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Research Article

The Effects of De-Escalation Under the Guidance of Procalcitonin in Sepsis

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Abstract

Objectives: The present study aimed to monitor the effects of antibiotic use under the guidance of culture and procalcitonin in patients admitted to the intensive care unit (ICU) due to sepsis or septic shock.

Methods: This prospective, cross-sectional, clinical trial was conducted on patients admitted with sepsis or septic shock to Dr. Sadi Konuk Training and Research Hospital Anesthesia and Reanimation Clinic Intensive Care Unit between 01.01.2018 and 30.06.2018. For each patient a record was made of demographic data, reason for hospitalization reasons, PCT, C-reactive protein (CRP), blood leukocyte levels (WBC), lymphocyte percentages, neutrophil percentages, platelet (Plt) counts on admission, in the 72nd hour and on the 7th day, Acute Physiology and Chronic Health Evaluation II (APACHE II) scores at the time of hospitalization and discharge, Sequential Organ Failure Assessment (SOFA) scores and modes of discharge (exitus, recovery). The blood, tracheal aspirate, urine and/or tissue cultures of the patients were followed. The patients who met the criteria underwent DE.

Results: The study included a total of 186 patients, comprising 102 (54.8%) males and 84 (45.2%) females, with a mean age of 66.64±17.6 years. DE was applied to 97 patients (52%) in the first 72 hours. Culture positivity obtained in the first 72 hours was higher in patients who underwent DE (OR=3.1, 1.6-6.5, CI=95%, p=0.001). It was seen that patients who underwent DE with culture positivity had a shorter stay in the intensive care unit (p=0.046). When the procalcitonin levels were analyzed, no statistically significant difference was found between the culture-positive DE group and the culture-negative DE group.

Conclusion: In conclusion, the culture results guide the DE management in patients who are followed up with the clinical picture of infection in the intensive care unit. It is thought that PCT monitoring can be used as a guideline for the discontinuation of broad-spectrum antibiotics in culture-negative infectious patients. There is a need for more extensive studies related to this subject to investigate survival outcomes.

Keywords: Antibiotics, blood culture, de-escalation, intensive care, procalcitonin, sepsis

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For patients diagnosed with sepsis or septic shock, an empirical broad-spectrum therapy with one or more antimicrobial agents is recommended to cover all possible pathogens (bacterial, fungal or viral agents).[1] The majority of current studies have focussed on the development and prevention of antimicrobial resistance.[2,3] Empirical antibiotic regimens should be selected based on the local resistance characteristics, the risk of development of the

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most common pathogens or resistant pathogens associated with the known or suspected infection site.[4] Optimal antibiotic use is especially important in the critical care setting when there is no increased antibiotic resistance and new antimicrobial growth. The results of a previous study showed that 30-60% of antibiotics prescribed in intensive care units are unnecessary, inappropriate or inadequate.[5,6] Epidemiological studies have clearly shown that there is a direct relationship between antibiotic consumption and the emergence and spread of resistant strains in hospitals and intensive care units.[7]

The clinical picture of sepsis, which is considered as a serious infectious manifestation, and infection, requiring intensive care, requires early initiation of appropriate antimicrobial therapy (<1 hour). The close follow-up of the cultures and biomarkers received after the hospitalization of the patients is very important for their survival.[8] However, when the pathogens causing the disease are identified, it is recommended to stop or reduce the use of antibiotics and/or narrow their spectrums. This strategy, which is called "De-escalation therapy (DE)", promotes therapeutic compliance, reduces costs and appears to be quite correct theoretically.[9,10] The de-escalation application has been carried out for many years on the culture basis. However, different opinions have been reported by authors about the implementation of de-escalation without waiting for the culture results because culture examinations require a long time (>72 hrs) and mostly give negative results.[11]

Many different biomarkers can be used to monitor infection therapy in the intensive care unit. PCT is currently one of the most commonly used parameters especially in patients diagnosed with sepsis. Following the determination of appropriate treatment, PCT can also be used to assist decisions related to the duration of antibiotic therapy. The aim of the present study was to monitor the effects of DE management in patients with severe infection, sepsis and septic shock in the intensive care unit.

Methods

The study, which was carried out between 01.01.2018 and 30.06.2018 in Dr. Sadi Konuk Training and Research Hospital Anesthesia and Reanimation Clinic, was planned as a prospective, cross-sectional, clinical study to evaluate the correlation between the PCT levels in the use of antibiotics in patients admitted to the Intensive Care Unit and the culture results defined in the first 72 hours and to evaluate survival in ICU and the length of stay in the intensive care unit.

Inclusion Criteria

Patients over the age of 18 years who were admitted to the intensive care unit with the diagnosis of sepsis or septic shock were included in the study.[12]

Exclusion Criteria

Patients with a history of hospitalization for the last 3 months, prolonged infection such as osteomyelitis, endocarditis and cerebral infection with broad-spectrum antibiotic treatment more than two weeks were excluded from the study.

Data

The demographic data of the patients, reason for hospitalization, PCT, C-reactive protein (CRP), and blood leukocyte levels (WBC), lymphocyte percentages, neutrophil percentages, and platelet (Plt) counts on admission, in the 72nd hour and on the 7th day, Acute Physiology and Chronic Health Evaluation II (APACHE II) scores at the time of hospitalization and discharge, Sequential Organ Failure Assessment (SOFA) scores, and modes of discharge (exitus, recovery) were recorded. The data were obtained from the electronic clinical decision support system (IMDSoft/Metavision5.46.38, EMRall-QlinICU©).

Ethical Approval

The necessary permission for the study was obtained from the hospital Ethics Committee (decision no: 2017-407). Verbal and written consents were obtained from the patients during their hospitalization or from first-degree adult relatives of patients who were not able to append a signature during the hospitalization.

Assessment of Infection Status

The required biological samples (at least 10 ml blood sample of 4 bottles from 2 separate regions, urine, tracheal aspirate, suspected infection focus sampling) were taken as soon as possible (45 minutes) and later from all patients undergoing intensive care due to sepsis or septic shock for the microbiological examinations. The treatment was started with the current sepsis guide in patients admitted to the intensive care unit with the diagnosis of sepsis. A new definition and diagnostic criteria of sepsis were implemented in the study.[13]

Antibiotherapy Algorithm

Considering the role of early antibiotic therapy in critically ill patients with suspected sepsis, antibiotic doses were adjusted according to the patient's kidney and liver functions. Empirical antibiotic regimens were re-evaluated after 72 hours with the microbiological culture results. Patients included in the study were closely monitored and their vital signs, respiratory, hemodynamic and laboratory parameters and changes in their clinical statuses were recorded.

De-escalation

Patients who underwent DE were defined as those who were administered appropriate empirical treatment and met the following three criteria: clinical improvement was defined as the identification of pathogens sensitive to more narrow-spectrum antibiotics and the absence of persistent neutropenia (<1000/mm^3) or other serious immunodeficiencies. In the present study, the empirical antibiotic treatment was started considering possible source site and PCT levels in patients with a body temperature of >380C at the time of admittance. The patients were re-evaluated with the culture and infection parameters after 72 hours. DE and antibiotic changes were made according to the antibiogram results in culture-positive patients after the 72nd hour. In culture-negative patients, DE was applied considering the PCT fall trend, normothermia, vasoactive agent and the need for mechanical ventilation support. The DE applied in the present study, was similar to that performed by Kollef et al.[5]

Statistical Analysis

SPSS 25.0 software (IBM Corporation, Armonk, New York, United States) was used in the analysis of the data. Conformity of the data to normal distribution was evaluated with the Lilliefors corrected Kolmogorov-Smirnov test and the Shapiro-Wilk test, and the homogeneity of variance with the Levene test. The Independent-Samples T test was used in conjunction with the Bootstrap results for the comparison of the two independent groups according to the quantitative data, while the Mann-Whitney U test was used with the Monte Carlo simulation method. The Partial Correlation test was used to examine the correlations of the variables with each other after bringing the main factors under control. In the comparison of categorical variables with each other, the Pearson Chi-Square and Fisher Exact tests were used with the Exact results and the column ratios were compared with each other and expressed according to Benjamini-Hochberg corrected p-value results. The odds ratio (OR) was used with 95% confidence intervals to show how many times those with a risk factor were more than those without. The quantitative variables were shown as mean±SD (Standard Deviation) and median (Minimum/Maximum) values and the categorical variables as number (n) and percentaage (%) in the tables. The variables were examined at 95% confidence level and a value of p<0.05 was accepted as statistically significant.

Results

A total of 186 patients, 102 (54.8%) males and 84 (45.2%) females, with a mean age of 66.64±17.6 years were included in the study. No statistical significance was found in the demographic data. Of the total 186 patients, pneumosepsis in 55 (29.6%) patients was the most common indication for hospitalization. Reproduction was detected in the cultures of 135 (72.5%) patients at the time of hospitalization and 33 (24.4%) of these had the clinical picture of septic shock. The blood cultures were positive in 45 (33.3%) patients. This was followed by DTA (27.4%) and urine culture (14.1%) positivity. The infection source sites (culture results) are shown in Table 1. While 124 (66.6%) of the patients in the study survived, 62 (33.3%) died in the intensive care unit (Table 2).

There was no significant difference between the culture-positive and negative groups in terms of age, SOFA score (admission), APACHE II score (admission), CRP, Pct, WBC, Neu % and Plt counts (p>0.05). Patients with culture positivity in the first 72 hours were determined to have a longer stay in the intensive care unit (p<0.001) (Table 2).

Patients who were observed to have a reproduction in their cultures in the first 72 hours were evaluated for DE. During the hospitalization, the same antibiotherapy was continued until reproduction was observed in the cultures. There were no significant differences in terms of gender, age, intensive care clinical scores, laboratory parameters and survival results in the DE and non-DE groups according to reproduction status (p>0.05). The mean duration of hospital stay of the DE culture-positive group (n:89) was 8.02±6.95 days, and 21.03±18.08 days in the non-DE culture-negative group (n=97). The duration of intensive care unit stay in the DE group was found to be significantly shorter than that of the other group (p<0.001). When evaluation was made within the DE group, the duration of intensive care unit stay [6 (3/43)] of the patients with reproduction was statistically significantly higher than that of the group without reproduction (5 (3/19)) (p=0.046) (Table 3). When the procalcitonin levels were examined, there was no statistically significant difference in patients with reproduction in their cultures.

Table1. Culture results of the patients

Reproduction Site (%)		
Blood	45	33.3
DTA	37	27.4
Urine	19	14.1
Blood+DTA	16	11.9
Urine+Blood	5	3.7
DTA+Blood+Urine	5	3.7
Wound site	8	5.8
Outcome (%)		
Exitus	62	33.3
Survival	124	66.7

DTA: Deep tracheal aspiration.

Table 2. Demographic characteristics of the patients, laboratory parameters and first culture positivity

	Reproduction in the culture (<72 hr.)		p
	Absent (n=51)	**Present (n=135)**	
Exitus	15 (29.4)	47 (34.8)	0.601
Survival	36 (70.6)	88 (65.2)	
Gender			
Female	23 (45.1)	61 (45.2)	1
Male	28 (54.9)	74 (54.8)	
	Median (Min./Max.)	**Median (Min./Max.)**	
Age (Years)	71 (19/94)	65 (18/101)	0.077
Hospitalization duration (day)	6 (3/38)	13 (3/100)	**<0.001**
SOFA Score (admission)	7 (0/16)	8 (0/23)	0.291
APACHE II Score (admission)	19 (8/48)	20 (2/40)	0.440
CRP (admission) (mg/L)	6.5 (0.12/54.78)	11.22 (0.13/46.26)	0.174
PCT (admission) (ng/mL)	0.80 (0.02/56.46)	1.44 (0.02/100)	0.33
WBC (admission)	11.52 (1.65/40.73)	13.16 (0.26/70.78)	0.229
% Neu (admission)	86.3 (42/98)	87.2 (39/97.2)	0.808
Plt (admission)	245 (6/464)	217 (9/762)	0.287

Pearson Chi-Square Test (Exact); Mann Whitney U test(Monte Carlo); *Odds Ratio (%95 Confidence interval); Hr.: hour, Min.: Minimum; Max.: Maximum; SOFA: Sequential Organ Failure Assessment; APACHE: Acute Physiology and Chronic Health Evaluation; CRP: C-reactive protein; PCT: Procalcitonin (ng/mL); Plt: Platelet count (*103µl); WBC: White Blood Cell (*103µl); Neu%: Neutrophil percentage.

Discussion

The use of an antibiotic therapy strategy with PCT monitoring in both initial treatment and the follow-up period is known in the literature.[6,14] Clinical algorithms based on specific PCT values are used as part of the antibiotic management program in various clinical situations and patient populations.[15] In the present study, in the de-escalation procedure performed with the culture antibiogram defined in the first 72 hours in the clinic, PCT, which is a fast-acting infection biomarker, was found to be a similar marker in the de-escalation application.[16]

It is very important to initiate antimicrobial therapy at an early stage and in an appropriate spectrum in patients diagnosed with sepsis or admitted to an intensive care unit due to infection. When confronted with sepsis, the empirical broad-spectrum antimicrobial therapy aims to provide adequate antimicrobial healing and thus reduce mortality. International guidelines for the management of sepsis treatment offer detailed recommendations on antimicrobial therapy, surgical interventions, and combined therapies.[12,16,17] However, there is a risk that empiric broad-spectrum antimicrobial therapy may expose patients to excessive use of antimicrobials.

The emergence of antibiotic resistance requires a more stringent effort to reduce the overuse of antibiotics. This is especially true for acute respiratory infections, where antibiotics are prescribed, although most infections are caused by viruses rather than by bacteria.[19] The rapid dissemination of the problem of antibiotic resistance is a significant threat to the existing antibiotics as well as a threat to the physicians and an important factor affecting the length of hospital stay and increasing the patient's overall healthcare costs. Although there are a number of factors among the main causes of the problem, the primary factor is the widespread and extensive inappropriate use of antibiotics in ICU, where infections are a common daily problem. This results in an intensive focus on the optimization of antibiotic therapy. However, in patients with a high risk of infection and in need of prevention of the dissemination of antibiotic resistance, adequate antibiotic therapy should be provided.

PCT, the precursor of the calcitonin hormone, has been used as a biomarker to aid in the diagnosis of bacterial infection or sepsis, as well as to help distinguish bacterial pneumonia from viral pneumonia and chronic obstructive pulmonary disease (COPD).[6,20,21] In particular, increased resistance to antibiotics, especially to carbapenems, has led to the implementation of antibiotic management programs in hospitals.[7,22] There is little information on antibiotic management programs for critically ill patients. PCT levels increase in the presence of bacterial infections but remain relatively normal in the presence of non-bacterial infections.[23] The main indication for PCT measurement is to aid in the diagnosis of bacterial infection and to guide antibiotic therapy as a marker. The use of PCT has been investigated in various studies in order to initiate, discontinue or increase antibiotic use based on specific algorithms. Attempts have been made to regulate the algorithms for PCT-guided antibiotic therapies in various observational and prospective studies.[24,25] In the present study, there was no statistically significant difference in procalcitonin sensitivity between the groups in terms of de-escalation.

In a multicenter clinical study, Leone et al. demonstrated similar rates of mortality in patients undergoing antibiotic de-escalation and in patients undergoing initial therapy.[26] Despite these different results, some authors support the

Table 3. Clinical and laboratory features of the patients grouped according to the de-escalation application

	Non-de-escalation Group (Group 1)		p	De-escalation Group (Group 2)		p
	No reproduction (<72 Hr) Med (Min./Max.)	Reproduction (<72 Hr) Med (Min./Max.)		No reproduction (<72 Hr) Med (Min./Max.)	Reproduction (<72 Hr) Med (Min./Max.)	
Age (years)	73.5 (20/88)	65 (18/101)	0.262	71 (19/94)	62 (24/89)	0.145
Hospitalization period (Day)	9.5 (7/38)	16 (3/100)	0.081	5 (3/19)	6 (3/43)	**0.046**
CRP (mg/l)	3.74 (0.12/44.1)	12.49 (0.13/42.16)	0.134	10.03 (0.57/54.78)	7.895 (0.23/46.26)	0.944
Pct (ng/ml)	3.77 (0.27/42.78)	1.49 (0.05/100)	0.438	0.7 (0.02/60.83)	0.63 (0.02/63)	0.839
WBC (*103µl)	13.05 (2.71/40.73)	13.31 (3.37/40.77)	0.813	11.14 (1.65/34.6)	11.71 (0.26/70.78)	0.418
% Neu	86.85 (74.6/98)	87.3 (52/97.2)	0.880	85.7 (42/95.8)	86.95 (39/97)	0.901
Plt (*103µl)	249 (34/447)	217 (14/515)	0.760	237 (6/464)	218.5 (9/762)	0.203
				Mean±SD	**Mean±SD**	
SOFA Score (admission)	7 (0/14)	8 (1/23)	0.955	6.97±3.52	7.76±3.40	0.241
APACHE II (admission)	18 (8/48)	21 (2/39)	0.078	20.77±6.79	20.11±6.78	0.706
	n (%)	**n (%)**		**n (%)**	**n (%)**	
Discharge						
Exitus	7 (43.8)	28 (34.6)	0.572	8 (22.9)	19 (35.2)	0.246
Survival	9 (56.3)	53 (65.4)		27 (77.1)	35 (64.8)	
Gender						
Female	8 (50.0)	35 (43.2)	0.784	15 (42.9)	26 (48.1)	0.668
Male	8 (50.0)	46 (56.8)		20 (57.1)	28 (51.9)	

Pearson Chi-Square Test (Exact); Fisher Exact Test (Exact); Independent Samples t-test (Bootstrap); Mann Whitney U test (Monte Carlo); SD.: Standard Deviation; Hr: Hour Min.: Minimum; Max.: Maximum; SOFA: Sequential Organ Failure Assessment; APACHE: Acute Physiology and Chronic Health Evaluation; CRP: C- reactive protein; Pct: Procalcitonin (ng/mL); Plt: Platelet count (*103µl); WBC: White Blood Cell (*103µl); Neu%: Neutrophil percentage.

use of DE as an important strategy against the development of antimicrobial resistance.[27] Similarly, the adequacy of antibiotic therapy is probably associated with decreased mortality in sepsis cases.[28,29] In the present study, results similar to those in the study by Leone et al. were obtained and there was no significant difference between the two groups in terms of mortality.

In many studies, it has been stated that it would be appropriate to use the DE method primarily in ventilator-associated pneumonia (VAP). Numerous studies have been carried out to evaluate the use of this method in large disease groups with different characteristics such as sepsis, septic shock or neutropenia, where empirical antibiotherapy is frequently used. There are suggestions that the use of DE in combination with appropriate guidelines for intensive care patients will be highly effective in reducing antibiotic resistance and health expenses. However, in a meta-analysis, Silva et al.[30] emphasized that there was no direct evidence that antibiotic DE was safe and effective in adults with severe sepsis and septic shock.

The DE treatment regimen is a method that aims to reduce the risk of developing antimicrobial resistance during the effective and balanced treatment of patients receiving antibiotherapy because of infections. This method allows for the use of empirically broad-spectrum antimicrobials and identification of the susceptibility of the microorganism breeding in the culture and then for a quick, effective and reliable reduction/change of the antibiotic regimen. In this way, the long-term exposure to highly effective antimicrobials, to which the microorganism is susceptible, can be shortened. In studies using the DE method, controversial results have been reported in terms of patient outcomes and antimicrobial resistance. The main reason for this is that there are many different DE definitions in the literature. There is no current consensus on the definition of DE, which can be used for all disease groups.[5,9,31] There are studies showing that DE application shortens the duration of hospital stay.[32,33] Consistent with previous findings in literature, the duration of hospital stay of the DE group in the current study was shorter than that of the non-DE group.

Before starting antimicrobial therapy, it is necessary to

obtain suitable cultures to identify the pathogens responsible for septic conditions. The point to be taken into consideration is that sampling does not delay antimicrobial therapy in patients with severe sepsis. A broad-spectrum antimicrobial therapy is often used for adequate antibiotic therapy as soon as possible, as early and adequate antimicrobial therapy reduces mortality rates.[34,35] However, it is often not possible to show the responsible microorganism in the culture. Culture-negative infections are the most difficult cases for the application of the DE method, particularly in the early period (<72 hrs.). In a retrospective study, antibiotic treatment was applied to 75% of VAP patients without reproduction and to 77% of patients with reproduction in their culture.[32] In the present study, reproductions were observed in the cultures of 135 (72.58%) patients who underwent intensive care and the antibiotherapy was continued in the same way in 65 (44.8%) of these patients. In this regard, the study findings are in conformity with the literature.[32,36]

Intravenous empirical antimicrobials should be administered in the first hour of septic shock and severe sepsis. The first antimicrobial therapy should include one or more drugs that are active against all possible pathogens (bacterial, fungal or viral) and penetrate at adequate concentrations to tissues that are thought to be the source of sepsis.[35,37] It has been reported that a delay in effective antibiotherapy increases mortality at the rate of 6.7% per hour.[38] Antimicrobials, however, should be re-evaluated daily for potential de-escalation. PCT or similar biomarkers can be measured to aid the clinician in deciding whether or not to suspend empirical antimicrobial therapy in patients initially suspected of having sepsis but with no subsequent symptoms of infection. PCT monitorization is routinely used in the follow-up of the infection in the clinic, and in this study, it was used to provide guidance for DE in patient groups without reproduction in their cultures. The empirical combination therapy should be applied for up to 3 to 5 days and DE must be performed to the most appropriate treatment when the sensitivity profile is known.[10,39]

Broad-spectrum antimicrobial therapy is defined as an extended and effective combination of antibiotics effective against disease-causing bacteria. Some antibiotic groups (i.e. piperacillin - tazobactam or carbapenems) have a broad antimicrobial spectrum and even their use as monotherapy is considered to be broad-spectrum therapy. It should be noted that carbapenems are the most frequently used antibiotics for nosocomial sepsis in the critical care environment.[40] Different strategies have been developed to solve problems related to the overuse of antimicrobials.[41]

Conclusion

In conclusion, the application of DE to patients admitted to the intensive care unit with either an elevated PCT value or with culture reproduction, decreases the length of stay in the intensive care unit. In the application of DE to cases with culture-negative intensive care infections, other infection indicators should be monitored together with procalcitonin. It is thought that the PCT change may be used as a guide in the discontinuation of broad-spectrum or combined antibiotherapy, especially in culture-negative infectious patients. There is a need for more extensive studies related to this topic to analyse survival outcomes.

Disclosures

Ethics Committee Approval: The study was approved by Local Ethics Committee of Bakırköy Dr. Sadi Konuk Training and Research Hospital (2017-407).

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Conflict of Interest: None declared.

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