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Factors associated with early treatment failure in adult hospitalized patients with community-acquired pneumonia

Faktori udruženi sa ranim neuspehom u lečenju odraslih hospitalizovanih bolesnika sa vanbolnički stečenom pneumonijom

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Abstract

Background/Aim. Early treatment failure (ETF) in patients hospitalized for community-acquired pneumonia (CAP) is associated with prolonged hospitalization, increased risk of mortality and high treatment costs. The aim of this study was to analyze the relative importance of factors influencing ETF in hospitalized adult patients with CAP that are still insufficiently explored. **Methods.** A retrospective case-control study was carried out on a sample of 126 adult patients treated for serious CAP at the Clinic for Pulmonary Diseases, Clinical Center of Serbia, Belgrade, Serbia, during the 5-year period (2007–2011). The cases (n = 63) were consecutive patients with ETF, observed within the three days upon the admission to hospital, while the control group consisted of the equal number of randomly selected patients without such an outcome. The association between potential risk/protective factors and ETF was estimated using logistic regression analysis. **Results.** The coexistence of gastrointestinal disorders [adjusted odds ratio (OR) 18.83, 95% confidence interval (CI) 1.15–309.04], higher CURB-65 (C – confusion; U – urea 7 mmol/L; R – respiratory rate ≥ 30 breaths/min; B – systolic blood pressure < 90 mmHg or diastolic blood pressure ≤ 60 mmHg; 65 – age ≥ 65 years) score on admission (adjusted OR 2.57, 95%CI 1.05–6.25), initial use of nonsteroidal anti-inflammatory drugs (NSAIDs) in hospital (adjusted OR 38.19, 95%CI 3.61–404.51) and previous outpatient use of inhaled corticosteroids (adjusted OR 22.41, 95%CI 1.03–489.06) were found to be significant risk factors for ETF. On the other hand, older age and use of antibiotics before the hospitalization were associated with a significantly lower chance of experiencing ETF, reducing the odds for 98% and almost 90%, respectively. **Conclusion.** The avoidance of the routine in-hospital use of NSAIDs as well as the outpatient use of appropriate antibiotics may be beneficial for patients hospitalized for CAP in terms of reducing the risk of ETF. The CURB-65 score could be a better predictor of ETF than Pneumonia Severity Index. Further prospective studies are required to confirm these findings.

Key words:
pneumonia; hospitalization; treatment outcome; risk factors; comorbidity.

Apstrakt

Uvod/Cilj. Rani neuspeh u lečenju (*early treatment failure* – ETF) hospitalizovanih bolesnika sa vanbolnički stečenom pneumonijom (*community-acquired pneumonia* – CAP) udružen je sa produženom hospitalizacijom, većim rizikom od smrtnog ishoda i visokim troškovima lečenja. Cilj ove studije bio je da analizira relativni značaj faktora koji utiču na pojavu ETF kod odraslih hospitalno lečenih bolesnika zbog CAP, a koji još uvek nisu dovoljno istraženi. **Metode.** Sprovedena je retrospektivna studija tipa slučaj-kontrola na uzorku od 126 odraslih bolesnika lečenih zbog težih oblika CAP na Klinici za plućne bolesti Kliničkog centra Srbije u Beogradu, u periodu 01.01.2007–31.12.2011. godine. „Slučajeve" su činila 63 uzastopno odabrana bolesnika sa uočenim neuspehom u lečenju u toku prva tri dana nakon prijema u bolnicu, dok se kontrolna grupa sastojala od identičnog broja nasumično izabranih bolesnika kod kojih takav ishod nije zabeležen. Povezanost između potencijalnih faktora rizika, odnosno protektivnih faktora i ETF procenjena je logističkom regresionom analizom. **Rezultati.** Udružena gastrointestinalna oboljenja [korigovani *odds ration* (OR) 18,83, 95% interval poverenja (CI) 1,15–309,04], viši CURB-65 (C – konfuzija; U – urea 7 mmol/L; *R* – frekvencija disanja ≥ 30 udisaja/min; B – sistolni krvni pritisak < 90 mmHg ili dijastolni krvni pritisak ≤ 60 mmHg; 65 – životno doba ≥ 65 godine) skor na prijemu (korigovani OR 2,57, 95% CI 1.05–6.25), inicijalna primena nesteroidnih antiinflamatornih lekova (NSAIL) u bolnici (korigovani OR 38,19, 95% CI 3,61–404,51) i prethodno ambulantno lečenje inhalacionim kortikosteroidima (korigovani OR 22,41, 95% CI 1,03–489,06), predstavljali su značajne faktore rizika za pojavu ETF. S druge strane, starije životno doba i upotreba antibiotika

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zbog iste infekcije pre prijema u bolnicu bili su povezani sa znatno nižim rizikom od razvoja ETF, smanjujući pritom šansu za 98%, odnosno za blizu 90%. **Zaključak.** Izbegavanje rutinske primene NSAIL u bolničkim uslovima i upotreba odgovarajućih antibiotika pre hospitalizacije mogu biti korisni za bolesnike obolele od CAP kod kojih je indikovano bolničko lečenje u smislu smanjenja rizika za nastanak ETF. CURB-65 skor na prijemu u bolnicu može biti bolji prediktor ETF od indeksa težine pneumonije. Dodatne prospektivne studije su potrebne kako bi se potvrdili ovi nalazi.

Ključne reči:
pneumonija; hospitalizacija; lečenje, ishod; faktori rizika; komorbiditet.

Introduction

In spite of recent progress in prevention, diagnosis and therapy of community-acquired pneumonia (CAP) remain serious public health problem worldwide. It is due to the relatively high incidence of CAP and its significant association with morbidity, mortality, reduced quality of life as well as increased healthcare costs, mainly in hospitalized older patients suffering from substantial comorbidities [1–8]. However, serious CAP requiring hospitalization and/or admission to the intensive care unit (ICU) also increases the risk of the aforementioned worse health outcomes even in younger adults without underlying chronic disorders [2, 4, 5, 7, 8].

While the majority of hospitalized patients with CAP achieve an adequate clinical response to initial empiric antibiotic and supportive therapy, some of them experience an early treatment failure (ETF) within 72 hours after initiation of the treatment, developing progression of underlying infection [9–15]. ETF inevitably leads to the more extensive use of microbiological and diagnostic tests, change in antimicrobial treatment and use of invasive therapeutic procedures, followed by prolonged hospitalization and much higher treatment costs [9, 11, 13, 14]. Moreover, there is a piece of evidence supporting a strong association between ETF and increased mortality [9, 10, 12–16]. As a consequence of considerable diversity in criteria used to define early CAP non-responders in hospitalized patients, there is a marked heterogeneity in reported prevalence of ETF with an average rate of 10–15% [9–13, 15, 16]. These criteria were mainly based on the deterioration of nonspecific clinical and radiological parameters previously used to diagnose CAP or the necessity to change antibiotic(s) [9–16]. However, previous studies showed that risk of death was significantly higher, up to five times, in patients experiencing ETF in comparison to satisfactory responders, regardless of criteria that were used to distinguish these two populations of inpatients with CAP [9, 10, 12, 13, 15–17].

Pursuant to the foregoing, adequate response to initial therapy is being regarded as essential for successful treatment of severe CAP. Therefore, a number of prior observational studies were particularly focused on determination of factors contributing to ETF [9–18]. According to their results, the occurrence of ETF can be influenced by factors related to characteristics of the pathogen, host and applied antimicrobial therapy, including also their mutual interactions. Many of these factors are well recognized, such as high-risk CAP according to Pneumonia Severity Index (PSI) scoring system (i.e., risk class IV or V) [12, 15, 16], multilobar lung involvement, pleural effusion, presence of pulmonary cavitations on radiological examination, CAP caused by *Legionella* or by Gram-negative bacteria, aspiration pneumonia, leucopenia, hyponatremia, high blood level of C-reactive protein (CRP), procalcitonin (PCT) and interleukin-6 (IL-6) in the first 24 hours upon admission to hospital, then coexisting malnourishment, malignant disease, neurological disorders and renal failure as well as initial use of inappropriate antibiotics (which is not aligned to susceptibility testing of causative pathogens) [12–18]. On the other hand, older age (≥ 65 years) [16], previous vaccination against influenza [12] and initial empiric use of moxifloxacin or combination of beta-lactam and macrolide antibiotics [11], may significantly reduce the risk of ETF. However, the literature data confirming consistency of clinical relevance of all aforementioned factors as well as the studies determining the relevance of the other potential risk and protective factors for ETF in hospitalized adults with CAP are lacking. Moreover, only a handful of previous studies [12, 15, 18] additionally addressed the factors contributing to late (after 72 hours) and/or any (early or late) treatment failure. These studies revealed not only the different factors associated with the observed outcomes (e.g., liver failure as a significant risk factor for late and any type of failure, and chronic obstructive pulmonary disease and initial use of levofloxacin as the important protective factors for any type of failure [12]), but also the differences in the strength of association for factors found to have a significant influence on the occurrence of ETF.

Thus, the purpose of this study was to analyze relative importance and potential synergistic effects of factors affecting the phenomenon of ETF in hospitalized adult patients with CAP that are still insufficiently explored.

Methods

Study settings

This study was conducted among adult patients who were admitted to the Clinic for Pulmonary Diseases (CPD), Belgrade, Serbia, due to serious CAP during the 5-year period (from January the 1st, 2007 to December the 31st, 2011). CPD, as a reference institution for lung disease operating within Clinical Center of Serbia (CCS), provides tertiary care to all adult inhabitants of city of Belgrade, and also to entire adult population of the Republic of Serbia as needed (patients referred to no CPD due to serious pulmonary disorders that can't be adequately treated in local hospitals). The diagnosis of CAP requiring hospitalization was based on typical clinical, laboratory and radiological signs according to internationally established standards [19], and left at the discretion of the attending physicians. All relevant data referring to demographic and clinical characteristics of patients, results of performed diagnostic exams as well as information on applied treatments and observed outcomes were gathered from

the patients' files. The study protocol had been approved by Ethics Committee of the CCS before the investigation begun.

Study design

A case-control design was chosen for this retrospective observational study. Based on outcome of interest, i.e. ETF in hospitalized patients with CAP, all participants were separated into two groups, as following: the cases were all patients from the study population in whom ETF was observed within the three days upon the admission to hospital, whereas the control group comprised of the equal number of patients treated in the same facility, but without such an outcome. Cases and controls were individually matched by age (± 1 year), gender and time of hospitalization (± one month), and then compared regarding the differences in the prevalence of exposure to putative risk factors. In addition, two groups were also compared in terms of differences in the death rate and the length of hospital stay. For each case, one of the matched controls was randomly chosen to participate in the study.

Pursuant to the recent study by Akram et al. [20], the identification of patients with ETF included the clinical instability according to standardized and validated Halm's criteria [21] in conjunction with any increase of CRP levels or decrease by less than 50% on third or fourth hospital day in relation to the values measured on admission to hospital, given that combined set of diagnostic parameters was found to be of greatest accuracy in predicting certain worse health outcomes [mortality, use of mechanical ventilation (MV) or vasopressor therapy, complicated pneumonia as well as their combination] in adult inpatients with CAP. In the present study, clinical instability was ascertained if any of the Halm's criteria had been "de novo" persistently abnormal for up to 72 hours upon the admission, i.e., temperature level above 37.8°C, pulse rate of over 100 beats *per* minute, systolic blood pressure of less than 90 mmHg, respiratory rate above 24 breaths *per* minute, oxygen saturation level of less than or equal to 90% or arterial partial pressure of oxygen below 8 kPa, altered mental function or inappetence [21].

Study population

A total of 126 consecutive adult patients (18 years of age and older) who required the hospital treatment of CAP during the observational period and underwent empiric antibiotic therapy within the 24 hours of admission lasting for at least two days, were enrolled in this study. As mentioned above, the allocation ratio of participants considering their outcome status was 1:1 (i.e. 63 patients were cases and 63 patients were randomly selected for the control group). All patients were referred to the CPD by their respective general practitioners and other medical doctors working at the primary health care facilities in the city of Belgrade and treated according to local CAP protocol of the CPD.

In order to distinguish the patients with high risk of nosocomial or health care-associated pneumonia due to the significant differences in their etiology, therapeutic approach and the prevalence of poor health outcomes compared to CAP [22], those who met any of the following criteria were not considered eligible for the study: transfer of patients from other hospitals or other wards who developed pneumonia after more than two days of admission, previous hospitalization for two or more days within the 90 days of pneumonia onset, use of intravenous antibiotics, chemotherapy or invasive procedures in the preceding 30 days, referral from nursing homes, actual hemodialysis treatment in health facilities, and underlying immunodeficiency due to any reason (e.g. malignant disease undergoing chemo- and/or radiotherapy, acquired immunodeficiency syndrome (AIDS), terminal stage of chronic progressive illness, use of long-term systemic corticosteroid therapy or other immunosuppressant drugs, etc.). Exclusion criteria also included patients who died due to any reason within the first two days of admission (that could be related to extremely severe, progressive infection with high risk of mortality despite the use of antibiotics), those with documented swine flu (influenza A H1N1 virus infection), those with tuberculosis, then pregnant and breastfeeding women as well as patients with lack of relevant information in their medical files.

The sample size calculation

A calculation of the adequate sample size was made by G*Power software [23], and based on the following input parameters: predicted differences between compared groups in the level of exposure to the most important risk factors for ETF in hospitalized CAP patients of 25% (which was assumed as a clinically relevant effect according to previous studies [11, 12, 16–18]), with its prevalence in the control group of 20%; statistical power of 90%; equal number of cases and controls; and a significance level (alpha) of 5% when using one-tailed z-test to compare two independent proportions of patients. Under these assumptions, a total of 118 participants (i.e., 59 *per* compared groups) were needed to provide for minimum sample size for this study.

Potential risk factors and other variables measured in the study

In the present study the following factors were investigated in terms of their association with ETF in adult hospitalized patients with CAP for each participant: body mass index of patients (kg/m^2); active smoking; alcohol consumption; associated chronic obstructive pulmonary disease (COPD); regular use of inhaled corticosteroids (ICS) for at least six months prior to the date of hospital admission; all patients were receiving ICS due to COPD; cardiovascular (CVS) comorbidity (e.g. arterial hypertension, angina pectoris, arrhythmias, chronic heart failure, cerebrovascular disorders and peripheral artery disease or combination of these disorders); coexisting diabetes mellitus (DM) type 1 or type 2; coexisting chronic renal failure (CRF) with exception of the patients on current dialysis treatment (as mentioned previously); it was defined as persistent decrease in creatinine clearance below 60 milliliters *per* minute *per* 1.73 square meters of body surface at least for three months [24] before the onset of the CAP; associated gastrointestinal disorders (GID) responsive to acid-suppressing medications, i.e., histamine H_2 receptor antagonists (H_2 blockers) and/or proton pump inhibitors (PPIs), such as chronic gastritis, peptic ulcer disease, gastroe-

sophageal reflux disease, etc.; all study subjects were treated with PPIs or H2 blockers before the hospitalization; use of PPIs in the preceding one month; use of H2 blockers in the preceding one month; pneumonia severity index (PSI) score calculated on admission to hospital based on retrospective data extracted from patients' files; it was set as an ordinal variable, distinguishing the patients into five classes (I–V) according to predicted risk of death [25]; CURB-65 (C – confusion, U – urea > 7 mmol/L, R – respiratory rate ≥ 30 breaths/min, B – systolic blood pressure < 90 or diastolic blood pressure ≤ 60 mmHg and 65 – age ≥ 65 years) score [26], which was also computed on admission to hospital based on retrospective data; presence of the multilobar involvement of lung parenchyma on initial radiographic exam; evidence of the pleural effusion based on initial radiographic exam; level of CRP on admission; leucopenia on admission, defined as the total white blood count below 4×10^9/L; hyponatremia on admission, defined as the sodium concentration below 130 mmol/L; initial admission to intensive care unit (ICU); initial use of mechanical ventilation; time interval in days from the onset of CAP symptoms to hospital admission; pre-hospital antibiotics therapy for the same infection; beta-lactams and macrolides were the only drugs from this group that were used before the admission to hospital; pre-hospital use of beta-lactam antibiotic (benzylpenicillin or amoxicillin ± clavulanic acid or oral cephalosporin); pre-hospital use of macrolides (azithromycin or clarithromycin); initial use of beta-lactams (amoxicillin + clavulanic acid or ceftriaxone or ertapenem); initial use of macrolides (azithromycin or clarithromycin); initial use fluoroquinolones (ciprofloxacin); ciprofloxacin was the only antibiotic from this group available as intravenous formulation and approved for the empiric treatment during the entire observational period; initial antimicrobial treatment with the combination of ceftriaxone and azithromycin or ceftriaxone and ciprofloxacin; these were the only combinations of antibiotics that had been used in our study patients; initial use of nonsteroidal antiinflammatory drugs (NSAIDs); only parenteral diclofenac 75 mg or ketorolac 30 mg were used in all patients treated with NSAIDs; initial use of paracetamol; initial use of H_2 blockers; intravenous ranitidine 50 mg was the only drug used in all patients treated with acid-suppressive medications; initial use of systemic corticosteroids; CAP of suspected pneumococcal origin based on detection of *Streptococcus pneumoniae* in the routine sputum culture; another tests that would increase the probability of confirming the diagnosis of pneumococcal CAP, such as isolation of pathogen from lung aspirate or pleural fluid or blood culture or urinary antigen assay, etc. were not performed in any of the patients with positive sputum culture; in addition, none of the patients was identified with penicillin resistant *Streptococcus pneumoniae* based on the usual antibiogram results, but E-test methods measuring minimal inhibitory concentrations as a gold standard for detection of resistant strains were not carried out; atypical CAP caused by *Mycoplasma pneumoniae* based on positive results of specific IgM and IgG antibodies testing; the other atypical pathogens, such as *Chlamydia pneumonia*, *Legionella pneumophila*, etc. were not detected in any of our study patients.

The age and gender of patients, as well as the date of admission to hospital, were recorded as the strong potential confounding variables used for matching cases and controls, as mentioned above. At that, the age was dichotomized in order to distinguish elderly patients (65 years and older) from younger participants. Finally, the mortality and the length of hospitalization were also observed as secondary outcomes in both compared groups.

Data analysis

All the collected data were summarized with descriptive statistics, as following: means and standard deviations were used for continuous data if they had followed normal distribution based on Kolmogorov-Smirnov test for normality ($p > 0.05$), while medians and interquartile ranges (IQR 25–75) were calculated when presenting non-normally distributed continuous data as well as ordinal variables; on the other hand, categorical variables were expressed as frequencies and percentages. Depending on the normality of actual data distribution the significance of differences in continuous variables between cases and controls was estimated using Independent Student t-test or alternate, non-parametric Mann-Whitney U test which was also used to compare ordinal data, while categorical data were analyzed using χ^2 tests for frequencies with Yates continuity correction only in 2*2 contingency tables. In order to determine factors influencing the observed dichotomous outcome (ETF) significantly as well as their possible additive effects, crude and adjusted odds ratios (OR) with corresponding 95% confidence intervals (95% CI) were calculated using univariate and a stepwise backwards conditional multivariate logistic regression analysis (with respect to matched pairs study design, as mentioned above). The alpha level of 5% was set in all analyses, while stepwise regression model removed all variables with an additional probability (p value) of 0.1 and above. The association between observed risk/protective factors and ETF was considered significant if 95% CI of adjusted OR did not include the value of 1. All statistical tests were performed using commercial software SPSS version 19.0 (SPSS Inc., Chicago, IL).

Results

Baseline characteristics of cases and controls and differences among them in the level of exposure to putative risk factors are presented in Tables 1, 2 and 3. In both groups, there were twice as many women than men and almost an equal number of elderly without significant differences regarding the both confounders observed. Two compared groups were also very similar in terms of majority of other demographic characteristics, clinical features and unhealthy behaviors as well as regarding the frequency of identified causative agent of CAP and initial therapy they were receiving, with exception of considerably higher prevalence of CRF (Table 2), initial admission to ICU and initial use of mechanical ventilation (MV) (Table 3) in the group of cases. Relative to controls, the cases were also found to have a significantly higher CURB-65 score on admission (Table 2). Significant differences between compared groups in the

frequency of any of modalities of empirical initial antibiotic treatment were not observed (Table 3).

The results of both univariate and well-strengthened multivariate logistic regression analysis (the last step of stepwise backward elimination method: Cox & Snell R square 0.440, Nagelkerke R square 0.578, Hosmer-Lemeshow χ^2 3.725, df = 8, $p = 0.881$, overall model accuracy of 80.8%) are shown in Tables 1, 2, 3 and 4. Statistically significant but also clinically important (according to large effect size) association with the occurrence of ETF in hospitalized patients with CAP was found only for the coexistence of GID, higher CURB-65 score on admission, initial use of NSAIDs and use of ICS on a daily basis for at least six months prior to admission to hospital (see adjusted OR with 95%CI in Table 4). Albeit the crude OR for the coexistence of CRF, initial admission to ICU and initial ap-

Table 1

Demographic characteristics of the study population

Variable	Cases (n = 63)	Controls (n = 63)	Test value and significance of null hypothesis	Crude odds ratio with confidence intervals (1.96*SE)
Gender (male/female), n (%)	42 (66.7)/21 (33.3)	44 (69.8)/30.2	$\chi^2 = 0.035$ $p = 0.852$	0.87 (0.42, 1.81)
Age (years), mean ± SD	57.8 ± 17.6	57.8 ± 18.1	T = 0.00 $p = 1.00$	1.00 (0.98, 1.02)
Elderly (≥ 65 years age), n (%)	26 (41.3)	27 (42.9)	$\chi^2 = 0.00$	0.94 (0.46, 1.90)
BMI (kg/m^2), mean ± SD	28.3 ± 3.1	24.5 ± 7.6	T = -1.846 $p = 0.070$	1.09 (0.97, 1.21)

χ^2 – Chi-squared test; T – Independent samples *t*-test; SD – standard deviation; SE – standard error; BMI – body mass index.

Table 2

Lifestyle habits, comorbidities and therapy of the study subjects before the hospitalization

Variable	Cases (n = 63)	Controls (n = 63)	Test value and significance of null hypothesis	Crude odds ratios with confidence intervals (1.96*SE)
Active smokers, n (%)	40 (63.5)	31 (49.2)	$\chi^2 = 2.614$ $p = 0.106$	1.80 (0.88, 3.66)
Alcohol consumers, n (%)	4 (6.3)	6 (9.5)	$\chi^2 = 0.434$ $p = 0.510$	0.64 (0.17, 2.40)
Coexisting COPD, n (%)	10 (15.9)	8 (12.7)	$\chi^2 = 0.065$ $p = 0.799$	1.30 (0.48, 3.54)
Prior regular use of ICS, n (%)	8 (12.7)	6 (9.5)	$\chi^2 = 0.321$ $p = 0.571$	1.38 (0.45, 4.24)
Coexisting CVS diseases, n (%)	39 (61.9)	34 (54.0)	$\chi^2 = 0.521$ $p = 0.470$	1.39 (0.68, 2.82)
Coexisting DM, n (%)	11 (17.5)	10 (15.9)	$\chi^2 = 0.057$ $p = 0.811$	1.12 (0.44, 2.86)
Coexisting CRF, n (%)	8 (12.7)	1 (1.6)	$\chi^2 = 4.308$ $p = 0.038$*	9.02 (1.09, 74.41)*
Coexisting GID, n (%)	7 (11.1)	4 (6.3)	$\chi^2 = 0.151$ $p = 0.697$	1.84 (0.51, 6.64)
Prior use of PPIs, n (%)	6 (9.5)	2 (3.2)	$\chi^2 = 0.640$ $p = 0.424$	3.21 (0.62, 15.56)
Prior use of H_2 blockers, n (%)	5 (7.9)	3 (4.8)	$\chi^2 = 0.896$ $p = 0.344$	1.72 (0.39, 7.55)
Duration of symptoms onset to hospital admission (days), mean ± SD	6.2 ± 3.8	6.8 ± 4.5	T = 0.855 $p = 0.394$	0.99 (0.95, 1.04)
Pre-hospital use of antibiotics, n (%)	32 (50.8)	39 (61.9)	$\chi^2 = 1.581$ $p = 0.209$	0.64 (0.31, 1.29)
Pre-hospital use of beta-lactams, n (%)	20 (31.7)	24 (38.1)	$\chi^2 = 0.559$ $p = 0.455$	0.76 (0.36, 1.58)
Pre-hospital use of macrolides, n (%)	9 (14.3)	8 (12.7)	$\chi^2 = 0.068$ $p = 0.794$	1.15 (0.41, 3.19)

χ^2 – Chi-squared test; T – Independent samples *t*-test; * – significant association; SD – standard deviation; COPD – chronic obstructive pulmonary disease; ICS – inhaled corticosteroids; CVS – cardiovascular comorbidity; DM – diabetes mellitus; CRF – chronic renal failure; GID – gastrointestinal disorders; PPIs – proton pump inhibitors; H_2 blockers – histamine H_2 receptor antagonists.

Table 3

Etiology of CAP, clinical and laboratory parameters on admission and initial in-hospital therapy of the study subjects

Variable	Cases (n = 63)	Controls (n = 63)	Test value and significance of null hypothesis	Crude odds ratios with confidence intervals (1.96*SE)
Suspected pneumococcal CAP, n (%)	17 (27.0)	18 (28.6)	$\chi^2 = 0.040$ $p = 0.842$	0.92 (0.42, 2.02)
Mycoplasma pneumoniae CAP, n (%)	5 (7.9)	6 (9.5)	$\chi^2 = 0.00$ $p = 1.00$	0.82 (0.24, 2.84)
PSI risk class (I–V), median (IQR)	3 (2.5–4)	3 (2–4)	U = 1759.500 Z = -1.143 $p = 0.253$	1.24 (0.89, 1.74)
CURB-65 score (0–4)[§], median (IQR)	2 (1–2)	1 (0–2)	U = 1510.500 Z = -2.408 $p = 0.016$*	1.53 (1.08, 2.15)*
Multilobar pneumonia, n (%)	21 (35.0)	29 (46.8)	$\chi^2 = 1.748$ $p = 0.186$	0.61 (0.30, 1.27)
Pleural effusion, n (%)	10 (16.9)	4 (6.7)	$\chi^2 = 3.030$ $p = 0.082$	2.86 (0.84, 9.69)
CRP (mg/L) mean ± SD	128.1 ± 127.8	155.0 ± 118.3	T = 0.359 $p = 0.722$	0.99 (0.99, 1.01)
Leucopenia, n (%)	3 (4.8)	4 (6.3)	$\chi^2 = 0.151$ $p = 0.697$	0.74 (0.16, 3.44)
Hyponatremia, n (%)	2 (3.2)	3 (4.8)	$\chi^2 = 0.208$ $p = 0.648$	0.66 (0.11, 4.07)
Initial ICU admission, n (%)	20 (31.7)	8 (12.7)	$\chi^2 = 5.556$ $p = 0.018$*	3.20 (1.29, 7.96)*
Use of MV, n (%)	11 (17.5)	1 (1.6)	$\chi^2 = 7.309$ $p = 0.007$*	12.90 (1.61, 103.32)*
Empirical use of beta-lactams, n (%)	53 (84.1)	50 (79.4)	$\chi^2 = 0.479$ $p = 0.489$	1.38 (0.55, 3.43)
Empirical use of macrolides, n (%)	9 (14.3)	15 (23.8)	$\chi^2 = 1.853$ $p = 0.173$	0.53 (0.21, 1.33)
Empirical use of ciprofloxacin, n (%)	44 (69.8)	37 (58.7)	$\chi^2 = 1.694$ $p = 0.193$	1.63 (0.78, 3.40)
Empirical use of ceftriaxone plus azithromycin, n (%)	8 (12.7)	12 (19.0)	$\chi^2 = 0.535$ $p = 0.465$	0.62 (0.23, 1.64)
Empirical use of ceftriaxone plus ciprofloxacin, n (%)	24 (38.1)	30 (47.6)	$\chi^2 = 0.810$ $p = 0.368$	0.68 (0.33, 1.38)
Use of NSAIDs, n (%)	24 (38.1)	14 (22.2)	$\chi^2 = 3.768$ $p = 0.081$	2.15 (0.99, 4.71)
Use of paracetamol, n (%)	50 (79.4)	47 (74.6)	$\chi^2 = 0.672$ $p = 0.179$	1.31 (0.57, 3.01)
Use of H_2 blockers, n (%)	30 (47.6)	22 (34.9)	$\chi^2 = 2.096$ $p = 0.148$	1.69 (0.83, 3.47)
Use of systemic corticosteroids, n (%)	10 (15.9)	5 (7.9)	$\chi^2 = 1.892$ $p = 0.169$	2.19 (0.70, 6.82)

χ^2 – Chi-squared test; T – Independent samples *t*-test; [§]CURB-65 – CURB-65 (C – confusion, U – urea > 7 mmol/L, R – respiratory rate ≥ 30 breaths/min, B – systolic blood pressure < 90 or diastolic blood pressure ≤ 60 mmHg and 65 – age ≥ 65 years) score of 5 was not calculated in any of study patients; * – statistically significant association; SD – standard deviation; SE – standard error; CAP – community-acquired pneumonia; PSI – pneumonia severity index; CRP – C-reactive protein; MV – mechanical ventilation; NSAID – nonsteroidal anti-inflammatory drugs; H_2 blockers – histamine H_2 receptor antagonists; ICV – intensive care unit.

plication of MV hinted at potentially significant contribution to the observed outcome after adjustment for other variables such effects disappeared. Contrary to the above mentioned, the older age and outpatient use of antibiotics before the hospitalization were associated with a significantly lower likelihood of experiencing ETF, decreasing the chance for 98% and almost 90%, respectively (Table 4).

By exploring the mutual interactions between observed predictors of ETF in a clinically meaningful manner, with the inclusion of the factors for which the possible additive effects had been anticipated, clearly evident synergism was demonstrated for a higher CURB-65 score on admission and initial use of NSAIDs (adjusted OR 5.169; 95% CI 1.466, 18.222). The joint effects on observed outcome between the initial use of NSAIDs and GID comorbidity, then between initial use of NSAIDs and prior regular use of ICS as well as between older age and use of antibiotics before admission were found not to be statistically significant.

Ultimately, 11 of total 63 patients (11.7%) in the group of subjects who experienced ETF died in contrast with only one death (1.6%) in the control group, yielding a high level

Table 4

Crude and adjusted odds ratios of the risk and protective factors for early treatment failure (ETF) in hospitalized patients with community-acquired pneumonia (CAP)[#]

Risk/protective factors	Crude OR (95% CI)	Adjusted OR (95%CI)
Older age (≥ 65 years)	0.94 (0.46, 1.90)	0.02 (0.01, 0.36)*
Coexisting CVS disorders	1.39 (0.68, 2.82)	5.462 (0.70, 42.45)
Coexisting GID	1.84 (0.51, 6.64)	18.83 (1.15, 309.04)*
CURB-65 score on admission	1.53 (1.08, 2.15)*	2.57 (1.05, 6.25)*
Pre-hospital use of antibiotics	0.64 (0.31, 1.29)	0.12 (0.02, 0.86)*
Pre-hospital use of macrolides	1.15 (0.41, 3.19)	0.17 (0.02, 1.46)
Initial use of NSAIDs	2.15 (0.99, 4.71)	38.19 (3.61, 404.51)*
Prior regular use of ICS	1.38 (0.45, 4.24)	22.41 (1.03, 489.06)*

[#] Results are obtained at the final step of multivariate logistic regression analysis; * Statistically significant association; OR – odds ratio; CI – confidence interval; CVS – cardiovascular comorbidity; GID – gastrointestinal disorders; CURB-65: C – confusion; U – urea > 7 mmol/L; R – respiratory rate ≥ 30 breaths/min; B – systolic blood pressure < 90 mmHg or diastolic blood pressure ≤ 60 mmHg; 65 – age ≥ 65 years; NSAID – nonsteroidal anti-inflammatory drugs; ICS – inhaled corticosteroids.

of significance of observed difference: $\chi^2 = 7.461$, df = 1, $p = 0.006$. On the other hand, in terms of the length of hospital stay the cases (median 13 days, IQR 7.5–18.5) did not significantly differ from controls (median 12 days, IQR 9–14): Mann-Whitney test – U = 1869,00, Z = -0.565, $p = 0.572$.

Discussion

In view of the relatively frequent occurrence of ETF in hospitalized patients with CAP and its high risk of producing poor health, humanistic and economic outcomes, identification of the factors contributing to this phenomenon is particularly important for planning appropriate preventive measures and improving the care of such patients [9–19, 20, 22]. According to our knowledge, this is the first study investigating the risk factors for objectively assessed ETF in CAP on the population of hospitalized patients in Serbia, the country passing through the period of socio-economic transition with the exceptional specificities of the functional organization and financing of the health system. The most important results point out that patients admitted to hospital due to CAP who suffer from chronic GID responsive to acid-suppressing drugs, those with increased CURB-65 score on admission, then patients initially treated with NSAIDs or who were regularly treated with ICS prior to hospitalization, have higher chances of having ETF compared to patients without such characteristics, while the elderly persons or those who received antibiotics before the hospitalization are less likely to experience the observed outcome.

An interesting finding of this study is distinction of PSI and CURB-65 scores on admission in terms of relevant influence on the appearance of ETF, as these reliable severity assessment criteria were both recommended to be incorporated in individual clinical judgment concerning the decision for hospitalization or outpatient care based on the predicted risk of mortality [19, 22, 24–26]; additionally, several prior studies reported that increased initial scores by both tools may also be linked to other important bad clinical and economic outcomes, such as prolonged time to achieve clinical stability, longer duration of hospital stay and increased costs of treatment [11, 14, 20, 27]. When it comes to contribution to the development of ETF, there are inconsistent data on the relevance of these criteria, from those that show significant association (CURB-65 [11], PSI [12, 15, 16]) up to those who indicate the absence of any connection with the aforementioned outcome [14, 17, 18]. Our study found the initial CURB-65 score to be a better predictor of ETF in inpatients with CAP than PSI, indicating that any increase by 1 in this score increases the odds of having ETF for approximately 2.6 times. This discriminative effect of CURB-65 is consistent with the study by Ott et al. [11], but distinct to the findings of Martin-Loeches et al. [18] who found the difference between CURB-65 and PSI in favor of CURB-65 only regarding the positive relationship with the late treatment failure, not with ETF, in hospitalized CAP patients [18]. Our findings may be partially explained by imprecisions in the retrospective calculation of PSI score, which includes 20 variables and a quite complex scoring algorithm. Some relevant elements of PSI scoring system, such as certain chronic comorbid conditions and referral of patients from nursing homes, could not be taken into account when calculating the total PSI score in our study, because they were either among the exclusion criteria (such as presence of coexisting malignant diseases and admission of nursing home residents) or were not registered in any of our patients (such as presence of liver failure); in addition, as previously mentioned, the presence of cancer [17] or liver failure [12] have already been linked with the treatment failure in hospitalized patients with CAP. Therefore, any incorrectness or incompleteness of retrospective data in the patients' files relating to these criteria could possibly lead to an underestimation of total PSI score implying reduced generalizability of obtained results. On the other hand, based on the results of our study and the results of recent study by Wesemann et al. [28] who found CURB-65 to be significantly associated with the long-term mortality, it is easily measurable score that could be assessed in each patient hospitalized due to CAP, and it may help recognizing the patients not only at risk of in-hospital death but also the risk of death after discharge from hospital.

NSAIDs are widely used for symptomatic treatment in patients with CAP, even as self-medication at early phases of

disease in outpatient settings [29]. However, the recent observational studies [30, 31] suggest that early use of these drugs in patients suffering from CAP may put them at risk of postponing hospital admission and effective antimicrobial treatment due to initial alleviation of symptoms, thus leading to progression of the infection with higher incidence of local complications, particularly pleural empyema and pulmonary cavitations; on the other hand, significant association between the NSAIDs and distant organ dysfunction [30] or death rate [31] in these studies was not observed. Similarly, the multicenter case-control study by Legras et al. [32] did not show any connection between the use of NSAIDs and development of severe sepsis or septic shock in various community-acquired infections of bacterial origin of whom pneumonia was the most frequent, but it demonstrated an important contribution of these drugs to the delay in receiving appropriate antibiotics. Such distinct effect of NSAIDs in terms of increasing local while blunting systemic inflammatory response [30], may be explained by possible imbalance in inhibition of prostaglandin and leukotriene action, the mediators who were found to be among the major factors influencing the complex immune response of lungs to acute infection [33], but whose role in the pathogenesis and evolution of CAP was not fully elucidated in humans. Additionally, various experimental models indicate either augmented or reduced phagocytic and bactericidal activities of leukocytes and alveolar macrophages after applying different cyclo-oxygenase inhibitors [34–36]. Anyway, a causal association between use of NSAIDs and bad clinical outcomes could not be ascertained, so current treatment guidelines do not advise against their use in patients with CAP [29]. Yet we are concerned with the finding that initial use of NSAIDs in the hospital could largely increase the risk of developing ETF in CAP patients. Despite the lack of complete retrospective data on pre-hospital use of NSAIDs and their dosage regimens when they were applied in the hospital, taking into account the fact that clinically relevant association between use of NSAIDs and ETF was evident after adjustment for the effects of other confounders, we believe that these drugs should be used with extreme caution in hospitalized patients with CAP, especially in patients with coexisting CRF or cardiovascular diseases and those with severe infection as assessed by CURB-65 score on admission, because these conditions may also predispose patients to the serious adverse effects of NSAIDs. Therefore, in these patients, paracetamol may be antipyretic of choice due to much better safety profile while not affecting the ETF as it was shown in our study.

Strong positive association between prior regular use of ICS for COPD and ETF in patients hospitalized for CAP is a novel and particularly exciting finding of this study, given that the previous observational studies examining the impact of these medications use on other relevant clinical outcomes have yielded inconsistent results. Namely, there are reports suggesting potentially beneficial effects of ICS used in ambulatory settings for COPD on the short-term risk of death [37, 38] and the need for use of MV [38] in patients who developed CAP and required hospitalization, while in contrast, some studies did not find any significant influence of these drugs on both short- and long-term mortality [39, 40] as well as on the occurrence of complicated CAP [40]. Regardless of the absence of impact on mortality, Ferrer et al. [39] demonstrated a favorable effect of the previous use of ICS in terms of mitigating the systemic inflammatory response, which is similar to the above-mentioned effect of NSAIDs [30]. But opposite to NSAIDs, there is evidence about the protective role of prior treatment with ICS on the development of pleuropulmonary complications in patients with CAP suffering from various coexisting chronic respiratory diseases [41]. The patients with CAP experiencing ETF in our study had less pronounced systemic inflammatory response on admission based on average baseline level of CRP (< 150 mg/L) than the subjects without such an outcome (155 mg/L); interestingly, utilization of both NSAIDs and ICS was higher in group of cases compared to controls, but without significant differences. In addition, despite well-known favorable effects of ICS in the treatment of COPD, there are also conflicting data regarding their association with increased risk of CAP in such patients [42, 43]. The mechanisms of these controversial effects of ICS in CAP patients with co-existing COPD have not yet been fully clarified, and it may be strongly influenced by medication type, dosage regimen and duration of outpatients use, then by the severity of COPD as well as by concomitant use of systemic corticosteroids [37–43]. As we were unable to adjust the observed association between regular use of ICS in outpatient settings and ETF in patients hospitalized for CAP for the most of the confounders listed here due to incompleteness of retrospectively obtained data, this our finding require further confirmation in prospective studies with appropriate design and conducted on larger sample of inpatients with CAP and coexisting COPD.

Although coexistence of chronic GID observed as potential risk factor for ETF in CAP in our study (e.g. peptic ulcer disease or gastroesophageal reflux), was not identified as independent predictor of CAP previously [44], there is a lot of data indicating that use of PPIs and/or H2 blockers (which are considered as a gold standard for pharmacological treatment of these disorders) may increase risk of developing CAP significantly [45–47]. Such effects of acid-suppressive drugs could be explained by increased bacterial growth and colonization of the upper gastrointestinal tract due to suppression of gastric acid secretion, followed by secondary aspiration and translocation of pathogens to lungs [45, 47]. Additionally, PPIs may lead to bacterial overgrowth directly in the lungs by affecting pH of seromucinous secretion due to inhibition of proton pump in the mucous cells and ducts of respiratory tract [48]. Finally, there is also evidence from *in vitro* studies suggesting inhibitory effects of both PPIs and H2 blockers on function of leukocyte and natural killer cells [49–51]. As all our patients were treated with acid-suppressive medications before the hospitalization, we believe that aforementioned mechanisms of the effects of these medications regarding host-pathogen interaction, could be also involved to some extent in explanation of the significant association between GID and ETF in CAP as observed in this study.

Nowadays, the outpatient antibiotic use for CAP requiring subsequent hospitalization is relatively common, with a prevalence of more than 20% [52]. This phenomenon is particularly important since it can strongly influence clinical picture and severity of disease at initial presentation, inflammatory response of the patient, selection of diagnostic tests to identify a causative agent of infection as well as a choice of empirical antibiotic treatment [52, 53]. However, there are scarce and contradictory data regarding the relevance of its association with the in-hospital mortality and other relevant outcomes. Simonetti et al. [53] did not find significant differences in 30-day mortality and ICU admission rate among the patients with and without pre-hospital antibiotic use, respectively, while bacteraemia was less prevalent, and the occurrence of lung cavitations was more frequent in patients who had received antibiotics before the hospitalization. Moreover, Johnson et al. [54] showed that patients who had been pre-treated with antibiotics were significantly less likely to die, especially if they received suitable antibiotics in line with the applicable guidelines. On the other hand, van de Garde EM et al. [55] found pre-hospital antibiotic use to be a significant risk factor for death only in patients with coexisting chronic heart failure, while the significant difference in the length of hospital stay between compared groups was not observed. Protective role of the outpatient use of antibiotics before the hospitalization on the development of ETF in patients with CAP, as shown in our study, has reaffirmed the importance of prompt and appropriate empirical antibacterial treatment when serious lower respiratory tract infection is suspected.

Older age is another significant factor associated with the reduced likelihood of experiencing ETF in hospitalized patients with CAP in our study. This finding is similar to the previous study by Rosón et al. [16], but still remains unclear. Additionally, authors did not find the more prevalent initial use of broad spectrum antibiotics in a group of patients aged 65 years and over, which also was not observed in our study. As the vast majority of our elderly patients had more severe CAP on initial presentation at hospital according to PSI and CURB-65 score (i.e. 42/53 or 79% of them), we believe that these patients were probably receiving more appropriate symptomatic and supportive therapy due to a greater awareness of attending physicians regarding the increased risk of potential complications.

At last, this study also hinted at the potential contribution of ETF to mortality of hospitalized patients with CAP, but it was neither designed nor powered to examine the magnitude of such effect (due to small number of deceased patients), as were the previous studies who did find a clear association between these two phenomena [9, 10, 12, 13, 15, 16]. In contrast to many prior investigations [9, 11, 13, 14], the difference in duration of hospital stay between patients with and without ETF, respectively, in this study was not observed.

There are certain limitations of this study that deserve to be mentioned mainly lying in its retrospective nature. Due to incompleteness of data extracted from the inpatient medical records we could not assess all relevant factors that are likely to be associated with the observed primary outcome of interest correctly, such as physicians' consultations before hospitalization for CAP, dose regimens and duration of pre-hospital drug therapy (antibiotics, NSAIDs, ISC, systemic steroids, PPIs, H2 blockers) as well as compliance with these treatments, severity of coexisting chronic disorders, extent of smoking and alcohol consumption and baseline serum levels of procalcitonin. Therefore, these variables were not analyzed at all. Furthermore, any erroneous or contradictory information taken from the patients' files could have led to an inaccurate estimation of both the risk factors and the outcomes that we have observed. Eventually, the generali-zability of the results could be questionable given that this study was carried out in a single hospital and in a small country such as Serbia.

Conclusion

With the aim of reducing the risk of early treatment failure, this study advises against the routine use of non-steroidal anti-inflammatory drugs in adult patients hospitalized for community-acquired pneumonia, particularly in those with increased severity of disease as assessed by increased CURB-65 score on admission. The CURB-65 score on admission is not only easy to calculate but also better predicts the development of early treatment failure in patients with community-acquired pneumonia compared to Pneumonia Severity Index. Previous regular use of inhaled corticosteroids as well as gastrointestinal disorders responsive to acid-suppressive medications may be also associated with the increased risk of early treatment failure in this population of patients. On the other hand, prompt empirical use of appropriate antibiotics in outpatient settings could be beneficial for patients with community-acquired pneumonia requiring hospitalization as it may reduce the risk of early treatment failure. However, due to possible selection and measurement bias, these findings should be further confirmed in larger prospective studies.

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Conflict of interest

The authors declare that they have no conflict of interest in this study.

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