **	0 (0) **	0 (0) **
Streptococci pneumonia	28 (14,4) *	7 (25) **	12 (42,9) **	9 (32,1) **
Homophiles	34 (17,4) *	10 (29,4) **	14 (41,2) **	10 (29,4) **

influenza				
Bordetella pertussis	2 (1) *	0 (0) **	1 (50) **	1 (50) **
Legionella	1 (0,5) *	0 (0) **	1 (100) **	0 (0) **
Mycoplasma	1 (0,5) *	1 (100) **	0 (0) **	0 (0) **
Chlamydia	3 (1,5) *	0 (0) **	2 (66,7) **	1 (33,3) **

* Total patients in number (n) and percentage (%)
**Number (n) and percentage (%) of agents detected among patients
RSV: Respiratory syncytial virush MPV: Human meta pneumonia virus

Table 6: Average values of acute phase reactants at the moment of putting diagnosis among groups

	A group	B group	C group
	Average ±standard deviation		
PCT (ng/ml)	6,1±16	0,11±0,75	0,12±0,07
CRP (g/L)	45,5±70,8	21,1±46,4	10,6±30,6
Leukocytes (10^3/uL)	14,7±8,1	13,3±7,1	13,3±5,2

Nasal PRC results of the patients included in the study are shown in table 4-5. In total, 114 (58.4%) patients were able to detect microorganisms due to nasal PCR and other methods. Significant statically difference between viral and bacterial agents among groups haven't been detected (p:0,33). This means, that the rate of bacterial detection in patients with high procalcitonin wasn't higher than in those with a low PCT.

In addition, there was no statistical difference between the groups in terms of additional treatments that patients received except antibiotics. When the patients were examined in detail, 36 (24.5%) patients in group A, 54 patients (36.7%) in group B and 57 patients (38.8%) in group C received salbutamol treatment. When we classified all patients into two groups according to procalcitonin value, we saw that 111 (69,2%) patients from B and C groups have received more salbutamol than patients from A group (p=0,001). The average results of acute phase reactants of our patients are given in table- 6. When examining treatment duration and physical examinations findings of all patients it became clear that treatment duration in the A group was longer (10,73± 3,7- 3,18±1,69) compared to the C group. As for the physical examination, the recovery time in A group (5,22±10,85-2,29±1,41) was much longer (p=0,001).

DISCUSSION

As it is especially difficult to differentiate pneumonia from acute bronchiolitis in infants, the term of low respiratory tract infection is used for these two diseases [11-15]. It has been determined in the literature that 56-59% of male, 41-44% of female child has a LRTI diagnosis [16-20]. This study included 54,9% male and %45 female patients. Similar to the literature, the rate of male patients is higher than female patients' rate. In addition, similar to the literature, 86,1% of patients are patients in their first 5 years of life. It has been found out that the majority of our patients (62,6%) were living in the city and 71 (36.4%) patients were found to have at least one person smoking in the family. Nineteen (65,5%) of the patients with premature birth history were in the B group. Although the PCT levels of these patients were low, it was thought that their premature condition was an additional risk factor for bacterial LRTI. This study also contained similar risk factors that have been mentioned in the literature [21,22]. Bacterial agents for LRTI have been more frequently seen during winter and spring time, while viral agents for LRTI have been more seen in autumn and early winter time [23]. When we look at the months of the patients in our study; It was seen that the patients in the group with antibiotic treatment and high PCT were more in the spring season. The World Health Organization has defined the clinical picture of LRTI as a disease accompanied by increased respiratory rate, acute cough or signs of respiratory distress. The aim of this definition is to provide access to life-saving antibiotics to a great extent of patients in developing countries where the incidence of LRTI is very high; however, this definition has a low specificity [6, 24]. As for the developed countries, LRTI has been defined as parenchymal involvement in the chest radiography with fever and / or acute respiratory symptoms [1]. In our study, the diagnosis of LRTI has been put to patients considering all above-mentioned criteria.

In a study by Bilkis *et al* [25]. it was shown that the sensitivity of fever, localized rales, decreased breathing sounds and tachypnea in demonstrating pneumonia in children is 93.8%. As for our study, the highest level of temperature was 39,7 ° C. In our study, 122 of 195 patient's tachypnea (62.6%), 128 (66.2%) ral, 118 (60.5%) rhonchus, 94 (48.2%) subcostal withdrawal and 34 (17.4%) wheezing were detected. If we compare frequency of tachypnea in our study with the literature cases, we found out that both are similar. As for the crepitant rales frequency, it is

higher than it is mentioned in the literature. Juven *et al*. [26] have found that rhonchus was more common among patients with LRTI and viral agents. In our study rhonchus have been found to be more frequent (78,8%) among patients with viral agents. All the radiologic findings haven't shown any specific features for viral and bacterial agents in LRTI [27]. In our study 62,5% of patients from A group happened to have alveolar infiltration and lobar involvement, also the rate of bacterial agents in this group isn't so significant in comparison with others. Clinicians have understood that radiologic observations could not provide any distinctive diagnosis for the agent. Agents for LRTI turned out to be various due to the different age of patients. Viruses are the most common pathogen among patients under age of 5 years, while much elder patients tend to more have such a new pathogens and viral agents as human metaopneumovirus (hMPV) and Boca virus [28]. In our study, 2 patients had a metaopneumo virus as an agent. Viral agents have been detected in 46,2% of patients and bacterial agents in 30,3% of patients, which were in our study. This have again shown thatviruses are the major pathogen in lower respiratory tract infections especially among patients under age of 5 years.

As today LRTI is an important health problem worldwide, treatment and different diagnosis guide has been prepared. The aim of this guide is to provide help in a putting an early diagnosis and find the best appropriate treatment for the patient. In this study, the diagnosis and treatment application have been made in accordance with the 2009 report of Turkish Thoracic Society "Acute bronchiolitis among children and diagnosis and treatment of community acquired pneumonia". Rate of mortalıty have been reduced when patıents, who were diagnosed LRTI with bacterial agents, received antibiotic treatment in first 4 hours [29,30]. However unnecessary use of antibiotics in LRTI with non-bacterial agents, led to the increased antibiotic resistance and side effects [31].

Mixt agents seem to play significant role alongside in the etiology of LRTI. Michelow *et al*. [10] report in their study that 34% of patients had bacterial agents, %16 of patients had only viral agents, 23% of patients had both viral and bacterial agents, % 3 of patients had mixed viral agents, %3 of patients mixed bacterial agents were detected. But21 % of patients didn't have any agents detected. Rate of the mixed infections incidence in developed countries is about 8-51% [32]. A prospective study conducted in the UK has reported the rate of etiologic agents as 49% [33]. Tajima *et al* [34]. from Japan in their study found the rate of etiologic agent as 80,3%. Along with it, other agents were: the viral infection by itself -17,8%; only bacterial infection-26,8%; mixed viral-bacterial infection - 17,8% and streptococcus pneumonia was the most frequently bacterial agent detected. Tanır *et al*. [35] put RSV infection diagnosis to 44,4% of patients. In our study we expected patients with a high level of procalcitonin and antibiotic treatment to have more bacterial agents, however viral agents turned out to be more often detected in all groups. We could detect agents among 58,4% of patients. Viral agents were found in 46,1% of patients, bacterial agents in 30,2% of patients and 17,9% of patients had viral + bacterial agents. RSV (31,8%) was determined as the most common viral agent, while hemophilia influenza (17,4%) was determined as the most common bacterial agent. Generally, all above mentioned results are similar to the results shown in the literature.

Many studies have shown that in order to differentiate bacterial and viral agents PCT cut-off values should be taken as 0,5 - 2 ng/ml [36-39]. In our study while making groups PCT cut-off level was accepted as 0,5 ng/ml. Long *et al*. [40] made a control randomized study for the same purpose. In this study they used 0,25 ng/ml of PCT cut-off and estimated that the standard antibiotic treatment use rate could be reduced from 15% to 2,5%. Werner *et al*. [31] in their 2013 multicenter study have been working on reliability and effectiveness of antibiotic use in PCT. They found out that PCT use can reduce the antibiotic use and prevent from complication risk. The study has shown that using algorithm in LRTI treatment reduced the use of antibiotic from 25% to 20%. Burkhardt *et al*. [32] in their metanalysis mentioned that %41,6 of antibiotic use have been reduced and that PCT value could be able to shed a light on the need of prescribing antibiotics for such diseases as bronchiolitis. One more study in our country have shown that ≥2ng/ml of procalcitonin serum has a 90 %sensitivity for the bacterial pneumonia and 100% specificity. This means that procalcitonin serum can be used as parameter in differentiation between bacterial and non-bacterial pneumonia [9] Moreover, a recent study showed that PCT level below 0,25 ng/ml can be a significant predictive measure for non- pneumococcal pneumonia [41]. In opposition to this view, Korppi and Remes [42] reported that it is impossible to use levels of procalcitonin serum for differentiating pneumococcal pneumonia and viral pneumonia in hospitalized children. Again, the same researchers stated that procalcitonin serum can't be an effective method in making diagnosis of pneumonia in children as levels of procalcitonin serum in pneumococci, mycoplasma, chlamydia and viral pneumonia are similar [43]. According these aims, patients were included in our study, however they were grouped respectively. It was detected that 133 (68%) of patients took an antibiotic treatment and 62 (32%) patients didn't take any antibiotic treatment. About 60 (45%) of patients who took antibiotic treatment had PCT value more above 0,5 ng / ml. The level of detected bacterial agents among patients with a high PCT wasn't statistically effective, on the contrary viral agents turned out to be more detected (p=0,33). Maybe if we had taken PCT value as 2 ng / ml and above, we could have gotten more significant results. Also, it is worth saying that due to the fact that groups were divided, mixed infections played a role in pneumonia or even though the acute phase reactant were low, clinical findings could have led us to a wrong use of antibiotics. In our study the duration of treatment among patients with a low PCT and viral infection is shorter than the duration of treatment of patients from A group with a higher PCT level. In our study, the bacterial ratio was not high in group A, but according to the other groups, PCT mean values were 6.1 ng / ml. PCT levels were normal in other groups. This result suggests that it can be meaningful as an option to start antibiotics.

CONCLUSION

It is critically important to explain pediatricians at every meeting about the significance of popularizing the diagnosis and the use

of treatment guides algorithms in LRTI. No matter how retrospective our study is, results which are different from expected ones have been obtained due to the not using special algorithms. Still we think that procalcitonin guidance of antibiotic treatment can help to reduce the unnecessary use of antibiotics and as a result to shorten the duration of treatment. Also, it can prevent the development of antibiotic resistance that occur due to the side effects of antibiotic use. In order to obtain better results among patients diagnosed with LRTI, there is a great need in making more planned and affective studies.

Conflicts of interest

There is not conflict of interest.

Authors' Contribution: Consept: NY,MK. Design: NY,MK. Supervision: NY,MY. Resources: NY,MK. Materials: data collection and/or processing: NY,MY. Analysis and/or interpretation: NY,MK, MY. Literature search: MK, NY.Writing manuscript: MK,NY,MY. Critical review:MK

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