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ORIGINAL ARTICLE

Etiology and Prognostic Factors of Community-Acquired Pneumonia

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Abstract

Introduction: Community acquired pneumonia (CAP) is an important health problem because of its high prevalence and mortality. In empirical treatment decision, clinical data have critical importance. In this study, we aimed to determine the etiological factors and prognostic markers in the patients who have CAP.

Methods: The present study was conducted with 65 patients with CAP, who were referred November 2011 and November 2012. For etiologic evolution, sputum, bronchial lavage, direct microscopic examination, and cultures of blood samples and bronchial lavage were performed. For prognostic evolution, complete blood count, C-reactive protein, sedimentation, and biochemical parameters were evaluated. The patients were classified according to ATS, PSI, and CURB-65 critera and their associations with prognosis were analyzed.

Results: According to the Turkish Thorax Society 2009 CAP Guideline, there were 44 patients (67.7%) in Group 1, 15 (23.1%) in Group 2, and 6 (9.2%) in Group 3. The most common used antibiotics were new generation quinolones, third generation cephalosporins, and macrolid combinations. The most common lung involvement was lober. In sputum culture and direct microscobic examination, the most common etiologic agent was coagulase negative staphilococci and there was no resistance to those antibiotics. The duration of treatment was ranged between 15 days.

Discussion and Conclusion: In the etiologic investigation, any agent was isolated in approximately 30% of patients. For this reason, empirical antibiotic therapy is important in prognosis. It should be started without delay in the presence of guidelines and considering the patient's clinical findings and previous antibiotic use. Prospective studies involving large numbers of patients are needed to investigate regional data.

Keywords: Mortality; pneumonia; prognosis.

Pneumonia is defined as an acute inflammatory disease affecting the pulmonary alveoli, respiratory bronchioles, and lung interstitium [1]. Community-acquired pneumonia (CAP) is caused by non-nosocomial microorganisms. The severity of the disease is variable. It can be mild in healthy individuals and can be confused with common cold and bronchitis. However, it can also occur in serious cases that require intensive care treatment [2]. Community-acquired pneumonia is a disease with high morbidity, mortality and cost [3]. Its incidence and mortality are related to age and comorbid diseases [4]. Initiation of treatment without delay has a positive effect on the prognosis, especially in elderly patients. For this purpose, scoring systems such as CURB-65 and pneumonia severity index (PSI) have been

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developed to identify patients with high mortality risk and to prevent unnecessary hospitalizations [5].

Causes, diagnosis-treatment approaches and prognosis in CAP are quite different compared to nosocomial pneumonia (NP) and pneumonia in immunocompromised individuals [6]. In the presence of compatible symptoms and physical examination findings, the appearance of infiltrates on the chest X-ray (CXR) is followed by microscopic examination of blood, sputum and respiratory tract samples. However, it is often not possible to identify the cause. Therefore, it is important to accurately predict possible factors that will be the basis for empirical treatment [7].

In this prospective study, it was aimed to evaluate the clinical, radiological, microbiological and laboratory parameters of patients diagnosed with CAP within one year, and to determine the etiological agents and prognostic factors, with a purpose of guiding clinicians.

Materials and Methods

Patients over the age of 20 who applied to the pulmonary diseases outpatient clinic or emergency service of our hospital between November 1, 2011 and November 1, 2012, and were diagnosed with CAP and receiving inpatient treatment, were included in the study. Patients with CURB-65 score ≥2, PSI Group 4 and Group 5 were hospitalized. All elderly (>65) patients who did not meet these criteria were also hospitalized. In addition, patients with comorbidities, toxic appearance, bilateral or multilobar involvement on CXR, or pleuropneumonia were also admitted. A voluntary consent form was obtained from each patient, stating that they accepted the study. The study protocol was approved by Atatürk University ethics committee (10.11.2011/34).

The patient's anamnesis was taken, physical examinations were made, and their files were prepared. Arterial blood gas (ABG) sample was taken during hospitalization. Hemogram test, C-reactive protein (CRP), sedimentation, major biochemical parameters, chest radiographs, blood, sputum or bronchoalveolar lavage direct examination and culture results were evaluated during hospitalization and discharge. Whether antibiotic changes were made during the treatment and complications, if any, were examined. CRP was studied with the nephelometry method and 5mg/dl was accepted as the limit value. In order to determine the severity of CAP as a prognostic marker, groups were formed by evaluating the clinical and laboratory findings and comorbidities of the patients. Patients were grouped according to their CURB-65 and PSI scores.

A minimum of three sputum samples were taken for etiological evaluation. If at least 2 out of 3 sputum samples showed growth, the culture was considered positive. After the patient's mouth was cleaned, a sputum sample was taken into a sterile capped container. Fiberoptic bronchoscopy (FOB) was performed in patients with pneumonia or atelectasis with delayed resolution, with no contraindications for FOB, and those who accepted the procedure. A sample of bronchoalveolar lavage was taken using a sterile catheter. Gram stain slide was prepared from sputum and bronchoalveolar lavage samples in the clinical bacteriology laboratory, and culture cultivations were performed. After the quality of the sputum samples was evaluated by looking at the leukocytes, epithelial cells and quantity, they were cultivated for quantitative culture and ARB. Bronchoalveolar lavage and sputum samples suitable for cultivation were inoculated on blood agar, Eosin Methylene Blue (EMB), chocolate agar, "Buffered Charcoal Yeast Extract" (BCYE) media and incubated at 35°C. Cultivations on blood agar, EMB, chocolate agars were incubated for 72 hours, and cultivation on BCYE medium for 7 days. Growth was evaluated daily. During hospitalization, 10 cc blood samples were taken at least 3 times, from two different veins each time, from each patient and from patients with fever, and placed in "Bactec" (Beckton Dickinson, USA) automated blood culture system bottles. Microorganism identifications were made by evaluating blood culture samples incubated at 35°C for 7 days.

SPSS 20 program was used in the analysis of the data; $p<0.05$ was considered significant. The Kolmogorov-Smirnov test was used in the analysis of the data's conformity to the normal distribution. The t-test was used in the analysis of the normally distributed data, and Mann-Whitney U test was used in the analysis of the non-normally distributed data. The Wilcoxon signed-rank test was used to compare the numerical data before and after treatment. Chi-square test was used to compare categorical variables.

Results

A total of 65 patients, 41 (63.1%) male and 24 (36.9%) female, were included in our study. The mean age of the patients was 60±20 years. Four patient (6.2%) in the 20-29 age range, 5 (7,7%) in the 30-39 age range, 9 (13.8%) in the 40-49 age range, 6 (9.2%) in the 50-59 age range, 20 (30.8%) in the 60-69 age range, 14 (21.5%) in the 70-79 age range, 6 (9.2%) in the 80-89 age range and 1 (1.5%) in the 90-99 age range was present. When grouped according to the Turkish Thoracic Society CAP guideline, 44 (67.7%) patients were present in Group1, 15 (23.1%) in Group 2, and 6 (9.2%) patients in Group 3. Patients who had a toxic appearance despite be-

ing in Group 1, patients with multilobar or bilateral involvement on CXR, who had pleurisy or comorbidity, and all patients over 65 years of age were also hospitalized. In total, 83.3% of the patients had comorbid diseases. 43% had lung disease, 16.9% diabetes mellitus (DM), 10.8% heart disease, 10.8% malignancy and 6.2% cerebrovascular disease (CVD). Six patients were transferred to the intensive care unit (ICU); 5 (83.3%) of these died. Of these 5 patients, 1 had heart disease, 1 had CVD, and 3 had malignancy. Were found to be one of the most important determinants of mortality and morbidity.

While 26 (63.4%) of the male patients had a smoking history, there was no smoking history in the females. Cough, sputum, shortness of breath, chest pain and flank pain were the most common symptoms, respectively. The most common physical examination findings were rales, cyanosis, tachypnea, decreased breath sounds and rhonchi. Hypothermia (fever <35ºC) or hyperthermia (fever >40ºC) was detected in 15 (23.1%) patients. The demographic characteristics, comorbidities, most common symptoms and physical examination findings of the patients are shown in Table 1. The mean respiratory rate of the patients was 26.0±6.5, systolic blood pressure was 113.9±21 mmHg, and diastolic blood pressure was 71.8±13.6 mmHg. While the mean fever measured on the first day of the treatment was 37.3±0.7 ºC, it was 37.1±0.7 ºC on the third day. 10% of patients had altered consciousness.

Table 1. Demographic characteristics, comorbidities, symptoms and physical examination findings of the patients

	n (%)
Gender	
Male	41 (63.1)
Female	24 (36.9)
Comorbidities	
Lung pathology	28 (43.1)
Diabetes mellitus	11 (16.9)
Heart disease	7 (10.8)
Malignancy	7 (10.8)
Cerebrovascular diseases	4 (6.2)
Symptoms	
Cough	60 (92.3)
Dyspnea	45 (69.2)
Sputum	43 (66.2)
Chest pain	19 (29.2)
Flank pain	15 (23.1)
Hemoptysis	6 (9.2)
Physical Examination	
Rales	52 (80.0)
Cyanosis	45 (69.2)
Tachypnea	30 (46.2)
Decreased breath sounds	21 (32.3)
Rhonchi	9 (13.8)

Evaluation of clinical and laboratory findings and comorbidities of patients with CAP and grouping according to CURB-65 and PSI scores are shown in Table 2.

On CXR of the patients, lobar involvement was most commonly detected in 30 (46.2%) patients, with bronchopneumonia in 17 (26.2%), interstitial pneumonia in 18 (27.7%) and accompanying pleurisy in 11 (16.9%). In the CXR taken during discharge, 51 (78.5%) of 65 patients had radiological response to antibiotic therapy. Antibiotic switch was made in 14 (21.5%) of the patients.

There was no significant difference between the sexes in terms of growth status in sputum culture (p=0.26). In sputum cultures, coagulase (-) staphylococci growth was seen in 22 (33.8%) patients, S. pneumoniae in 8 (12.3%) patients, and enterococci in 3 (4.6%) patients. There was growth in the blood culture of 4 of 6 patients who were transferred to the ICU. Methicillin-resistant Staphylococcus aureus (MRSA) growth was seen in 3 of the blood cultures taken here, and Methicillin-susceptible Staphylococcus aerus (MSSA) was seen in 1 of them. All of these patients died. There was no growth in the blood culture of the patients we followed in the service.

There was a significant improvement in leukocyte, hemoglobin (Hb), CRP, creatinine, and ALT values before and after treatment (p=0.0001, p=0.0001, p=0.0001, p=0.002, p=0.014, respectively). No significant difference was found in other laboratory parameters.

The mean duration of treatment was found to be 15 days. A borderline significant relationship was found between the CURB-65 score and the duration of treatment (p=0.05)

Table 2. PSI and CURB-65 groups

	n (%)
PSI groups	
1	13 (20)
2	17 (26.2)
3	14 (21.5)
4	14 (21.5)
5	7 (10.8)
CURB-65 scores	
1	38 (58.5)
2	18 (27.7)
3	9 (13.8)

(Table 3). It was observed that the duration of treatment was longer in those with a CURB-65 score of 3 and above, than in those with a CURB-65 score of 0, 1 and 2.

No statistically significant correlation was found between the CURB-65 and PSI scores of the patients and their gender, comorbidity, smoking, duration of symptoms, and radiological findings. Sixty (92.3%) of the patients were discharged with recovery. As the CURB-65 score of the patients increased, it was observed that transfer to ICU increased significantly (p=0.002) (Table 4). There was no significant relationship between the CURB-65 scores of the patients and their death status (p=0.13). There was a significant correlation between the PSI groups of the patients and their death status (p=0.002) and the transfer rate to ICU (p=0.001) (Table 4, Table 5).

The antibiotics used in the treatment are shown in Table 6. The most commonly used first 3 antibiotics were determined as new generation quinolones, 3rd generation cephalosporin and macrolide combination, and ampicillin-sulbactam combination. In cases where antibiotic switches were made, piperacillin-tazobactam or meropenem options were used. Transfer rate to ICU was found to be significantly higher in patients who underwent antibiotic switches (p=0.01). Four (28.6%) of 14 patients who underwent antibiotic switches in the service were transferred to the ICU. A significant correlation was found between antibiotic switch status and death (p=0.006).

Table 3. CURB-65 groups and duration of treatment

CURB-65	Treatment duration n (%)		Total n (%)	p
	15 days	25 days		
Score 0,1,2	52 (92.9)	4 (7.1)	56	0.05
Score 3	6 (66.7)	3 (33.3)	9	

Table 4. PSI and CURB-65 score and transfer to intensive care unit

	Transfer to intensive care unit			
	No	Yes	Total n	p
PSI groups				
Group 1,2,3	44 (100)	0	44	0,002
Group 4,5	15 (71,4)	6 (28,6)	21	
CURB-65				
Score 0,1,2	54 (96,4)	2 (3,6)	56	0,001
Score 3	5 (55,6)	4 (44,4)	9	

Table 5. PSI groups and death

	Exitus		
	No	Yes	Total
PSI groups			
Group 1,2,3 n (%)	44 (100,0)	0	44
Group 4,5	16 (76,2)	5 (23,8)	21

Table 6. Used antibiotics

	n (%)
Ampicillin-sulbactam	11 (16.9)
Cefuroxime	2 (3.1)
Ceftriaxone	1 (1.5)
Levofloxacin/moxifloxacin	14 (21.5)
Piperacillin-tazobactam	1 (1.5)
Ampicillin+clarithromycin	6 (9.2)
Ceftriaxone+clarithromycin	14 (21.5)
Piperacillin-tazobactam+clarithromycin	2 (3.1)
Antibiotic changed	14 (21.5)
Total	65 (100)

Discussion

In our study, we determined that patients with pneumonia had a high transfer rate to ICU and a high mortality rate in patients transferred to the ICU. We found that hemogram, serum electrolytes, liver and kidney function tests are important in determining the prognosis of the disease. As CURB 65 and PSI scores increased, the rate of antibiotic switches and transfer rate to ICU increased. We found that the higher the PSI score, the higher the mortality rate.

Community-acquired pneumonia has high mortality and morbidity in adults and older ages [8]. Although it is seen especially in winter, it is an infectious disease with high treatment rate and costs in every period of the year [9]. The incidence is increased in the older age group and those with chronic diseases. The annual incidence, which is 1.7% in the general population in the USA, is reported to increase to 2.8% in people over 65 years of age, and the annual incidence, which is 0.6% in the 16-59 age group in Finland, is increased to 2% in the 60-74 age group, and to 3.4% in the age group of 75 and above [10,11]. In our study, the mean age was between 60-80 years and the incidence of pneumonia increased with increasing age.

With increasing age, there was an increase in transfer to ICU and mortality with comorbid disease. It is stated that 58-89% of patients with pneumonia have one or more underlying chronic diseases [12]. Among these diseases, COPD, cardiovascular diseases, neurological diseases and DM are the most common diseases. In the study of Bircan et al. [13]

from our country, comorbidities were found in 44.1% of the cases, the most common being COPD (23.7%), DM (17.2%) and heart failure (15.1%). In addition, up to 60% of patients with pneumonia had immunosuppressive factors such as malignancy, neutropenia, and chronic steroid use [14]. Consistent with the literature, the most common comorbid diseases in our study were COPD, Coronary Artery Disease (CAD) and DM. Lung pathology was detected in 43%, heart disease in 10.8%, and DM in 16.9%.

Fever with chills, chest pain, mucopurulent sputum, and extrapulmonary symptoms can be seen in CAP. The onset of symptoms takes an average of 6 days after the onset of the disease [12]. In the study of Metlay et al., [10] which included 1812 patients with CAP, the most common symptoms were malaise (91%), cough (86%), fever (84%), chills (73%), anorexia (71%), dyspnea (72%), sputum production (64%) and sweating 69%. In the same study, tachypnea was observed in 45-69%, tachycardia in 45%, and rales in 29%. In our study, fever was not among the most common symptoms in our patients. Cough, sputum, shortness of breath, chest pain and flank pain were the most common symptoms. The most common physical examination findings were rales, cyanosis, tachypnea, and decreased breath sounds. Complaints at admission and extrapulmonary symptoms were found to be compatible with the literature [15].

Increase in liver enzymes and bilirubin in bacterial CAPs is evident with bacteremia. Hyponatremia can be seen in 50% of Legionella pneumophila cases. In the study of Musonda et al., [16] ALT, cholesterol and albumin levels were found to be significantly lower in 302 patients with pneumonia compared to the control group. In the study of Daxboeck et al., [17] M. pneumonia and, S. pneumoniae cases were examined and ALT elevation was found to be 36% and 10%, respectively. In our study, the leukocyte, Hb, creatinine, and ALT values of the patients were found to be high during the hospitalization period, when they had bacteremia. Complete blood count, serum electrolytes, liver and kidney function tests contribute to determining the prognosis of the disease, choosing the treatment and adjusting the antibiotic dose [18]. In our study, significant improvement was found in WBC, Hb, CRP, creatinine, and ALT parameters in line with the treatment response. These findings suggest that laboratory follow-up will be useful in monitoring the clinical response as well as the severity of the disease and the type of treatment. There was no correlation between serum ALP, electrolyte and platelet levels and treatment response. CRP is an acute phase protein synthesized from hepatocytes by the action of IL-6, IL-1 and TNF in response to infection or tissue damage [19]. Korppi et al. [20] found high sedimentation and leukocyte values in their study with 200 patients, 69 of whom had bacterial pneumonia, but did not find a statistically significant difference. In our study, it was also found to be a guide in determining the prognosis.

Changes in the frequency and type of etiological agents occur in patients with CAP due to the aging population, the presence of comorbid diseases in many patients, and the increase in the number of immunosuppressed patients. While S. pneumoniae was reported as the most common cause in CAP, in our study, it was coagulase (-) staphylococci (33.8%) [21]. This was followed by S. pneumoniae (12.3%) and enterococci (4.6%), respectively. In a retrospective study of 5160 patients with CAP and nursing home pneumonia, the most frequently isolated agents were S. pneumoniae, Gr (-) enteric bacteria, and H. influenzae [22]. C. pneumoniae and M. pneumoniae are among the most frequently detected agents in studies conducted with CAP in recent year. It is seen that S. pneumoniae is detected at a lower rate and the frequency of atypical factors is increased. In a study conducted with 500 patients with CAP, the most common causative agents were viruses (36%), M. pneumoniae (18%) and bacteria (14%) [23]. In another study, 510 hospitalized patients between November 2010 and May 2012 were examined and the most common isolated agents were viruses, M. pneumoniae and mixed pathogens, respectively. Influenza virus was detected in the majority (54%) of viral infections [24]. In 22 (33.8%) of our patients, the most frequently isolated agent from sputum was coagulase (-) staphylococci, followed by S. pneumoniae. This may be due to the fact that the majority of the patients in our study were over 60 years of age (n=41, 63.1%) and the younger patients had a comorbid disease. Coagulase negative staphylococci can cause pneumonia. However, its detection in the first place in our study suggests contamination from the oral and throat flora in some patients, although appropriate sampling was performed. It is thought that the differences in regional data also have an effect on these results.

In their study conducted by Erdem et al. [25] in 12 different centers with 413 patients, 19 of whom were in ICUs, the most frequently isolated agents in patients with CAP who needed ICU were Gr (-) bacteria, S. aureus, and S. pneumoniae, respectively. In our study, S.aureus was shown in the blood cultures of 4 of 6 patients who were transferred to the ICU.

Lung involvement was most common in our patients as lobar pneumonia (46%) and interstitial pneumonia (27.7%).

This suggests that there is an involvement due to typical-atypical pneumonia agents. In the study of Sever et al., [23] infiltrates were predominantly segmental (61.1%) and unilateral (81.9%). In another study, radiological involvement was detected as bilateral multilobar infiltrates [25]. In our study, pleural effusion was detected in 16.9% of the patients, no relationship was found between the presence of effusion and the causative agent and prognosis. Radiological response was obtained in 78% of the patients. The patients were treated for an average of 10-19 days. In the literature, the mean length of hospitalization for CAP was found to be 13±7 days in patients without comorbid disease, and the mean hospitalization time in patients with comorbid disease was found to be 15 days [26]. The length of hospital stay of our patients was similar to the literature.

Treatment of patients with CAP can be done at home, in the ward or in the ICU, depending on the severity of the disease. It is important that patients are treated in the right place. Tables and indices have been developed to estimate results from a combination of disparate factors. In our study, it was determined that patients over 60 years of age and with comorbidities should be hospitalized and treated.

In a prospective study of 200 hospitalized patients with a diagnosis of CAP, major antibiotics were cephalosporin (80%), aminoglycoside (65%), penicillin (50%) monotherapies or combination therapy [27]. In another study, fluoroquinolone monotherapy was found to be the most commonly used antibiotic in CAP, with levofloxacin being the most common [28]. In our study, the most frequently used and responded antibiotic therapy options were new generation quinolones (moxifloxacin, levofloxacin) and a combination of 3rd generation cephalosporin and clarithromycin.

CURB, CRB, CURB-65 and PSI indices have been developed to be used to determine hospitalization indication and prognostic factors in CAP cases. In the study of Sevda Cömert et al., [29] it was seen that 60.4% of hospitalized CAP cases according to CURB-65 and 41.7% according to PSI did not require inpatient treatment, and these cases could be treated on an outpatient basis. In the study of Fidan et al., [30] in which they evaluated compliance with national pneumonia diagnosis and treatment guidelines, it was observed that compliance increased over the years and with this increase, hospitalizations of Group 1 and Group 2 cases have been shown to decrease in relation to the "Thoracic Society Adult and Children's Community-Acquired Pneumonia Diagnosis and Treatment Guidelines", which was published in 2002. Dean et al. [31] also achieved a 50% reduction in hospitalizations with adherence to the guideline. In our study, the PSI and CURB-65 indices were found to be statistically significant and sufficient in deciding on hospitalization and transfer to the ICU, determining the duration of treatment and antibiotic switch. It was observed that the mortality rate increased with the increase in the PSI score.

Conclusion

In our study, we found that the risk of mortality was high in cases with pneumonia and a comorbid disease. We have seen that the follow-up of laboratory findings is important in determining the severity of the disease and the type of treatment, as well as in the follow-up of clinical response. Etiological evaluation was possible in approximately 40% of patients. We found that the majority of the patients transferred to the ICU had growth in their blood culture and all of these patients died. In addition, we found that the prognosis of pneumonia worsened and ICU hospitalization increased with the increase in CURB-65 and PSI scores. We found that an increase in PSI score increased the mortality rate. It is important to determine the pneumonia scores of the patients in the presence of their clinic, physical examination findings and comorbidities, to determine the severity of the disease according to them, to organize their empirical treatments and to take their cultures in line with the guidelines. Although most physicians know this, we think that there is an inadequacy in clinical practice. More widespread use of CURB-65 and PSI scores is recommended when treating pneumonia.

Ethics Committee Approval: The study protocol was approved by Atatürk University Ethics Committee (10.11.2011/34).

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