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TREATMENT FAILURE AND EMPIRIC ANTIBIOTIC CHOICE FOR HOSPITALIZED PATIENTS WITH COMMUNITY-ACQUIRED PNEUMONIA: B-LACTAM/B-LACTAMASE INHIBITOR COMBINED WITH MACROLID OR FLUOROQUINOLONE ALONE?

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Abstract

Background
A considerable percentage of empirical antibiotic treatment fails in hospitalized patients with community-acquired pneumonia (CAP). β-lactams and macrolid (BLM) combination or respiratory fluoroquinolones (FQ) are the most frequently used in these patients. The aim of the present study is to compare the treatment failure (TF) rates in BLM and FQ treatment and to analyze the predictive factors of TF.

Method
Hospitalized patients who were initially treated with either BLM or FQ were included retrospectively and treatment results of the two regimens were compared.

Results
Of the 144 patients included in the study, the mean age was 67±16 and 102 (71%) were male. Each group constituted of 72 patients. Antibiotic selection did not alter TF rates, length of stay (LOS) and 30-day mortality. Baseline higher levels of leucocytes, neutrophils to lymphocytes ratio (NLR), C-reactive protein (CRP), BUN/albumin, lactate dehydrogenase/aspartat aminotransferase (LDH/AST) levels and pneumonia severity index (PSI) scores were detected as predictors of TF.

Conclusion
Empirical treatments with either BLM or FQ do not correlate with TF, LOS and 30-day mortality. NLR, BUN/albumin and LDH/AST may suggest TF. These inexpensive and easily-reachable parameters have the potential as predictors of the treatment outcome in CAP.

Keywords: Lactate Dehydrogenase; Lymphocytes; Neutrohils; Pneumonia.

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1. Introduction

Pneumonia is a serious health-issue with an incidence of 5-11/1000 adults every year [1]. Community-acquired pneumonia (CAP) is known to be one of the most frequent cause hospital admissions and one of the most leading causes of mortality worldwide [2,3].

The initial treatment of CAP is empirical which may fail in 6-24% of hospitalized patients [4,5]. Treatment failure (TF) results with complications, longer hospitalization and higher mortality [4,6]. Empirical regimen selection is a challenging issue. Empirical treatment is desired to cover a broad microbiologic spectrum, but drug resistance is desired to be prevented. For hospitalized patients with CAP, the current guidelines recommend respiratory fluoroquinolone (FQ) or β-lactam plus macrolide (BLM) [4,7].

Contradictive results have been reported in studies that compare the effectiveness of these regimens. Several studies have found FQ treatment to be more efficacious with lower failure rates. [8,9]. However similar treatment outcome results have been reported in different studies [10,11]. In most studies, overall mortality rates and length of hospital stay (LOS) are not statistically significant [10,11]. In contrast, severe CAP patients are asserted to have lower mortality with BLM [12]. Limited data on predictive factors for TF are defined. Advanced age, male gender, radiological extensity, co-morbidities have been attributed as predictors of TF [5,6].

The aim of the present study is to compare treatment outcome with empirical BL-M and FQ and to analyze the predictors of TF in these patients.

2. Materials and Methods

The present study is a single-centre, retrospective, observational one, designed in a 34-bed capacity sub-clinic of a respiratory teaching and research hospital.

Patient Selection

A hospital database system search was conducted via International Classification of Diseases 10th version codes of J18 (pneumonia) among hospitalized patients between January 2016 and January 2017. All patients' clinical files were investigated to verify a diagnosis of CAP. Patients receiving either BLM or FQ empirical treatment were included in the study. Patients with hospital acquired pneumonia and who have taken BLM or FQ treatment before hospitalization were excluded (Figure 1).

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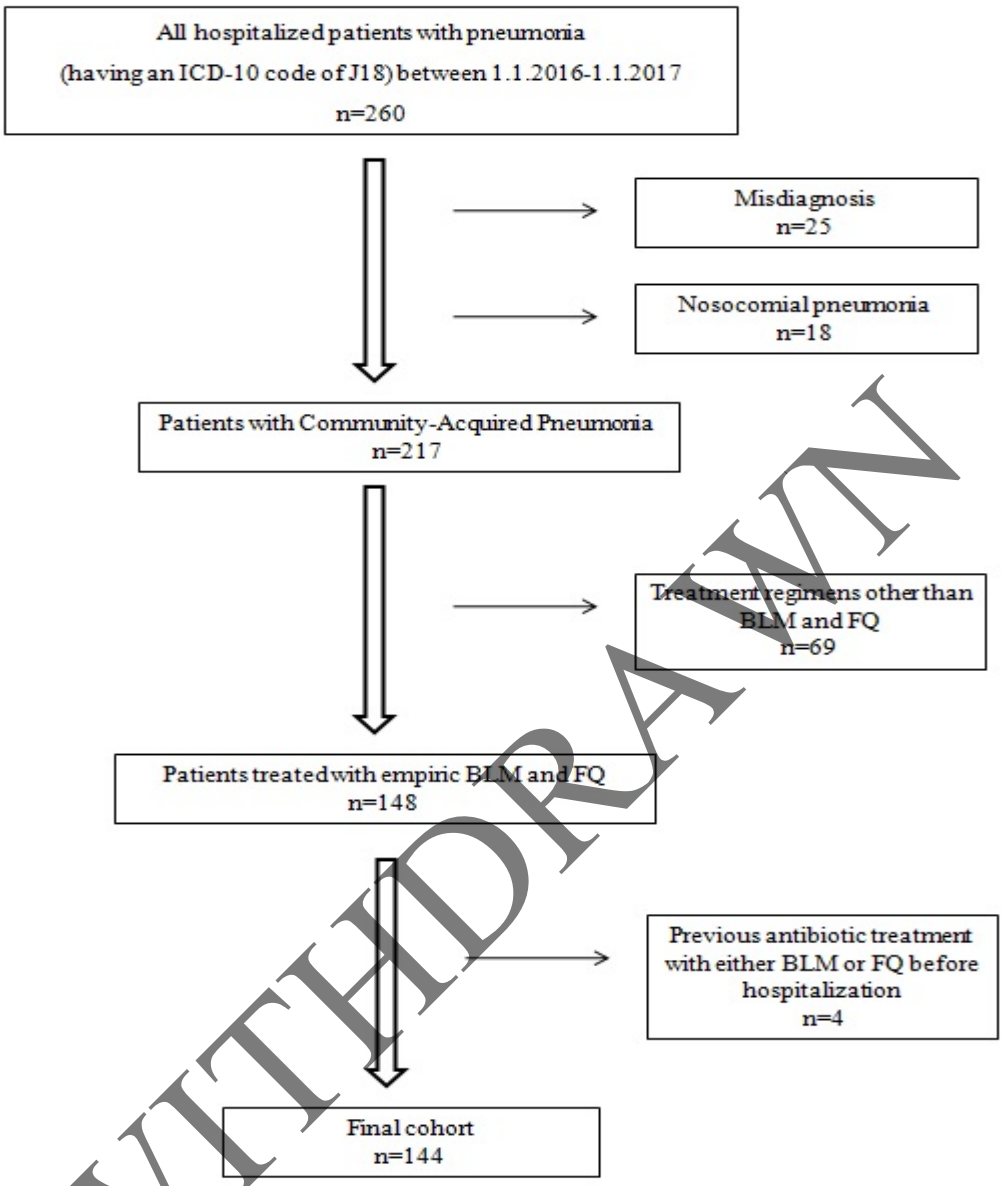

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Figure 1: Flowchart of the patients included in the study

Definitions

CAP: Compatible symptoms (cough, sputum, shortness of breath), physical examination findings and imaging findings on chest X-ray or thorax computerized tomography (CT) [7].

Treatment failure (TF): Death, intensive care unit (ICU) treatment or mechanical ventilation need, antibiotic alteration due to inadequate regression or progression in clinical status, laboratory or radiological findings [13].

Antibiotic Regimens: BLM: penicillin, amoxicillin, amoxicillin plus clavulanate, or a third-generation cephalosporin and third generation cephalosporin combined with azithromycin, clarithromycin and erythromycin.

FQ: levofloxacin, moxifloxacin

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Data Collection

Age, gender, complaints (shortness of breath, cough, sputum, fever, chest pain, hemoptysis), physical examination findings at presentation, co-morbid diseases, baseline complete blood count parameters of leucocytes (/µL), hemoglobin (g/dl), platelet (/µL), neutrophils (/µL) and lymphocytes (/µL), C-reactive protein (CRP) (mg/L), glucose (mg/dL), blood urea nitrogen (BUN) (mg/dL), aspartat aminotransferase (AST) (U/L), lactate dehydrogenase (LDH) (U/L), albumin (g/dl), sodium (mEq/L) levels were recorded. Radiological findings of either unilateral or bilateral involvement and the presence of pleural effusion were investigated. Neutrophils to lymphocytes ratio (NLR), LDH/AST ratios and pneumonia severity index PSI scores were calculated [7]. NLR values categorized with a cut-off value of 11.12 [14]. BUN to albumin ratios were analyzed [15]. Treatment results of initial antibiotic regimens were investigated, Mortality was questionnaired via National Death Database (www.obs.gov.tr).

Study Protocol

Patients were divided into two groups according to empirical antibiotic regimens: BLM and FQ groups. Recorded parameters, treatment results, LOS and 30-day mortality were compared between the groups. Also, predictive values of recorded parameters on treatment outcome were analyzed for all patients.

Ethics committee approval was received for this study from the ethics committee of local research committee of Sureyyapasa Chest Diseases and Thoracic Surgery Training and Research Hospital Date: 09.05.2019, protocol number: 116.2017.088.

Statistical Analysis

All statistical analyses were conducted using a statistical software package (SPSS for Windows, version 16.0; SPSS Inc.; Chicago, IL, USA). Quantitative data are expressed as mean ± standard deviation (SD) and qualitative data are expressed as frequencies. Independent sample t-test was used for the comparison of averages and chi-square test was used for the categorical variables. A p value of ≤ 0.05 was considered to be significant.

3. Results

Of all the 144 patients included, the mean age was 67±16 and 102 (71%) were male. The most common symptoms at presentation were shortness of breath, cough, sputum and fever. Airway disease (asthma or COPD) was present in 79 (55%), diabetes mellitus in 30 (21%) congestive heart failure in 22 (15%) of the patients. The average score of PSI was 97±33.

In each group, seventy-two patients were initially treated with BLM and 72 with FQ. Demographics, complaints at presentation, additional diseases, physical examination findings, baseline laboratory findings and PSI scores were similar between the two groups ($p>0.05$). Empirical antibiotic treatment failed in 23 (16%) patients. These failures were almost equally distributed in the two groups of regimens: BLM in 12 (16.7%) and FQ in 11 (15.3%) patients ($p=0.998$). 30-day mortality was recorded in 13 (9%) patients; initial antibiotic regimen did not correlate with 30-day mortality ($p=1.000$). The duration of hospitalization was similar between the treatment groups (8.4±4.2 vs. 8.5±4.4 days, $p=0.939$) (Table 1).

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Table 1: Characteristics and baseline laboratory parameters of the patients according to treatment groups

	All patients	BLM	FQ	*p*
	n=144	n=72	n=72	
Male gender (n,%)	102 (71)	52 (72)	50 (69)	0.855
Age (years)	68±16	66±16	69±16	0.414
Co-morbid diseases				
DM (n,%)	30 (21)	17 (24)	13(18)	0.539
Asthma or COPD (n,%)	79 (55)	40 (56)	39 (54)	0.998
CHF (n,%)	22 (15)	9 (13)	13 (18)	0.488
SVD (n,%)	13 (9)	7 (10)	6 (8)	1.000
Malignancy (n,%)	17 (12)	6 (8)	11 (15)	0.302
Laboratory findings				
Leucocyte (/µL)	13.8±7.5	13.6±7.4	14.1±7.7	0.682
Hemoglobin (g/dl)	12.1±1.9(/µL)	12.4±1.6	11.8±2.1	0.052
PLT (/µL)	287±140	268±139	306±139	0.099
NLR	12.7±14.1	11.8±12.4	13.4±15.6	0.482
CRP (mg/dl)	140±116	267	306	0.730
Glucose(mg/dL)	147±69	146±72	147±65	0.930
BUN(mg/dL)	24.4±7.4	22.8±11.9	25.9±15.9	0.181
AST(U/L)	35±29	36±33	35±26	0.937
LDH(U/L)	294±178	305±186	282±171	0.512
Albumin(g/dl)	3.4±0.6	3.5±0.5	3.4±0.6	0.165
BUN/albumin	7.5±4.9	6.8±4.0	8.1±5.4	0.128
LDH/AST	10.9±7.0	10.6±4.7	11.2±8.9	0.634
Sodium(mEq/L)	135±4.7	135±0.5	136±4.9	0.332
Radiology				
Bilateral involvement (n,%)	42 (29)	21 (29)	21 (29)	1.000
Pleural effusion (n,%)	46 (32)	24 (33)	22 (31)	0.858
PSI score	97±33	91±33	103±32	0.083
Treatment failure (n,%)	23 (16)	12 (16.7)	11 (15.3)	0.998
30-day mortality (n,%)	13 (9)	7 (9.7)	6 (8.3)	1.000
Length of stay (day)	8.4±4.3	8.4±4.2	8.5±4.4	0.939

AST:aspartat aminotransferase, BLM: β-lactams and macrolid, BP:blood pressure, BUN:blood urea nitrogen, CHF: congstive heart failure, COPD: chronic obstructive pulmonary disease, CRP:C-reactive protein, DM:diabetes mellitus, FQ: fluoroquinolone, LDH:lactate dehydrogenase, NLR: neutrophils to lymphocytes ratio, SVD: serebrovascular disease, PLT:platelet

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The analysis of predictive factors for TF revealed no relationship between symptoms at presentation and additional diseases (p>0.05). Higher levels of leucocytes (17.8±5.7 vs. 13.1±7.6 p=0.001), NLR (22±18 vs. 10±10, p=0.002), CRP levels (187±122 vs. 131±114, p=0.011), higher BUN/albumin (10.2±5.6 vs. 6.9±4.5, p=0.003) and LDH/AST levels were higher in patients with TF (14.1±8.4 vs. 10.2±5.5, p=0.03). Eight out of 94 patients having NLR values lower than 11.12, and 12 out of 50 patients higher than 11.12 experienced TF (p=0.02). PSI scores were higher in patients with TF (118±36 vs. 93±31, p=0.009) (Table 2).

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Table 2: Predictive factors for treatment failure

	Treatment success n=121	Treatment Failure n=23	P
Male gender (n,%)	87 (72)	15 (65)	0.615
Age (years)	67±16	72±13	0.125
Co-morbid diseases			
DM (n,%)	27 (22)	3 (13)	0.439
Asthma or COPD (n,%)	65 (54)	14 (61)	0.649
CHF (n,%)	17 (14)	5 (22)	0.350
SVD (n,%)	10 (8)	3 (13)	0.437
Malignancy (n,%)	12 (10)	5 (22)	0.151
Laboratory findings			
Leucocyte(/µL)	13.1±7.6	17.8±5.7	**0.005**
Hgb (g/dl)	12.1±1.9	11.9±2.0	0.735
PLT (/µL)	284±144	302±117	0.580
NLR	11.1±12.6	21.5±18.7	**0.002**
CRP (g/dl)	131±114	187±122	**0.037**
Glucose (g/dl)	147±72	144±54	0.841
BUN (mg/dl)	23±13	31±17	**0.008**
AST (U/L)	34±28	40±33	0.382
LDH (U/L)	271±120	401±320	**0.004**
LDH/AST	10.2±5.5	14.1±8.4	**0.030**
Albumin (g/dl)	3.5±0.6	3.2±0.5	0.068
BUN/albumin	6.9±4.5	10.2±5.6	**0.003**
Sodium (mEq/L)	135±4.5	134±5.3	0.155
Radiology			
Bilateral involvement (n,%)	38 (31)	4 (17)	0.217
Pleural effusion (n,%)	39 (32)	7 (30)	1.000
PSI score	93±31	118±36	**0.009**
30-day mortality (n,%)	4 (3)	9 (39)	<0.001
Length of stay (day)	7.6±2.9	12.8±7.1	<0.0001

AST:aspartat aminotransferase, BP:blood pressure, BUN:blood urea nitrogen, CHF: congstive heart failure, COPD: chronic obstructive pulmonary disease, CRP:C-reactive protein, DM:diabetes mellitus, LDH:lactate dehydrogenase, NLR: neutrophils to lymphocytes ratio, SVD: serebrovascular disease, PLT:platelets

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4. Discussion

The present study represents a comparison of treatment results of FQ and BLM in hospitalized CAP patients. The study revealed an indifferent TF rate of 16% with either BL-M or FQ treatment. Antibiotic choice did not make any difference in treatment outcome, LOS and 30-day mortality. TF correlated with baseline leucocytes, NLR, CRP, BUN/albumin, LDH and LDH/AST levels. To our knowledge, BUN/albumin, LDH and LDH/AST levels have been shown as predictors of TF in the literature previously.

The Infectious Diseases Society of America and the American Thoracic Society guidelines for patients with CAP conclude respiratory FQs to be equally effective with BLM. Either of these treatments is suggested to be preferable in hospitalized patients [4]. In general, BLM is effective on most of the pathogens responsible for CAP [16]. Once daily administration and a possible coverage of a broader spectrum are the advantages of FQs. Drug resistance rate of FQs is reported to be low among common respiratory pathogens [9].

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In China, among 18.043 hospitalized CAP patients, FQs were the mostly-preferred regimen [6]. Simonetti et al. selected FQ treatment more frequently than BLM [17]. In the report of Doruk et al. in 2009, BLM was the first line antibiotic regimen and FQ, the second line [14]. The different empirical antibiotic selection may have an unintended consequence of a delayed diagnosis of tuberculosis in our country. In present study including one year hospitalized CAP patients the most common preferred regimens were equal.

Rates of TF are between 6-24% in hospitalized CAP [4,5]. A multicentre prospective study in Spain reported 15.1% of TF. A multicentre analysis from Turkey has documented TF in 11% of the patients [13]. In China, initial antibiotic treatment regimen failed in 22.4% of the patients [6]. TF rates of the claimed two most-preferred regimens in present study are thus compatible with the literature.

The comparison of treatment results of the two empirical antibiotic regimens is contentious. The probable differences in the frequency of pathogens in different geographical areas, different study populations and study designs complicate reaching a consensus on a potential superiority of one of these regimens to its counterpart [1]. In 2004, a multicentre study by Menéndez et al. reported that FQ treatment is an independent factor for lower TF [5]. Two meta analyses in 2008 and in 2015, have revealed better clinical outcome in favor of FQ therapy [9,19]. Again, a recent study has reported less common clinical failure with FQ monotherapy [8]. In contrast, Ott et al. has compared moxifloxacin and BL-M therapies concluding no significant treatment outcome difference [10]. The current study has found similar TF rates with either BLM or FQ. One reason for this result may be the previously lower preference in favor of FQ treatment in our country. Less frequent usage may have suppressed pathogen resistance. The other reason may be the possibility of different pathogens in our country. The last potential explanation for the deviant results may be the different designs of the studies. We believe that prospective multi-center studies are needed in this regard.

The duration of hospitalization and rates of mortality are more commonly reported to be similar with the two regimens [8,9,19,20]. A meta-analysis has concluded that the mean duration of hospital stay is not altered with the preferred antibiotics [9]. In line with the literature, the present study also has revealed LOS and mortality rates to be similar in these patients.

Leucocytes, CRP levels and PSI scores have previously been found as correlatives of TF in several studies. Menendez et al. has reported leucopenia as a predictive factor for TF [5]. Higher leucocytosis is defined as a predictive for TF [17,21]. Gündüz et al.'s study found no difference in CRP levels at admission between TF and TS groups [13]. In contrast, higher CRP levels are shown to be as a demonstrator of deterioration with CAP in more severe and more risky patients [21,22]. Higher PSI score has been found to be the only significant parameter in the multicenter study of Gunduz et al. [13]. Similarly, PSI class was found to increase risk [5]. The present study also suggested that higher CRP and leucocytes and PSI scores are associated with TF of the regimens in question.

The ratio of neutrophils to lymphocytes is an easily detectable and inexpensive method which is recently reported to have prognostic value in several diseases [23]. A recent prospective study in elderly CAP patients, NLR values better predicted 30-day mortality than did PSI, leucocytes and

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CRP values. Patients having NLR values lower than 11.12 are suggested to be early-dischargeable. It was found that the higher were the values of NLR the more frequent was the 30-day mortality [14]. In parallel, the present study suggests that NLR values higher than 11.12 experience more frequent TF. Different from the aforementioned study, all adult patients were included in current study. So as an inexpensive and easy method, higher NLR values may require a closer monitoring or a broader spectrum antibiotic treatment. We propose that it may be a research subject for future studies.

BUN/albumin ratio is determined to be a demonstrator of severe CAP and short-term mortality [15]. Also this ratio has been shown to predict long-term mortality in CAP patients [24]. The current study additionally demonstrated this ratio as a predictor of TF in hospitalized CAP patients. Further studies are needed to analyze the clinical significance of this ratio and if verified, to specify a cut-off value.

LDH is a cytoplasmic enzyme present in major organs. Detection of extracellular LDH reflects cell damage or death. In pulmonary diseases as well as infectious lung diseases; bronchopneumonia, *pneumocystis jirovecii* pneumonia (PJP) and tuberculosis, LDH levels may increase [25]. In adolescents and adults, high LDH levels are taken as an indication to start steroid therapy in *mycoplasma pneumonia* pneumonia. Furthermore, higher LDH levels are reported to predict in-hospital mortality in severe CAP patients [26]. The present study also revealed that higher levels of LDH predict TF in hospitalized CAP patients. Quist et al. compared LDH levels of PJP, tuberculosis and bacterial pneumonia and reported that LDH levels increase more significantly in PJP. They also reported that LDH/AST levels may increase without clinical significance between the etiologies of infection [27]. We assume that to differentiate LDH specificity other than lung diseases, LDH/AST ratios may be more useful. The present study has revealed that higher levels of LDH/AST are related to more frequent TF. This ratio, if supported by novel investigations, may be an inexpensive method for detecting patients of higher risk.

The current study has several limitations. First, it was a retrospective, single-center study. Secondly, TF was not categorized as ‘early` and ‘late’ failure Lastly, a multivariate analysis could not be performed due to the inadequate number of patients with TF. However, the strength of the study is that it is designed in a reference center with close monitoring by chest specialists. One other important strength of the study is that novel parameters have been investigated to cast light upon future studies.

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5. Conclusions

In conclusion, TF, LOS and 30-day mortality rates are not correlated with the treatment selection of either BLM or FQ. Higher leucocytes, CRP, NLR, BUN/albumin, LDH/AST levels and PSI scores are predictive factors of TF in patients with hospitalized CAP.

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WITHDRAWN

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