Hospital-acquired pneumonia in patients receiving immunosuppressive therapy

İmmunsupresif tedavi alan hastalarda gelişen hastane kökenli pnömoni

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Abstract

Objective: The aims of this study were to determine the clinical success rates, effect of neutropenia on treatment success rates, risk factors related to mortality, and survival in patients who developed hospital-acquired pneumonia (HAP) while receiving immunosuppressive therapy.

Materials and Methods: Forty-three adult patients receiving immunosuppressive therapy who developed HAP were included in this prospective study. Transplantation patients and human immunodeficiency virus (HIV)-positive patients were not included. Antibiotic treatment was managed by a multidisciplinary team. The Kaplan Meier method was used for the survival analysis and Cox regression was used for the identification of mortality-related independent risk factors. The relationship between neutropenia and the clinical success rate was determined using the chi-square test.

Results: Although anti-pseudomonal antibiotics were started empirically in 40 of the 43 patients (93%) at the beginning of the treatment, the most frequently isolated pathogens were *Acinetobacter spp*. and *Escherichia coli.* The success rate at the end of the treatment was 65.1%. The survival rates for the 3rd, 14th, 42nd, and 365th days were 97%, 86%, 58%, and 19%, respectively. Elevated levels of urea [Hazard Ratio=1.01 (95% CI: 1.00–1.02)] and blood glucose [HR=1.01 (95% CI: 1.00–1.02)] were found to be independent risk factors affecting survival. The treatment success rate was higher in patients without neutropenia (n=23) than in those with neutropenia (n=20) (p=0.05).

Conclusion: The treatment success rate was low in patients who developed HAP while receiving immunosuppressive therapy. *(Turk J Hematol 2010; 27: 20-4)*

Key words: Immunocompromised patients, hospital-acquired pneumonia, survival

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Özet

Amaç: Çalışmamızda immunsupresif tedavi alırken hastane kökenli pnömoni (HKP) gelişen hastalarda klinik başarı oranlarını, nötropeninin tedavi başarısına olan etkilerini, mortalite ile ilişkili risk faktörlerini ve survi oranlarını saptamayı amaçladık.

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Yöntem ve Gereçler: İmmunsupresif tedavi alırken HKP gelişen 45 erişkin hasta prospektif olarak çalışmaya alındı. Transplant hastaları ve human immunodeficiency virus (HIV)-pozitif olan hastalar çalışmaya alınmadı.Antibiyotik tedavisi multidisipliner olarak yönetildi. Survi analizlerinde Kaplan Meier, mortaliteyle ilişkili bağımsız risk faktörlerini saptamak için Cox regresyon uygulandı. Nötropeninin klinik başarı oranları ile ilişkisi Chi Square yöntemiyle karşılaştırıldı.
Bulgular: Ampirik tedavi olarak 43 hastanın 40'da (%93) antipseudomonal tedavi başlanmasına rağmen en sık izole edilen etkenler *Acinetobacter spp* ve *Escherichia coli* idi. Tedavi sonu klinik başarı oranı %65.1 idi. Sürvi oranları 3.,14., 42. ve 365. gün sırasıyla % 97, 86, 58 ve 19 olarak bulundu. Üre yüksekliği [Hazard Ratio=1.01 (%95 GA: 1.00-1.02)] ve kan şekeri yüksekliği [HR=1.01 (%95 GA: 1.00-1.02)] surviyi olumsuz etkileyen bağımsız risk faktörleri olarak bulundu. Nötropenik olmayan (n=23) hastalarda klinik başarı oranları nötropenik (n=20) olanlara göre daha yüksek bulundu (p=0.05).
Sonuç: İmmunsupresif tedavi alan hastalarda gelişen HKP'lerde tedavi başarı oranları düşüktür.
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Anahtar kelimeler: İmmunsupresif hasta, hastane kökenli pnömoni, sürvi

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Introduction

In spite of prophylactic measures and the use of wide-spectrum antibiotics, hospital-acquired pneumonia (HAP) is still an important cause of morbidity and mortality in patients receiving immunosuppressive therapy [1].

Algorithms for empirical antimicrobial treatment for suspected pathogens have been developed for some immunosuppressed patient groups. The principle of empirical treatment is based on an anti-pseudomonal approach, and in cases where there is no response and no pathogen is detected, treatment aimed at *Aspergillus spp.* or methicillin-resistant *Staphylococcus aureus* (MRSA) should be initiated. Invasive methods are only recommended in patients who do not respond to the initial antimicrobial treatment. Despite these structured empirical antimicrobial treatments using algorithms and the many invasive and non-invasive methods for pathogen isolation in these patients, mortality rates remain high.

The aims of this study were to determine the clinical success rates, effect of neutropenia on treatment success rates, risk factors related to mortality, and survival in patients who developed HAP while receiving immunosuppressive therapy.

Materials and Methods

Adult patients who developed HAP while receiving immunosuppressive therapy for solid organ tumors and hematological malignancies at the Trakya Universty Medical Faculty Hospital between March 2005 and February 2006 were included in this prospective study.

a) Patients who were known to have no previous pneumonia history and whose chest X-rays showed new infiltration at least 48 hours after hospital admission (that could not be explained otherwise) were diagnosed as HAP if one of the following criteria was present [2]:

• Fever (> 38°C) or hypothermia (≤ 36°C)

• Clinical findings such as dyspnea, coughing, new-onset purulent sputum, or a change in the characteristics of the sputum

• Leukocytosis, leukopenia, and/or elevated C-reactive protein (CRP) (not associated with primary diseases and drug therapy)

• Consolidation findings on the physical examination

• Pathogen isolation in blood culture and/or sputum/transtracheal aspirates

b) In the presence of one or more of the following criteria, patients were diagnosed as having severe HAP [2]:

• Arterial oxygen pressure (PaO2)/fraction of inspired oxygen (FiO2) <250

• Severe sepsis or signs of septic shock

• Bilateral or multilobar involvement, cavitation, abscess or effusion

c) Pneumonias that developed >4 days after hospitalization were classified as "late pneumonia" [2].

d) Neutropenia was defined as either a neutrophil count of $<500/mm^3$ or a neutrophil count of $<1000/mm^3$ that would be expected to decrease [2].

Patients with fever and neutropenia but without new infiltration in the chest X-ray were excluded from the study.

Study Protocol

Patients included in the study were evaluated prospectively. At the planning stage of the study, approval from the local ethics committee was obtained, and each patient (or his/her caregivers) gave informed consent prior to participation in the study. Patients who had had consultations with a pulmonary medicine or infectious disease specialist and who were suspected of having developed HAP according to the above criteria while receiving immunosuppressive therapy were included in this study.

Demographic data, risk factors, and the date of pneumonia development were recorded. Chest X-rays, complete blood counts, biochemistry parameters, arterial blood gases, CRP levels, and cultures of blood, sputum, or tracheal aspirate were studied prior to treatment, and pleural fluid was examined in patients with pleural effusion. The etiologic diagnostic criteria were defined as follows: by isolation of a microorganism in blood cultures or pleural fluid or with isolation of adequate sputum/tracheal samples in a pure or predominant culture, which correlated with the predominant morphology in the gram stain. Computerized tomography scans of the thorax were performed when indicated, and if the pathogen could not be isolated, empiric anti-pseudomonal treatment was initiated in line with national and international guidelines [2,3]. All patients were re-evaluated after 3-5 days to determine the success of the empirical treatment. If the pathogen was isolated, specific antibiotic treatment was initiated. When necessary, the treatment regimen was redesigned in patients receiving empirical

treatment, even if the pathogen was isolated afterwards. Alternative empirical treatment was given to patients who showed no response to the initial empirical antibiotic treatment and in patients in whom the pathogen could not be isolated. Bronchoscopy and bronchial lavage were performed when required, and all of the patients were evaluated by a team of physicians from pulmonary and infectious disease specialties, as well as by the physicians responsible for the patient. Patients showing clinical improvement after treatment were discharged home and reassessed after six weeks. The follow-up period was one year and all patients were contacted by telephone at the end of the year to determine their survival status. In the case of death, the date of death was recorded.

Statistics

Statistical analyses were conducted using the SPSS 9.0 (SPSS Inc.; Chicago, IL, USA) statistical software, and descriptive statistics and frequency analysis were performed. The Kaplan-Meier analysis was used for the analysis of survival. Factors that may have independently affected mortality were assessed using the univariate Cox regression analysis, and after the univariate analysis, the variables with a p value of <0.1 were analyzed using a multivariate Cox regression model. The level of significance was set as $p<0.05$. The relationship between neutropenia and the clinical success rate was studied using the chi-square test.

Results

A total of 43 patients [15 females (34.9%), 28 males (65.1%)] were included in the study. The mean age was 56.58 ± 15.31 years (range: 17-95 years). Severe pneumonia was observed in 27 patients (62.8%) and late pneumonia in 40 patients (93%); the mean number of days before the development of pneumonia was 24.8±20.2. Of the patients, 27 were receiving immunosuppressive therapy for hematological malignancy (14 patients had acute myeloid leukemia, 7 multiple myeloma, 4 non-Hodgkin's lymphoma, 1 myelodysplastic syndrome, and 1 mycosis fungoides) and 16 for solid tumors (9 patients had lung cancer, 3 colon cancer, 2 stomach cancer, 1 breast cancer, and 1 nasopharyngeal cancer). Twenty patients were neutropenic and 23 were non-neutropenic at the time of diagnosis. All the patients were considered to be high-risk patients because they were receiving immunosuppressive therapy and had pneumonia.

The most commonly observed patient-related risk factors were hypoalbuminemia (93%), smoking (46.5%) and advanced age (27.9%) (Table 1).

Of the patients, 42 (97.6%) were given empirical treatment whilst the other patients underwent specific treatment, as the pathogen was isolated before the initiation of treatment. One patient had *Acinetobacter spp.* and was given cefepime in addition to an aminoglycoside.

One non-neutropenic patient who developed HAP early (≤4 days) was suspected of having HAP due to aspiration, and was therefore started on parenteral ampicillin-sulbactam. The other patient had a suspected atypical pathogen and was given ceftriaxone plus clarithromycin.

Table 1. Patient-related risk factors

Risk factors related to patients	N	%
Hypoalbuminemia (< 3.5 mg/dl)	40	93
Smoking	20	46.5
Age >65	12	27.9
Alcohol	8	18.6
COPD	4	9.3
CVD	4	9.3
Diabetes	3	7.0
CRF	2	4.7

COPD: Chronic obstructive pulmonary disease; CVD: Cerebrovascular disease; CRF: Chronic renal failure

Of the 43 patients, 40 were started on empirical anti-pseudomonal treatment (ceftazidime plus aminoglycoside: n=13; ceftazidime plus ciprofloxacin: n=2; piperacillin/tazobactam plus aminoglycoside: n=6; piperacillin/tazobactam plus ciprofloxacin: n=5; carbapenem plus aminoglycoside: n=14).

The pathogen was isolated in 16 (37.2%) of the 43 patients. Three patients had 2 pathogens, and 1 patient had 3 pathogens. The most commonly isolated pathogens were *Acinetobacter spp.* (n=4), *Escherichia coli* (n=3), *Streptococcus pneumoniae* (n=2), *Klebsiella spp.* (n=2), *Serratia spp.* (n=2), *Aspergillus fumigatus* (n=2), MRSA (n=1), *Streptococcus viridans* (n=1), *Staphylococcus epidermidis* (n=1), *Proteus spp.* (n=1), *Stenotrophomonas maltophilia* (n=1), and *Candida spp.* (n=1). Twenty-one pathogens were isolated from 16 patients. Blood culture was positive in 4, sputum/aspirate culture was positive in 10, pleural samples were positive in 5, and bronchoalveolar lavage culture was positive in 2. In 12 patients, the pathogens were isolated before the initiation of empirical treatment. Six of these 12 patients had pathogens that were sensitive to the empirical treatment and the treatment regimen was not changed, whereas the regimen was changed in the other 6 patients. In 3 patients in whom the pathogen could not be isolated before initiation of the empirical antibiotic treatment, the pathogen was isolated at a later time. Glycopeptides (teicoplanin) were started in 6 patients and antifungal therapy was started in line with guidelines in 12 patients (amphotericin B: n=9; liposomal amphotericin B: n=2; Caspofungin: n=1) who were not responding to the initial antibiotic treatment [3].

Clinical success at the end of the treatment was achieved in 28 (65.1%) patients and clinical success at the end of the sixth week (follow success) was achieved in 24 (55.8%) patients. Four patients with clinical success at the end of treatment died due to the primary disease at the end of the follow-up period, and the pneumonia relapsed in 1 patient.

When the 16 patients with isolated pathogens and the 27 patients with non-isolated pathogens were compared, the difference in the rates of clinical success at the end of treatment was significant (p=0.024). The difference between the clinical success rates at the end of the follow-up period was also significant (p=0.013). The success rate was higher in patients in whom the pathogen could not be isolated.

When the 20 neutropenic and 23 non-neutropenic patients were compared, the difference in the rates of clinical success at

the end of treatment was significant (p=0.05), whereas the difference between the clinical success rates at the end of the follow-up period was not significant. The success rate at the end of treatment was higher in patients who were not neutropenic.

Eighteen (42%) of the 43 patients had died by the end of the six-week follow-up period. According to the Kaplan Meier survival analysis, the survival rates for the 3rd, 14th, 42nd, and 365th days were 97%, 86%, 58%, and 19%, respectively.

There were no significant differences between living and exitus patients in terms of age, gender, the mean number of days before the development of pneumonia, severe pneumonia, hypotension, comorbid status, medical treatment, or radiology.

Three patients suffered from pneumonia attacks in the study year while they were in the hospital for the second time to receive immunosuppressive therapy. Two patients developed community-acquired pneumonia, and 11% of the patients developed recurrent pneumonia during the year.

The effect of risk factors on survival was studied using univariate Cox regression analysis. Urea and fasting blood glucose (FBG) were found to be p<0.1 and were re-analyzed using multivariate analysis; urea (p=0.012) and FBG (p=0.004) were found to be the independent factors affecting survival. Elevated levels of urea [hazard ratio (HR) (95% confidence interval): 1.01 (1.00-1.02)] and FBG [HR (95%CI): 1.01 (1.00-1.02)] were the independent risk factors adversely affecting survival.

Discussion

Due to the widespread use of immunosuppressive therapies, hospital-acquired infections in patients receiving immunosuppressive therapy are an important problem for today's clinicians.

The most common pathogen found in our study was *Acinetobacter spp.*, followed by *E. coli.* The most common pathogen responsible for HAP in our previous study (which included patients receiving immunosuppressive therapy and others as well) was also *Acinetobacter spp.* [4]. In another study, *Pseudomonas spp*. was the most common pathogen in patients receiving immunosuppressive therapy who developed HAP; therefore, they are a target for empirical treatment, especially in neutropenic patients [5]. However, *Pseudomonas spp.* were not isolated in our study. Fungal pathogens, in particular *Aspergillus spp.,* were responsible for the HAP in patients with hematological malignancies, and they contributed to a high mortality rate [6]. In patients with a hematological malignancy, the rate of definitive *Aspergillus spp.* was 5-6% [7]. *Aspergillus spp.* was isolated in two patients (4%), and this rate was consistent with the literature.

The treatment success rate was low and the mortality rate high in patients receiving immunosuppressive therapy who developed HAP [8]. We found the clinical success rates at the end of the treatment and at the end of the follow-up period to be 65% and 56%, respectively. In a study comparing the HAP of 20 immunocompetent patients with that of 54 immunocompromised patients, the mortality rates were found to be high in both groups (60% and 50%, respectively) [9].

There are many comparative studies on pathogen isolation in patients receiving immunosuppressive therapy [10]. However, despite the widespread use of non-invasive and/or bronchoscopic methods to isolate pathogens, we could not find any studies in the literature on the relationship between pathogen isolation and clinical success rates in these patients [except the studies involving transplantation and human immunodeficiency virus (HIV)].

In our study, the success rate of the group in which the pathogen could not be isolated was higher than that of the group in which the pathogen was isolated (there were no significant differences between the groups in terms of age, gender, comorbid status, or APACHE II scores).

It is difficult to explain this fact. Are the microorganisms responsible for pneumonia in patients with higher clinical success rates the ones that are difficult to isolate? Are the patient-related factors more important than the pathogen-related factors in clinical success? We think that larger studies should be conducted to answer these questions. However, the higher treatment success rates in non-neutropenic patients than in neutropenic patients may be considered a finding that supports the importance of patient-related factors.

According to the Kaplan Meier survival analysis, the survival rates for the 3rd, 14th, 42nd, and 365th days were 97%, 86%, 58%, and 19%, respectively. We could not find any other study in the literature with such a long follow-up period. The reason for the low one-year survival rates may be the progressive characteristics of the underlying disease in these patients and the toxic and immunosuppressive characteristics of the medications they were receiving. Although the one-year survival rates were low, 11% of the patients had recurrent pneumonia, which indicates the high susceptibility of these patients to serious infections.

We found elevated urea and FBG levels to be the independent risk factors that negatively affected survival. These results show that it is necessary not only to choose the antimicrobial drugs in HAP treatment, but also to address the metabolic problems. Notably, the limitation of our study with respect to the small number of patients may have prevented us from finding other independent risk factors. Elevated urea and FBG levels have been reported in community-acquired pneumonia [11], but we could not find any studies in the literature on the factors affecting the survival of patients receiving immunosuppressive therapy who developed HAP.

In conclusion, the treatment success rate was low in patients who developed HAP while receiving immunosuppressive therapy.

Conflict of interest

No author of this paper has a conflict of interest, including specific financial interests, relationships, and/or affiliations relevant to the subject matter or materials included in this manuscript.

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