Failure of Ambulatory Treatment in CAP Patients Leading to Subsequent Hospitalization and its Association to Risk Factors - Prospective Cohort Study

Creutz P[1]*, Kothe H[2], Braun M[2], Bauer T[3], Suttorp N[1], Welte T[4], Dalhoff K[2] and the CAPNETZ study group

[1]Department of Internal Medicine/Infectious Diseases and Pulmonary Medicine, Charité, Humboldt-University – Medicine, Berlin, Germany
[2]University of Luebeck, Medical Clinic III, Department of Respiratory Medicine, Luebeck, Germany
[3]Center for Pneumology and Thoracic Surgery Heckeshorn, HELIOS Clinic Emil von Behring, Berlin, Germany
[4]Department of Pneumology, Hannover Medical School, Hannover, Germany

Abstract

Background: Outpatient treatment is an increasingly used option in Community-Acquired Pneumonia (CAP). Risk factors for deterioration and subsequent hospitalization are poorly characterized.

Material and Methods: A prospective study was conducted to assess risk factors associated with hospitalization of CAP-patients initially treated in an outpatient setting. Clinical history, severity of disease, physical examination findings, laboratory test results, initial treatment and outcome were prospectively documented in both groups.

Data derived from a multicenter prospective study initiated by the German competence network for community-acquired pneumonia CAPNETZ. The network includes 10 clinical centers representing hospital and outpatient facilities from all levels of health care.

5431 patients with CAP were screened for inclusion. 1517 of these patients were initially treated as outpatients and included. 1403 patients were treated exclusively in an outpatient setting, 114 (8.1%) were hospitalized after initial outpatient treatment.

Results: Compared to patients treated exclusively in an outpatient setting patients with subsequent hospitalization had a significantly higher 28-day mortality rate (4.2% vs. 0.2%, p=<0.001), advanced mean age (56.7 vs. 50.9 years, p=<0.05), and a higher CRB-65 score. However 53.3% of subsequently admitted patients had CRB-65=0, and 23% had CRB-65=1 with age >65 years as the only risk factor. Cerebrovascular disease, chronic kidney disease and diabetes mellitus were overrepresented in this patient group. In addition, cephalosporin monotherapy was identified as independent risk factor for hospitalization.

Conclusion: In ambulatory CAP patients subsequent hospitalization was observed mainly in low CRB-65 risk classes and was associated with comorbidities and the choice of initial therapy.

Introduction

Community Acquired Pneumonia (CAP) represents a public health problem of substantial magnitude. In western countries CAP remains the leading cause of morbidity and mortality due to infectious diseases [1,2]. An increasing proportion of these patients is treated as outpatients since ambulatory care has improved considerably and new concepts such as "hospital at home" are implemented [3]. Outpatient management is the most effective approach to cost reduction since the magnitude of resource use for CAP is directly related to inpatient treatment, with costs approximately 20 times higher than in ambulatory care [4]. In addition, outpatient treatment is often preferred by the patients and may be associated with better functional outcomes, particularly in the elderly [4]. Previous investigators have demonstrated that physicians may overestimate the severity of illness in CAP patients, leading to unnecessary hospitalizations [4].

Conversely, a small proportion of patients with CAP initially treated in the outpatient setting are subsequently hospitalized. Little is known regarding the etiology of CAP, risk factors, the role of antimicrobial therapy, and outcomes in this patient group [5-10]. Prognostic scoring systems for CAP have been developed to assess the severity of illness and the mortality risk [11,12]. The Pneumonia Severity Index (PSI) and the Confusion, Urea, Respiratory rate, Blood pressure and Age Score (CURB-65) are used as predictors of mortality. In addition the PSI has been used in clinical pathways for site of care decisions [13]. In a previous study from the CAPNETZ group Bauer et al. demonstrated

that scoring by both the CURB score and Confusion, Respiratory rate, Blood pressure, Age Score (CRB-65) can be used with equivalent results to assess pneumonia severity and the risk of death [14]. CRB-65 scoring appears to be preferable in the ambulatory setting where blood urea nitrogen measurement is not readily available.

To define risk factors associated with hospitalization of patients initially treated in the outpatient setting we analyzed data from the German network for community-acquired pneumonia (CAPNETZ). A prospective multicentre study was conducted in order to assess risk factors influencing hospitalization after initial CAP treatment in an outpatient setting, with a special emphasis on age, residence status, underlying conditions and antimicrobial treatment. CAPNETZ is funded by the German Ministry of Education and Research (BMBF) and recruits nationwide CAP-patients in Germany.

Material and Methods

Setting

Data are derived from a multi-centre prospective study initiated by the German Competence network for community-acquired pneumonia. The network has been described in detail elsewhere [15]. In brief, the network comprises 10 clinical centers throughout Germany. These centers represent hospitals and outpatient departments at all levels of health-care provision. A total of 670 private practitioners, physicians, and respiratory specialists as well as more than 30 hospitals cooperate within CAPNETZ. The decision where to treat the patient and the choice of treatment was left to the attending physician. No attempt was made to implement standardised criteria or rules regarding the decision to hospitalize or choice of antibiotic therapy. Data collection started in March 2003 and ended for this analysis on June 2006. Consecutive, non-selected patients presenting with CAP were prospectively recorded.

Ethical considerations

The local Ethical Committees approved the study design. All patients gave written informed consent and received a pseudonym from an independent third party to ensure data safety.

Study population

Patients presenting with a new pulmonary infiltrate on chest radiography together with at least one symptom or sign of lower respiratory tract infection (fever, cough, purulent sputum, focal chest signs, dyspnea, and/or pleuritic pain) were eligible. Exclusion criteria were:

1. Acquisition of pneumonia after hospital discharge <28 days.

2. Presence of severe immunosuppression associated with a relevant risk for opportunistic infections.

3. Pneumonia as an expected terminal event of a severe chronic disabling comorbidity.

4. An alternative diagnosis evolving during follow-up.

5431 patients with CAP were screened for inclusion. 1517 of these patients were initially treated as outpatients. The 3914 patients who were hospitalized at first clinical presentation were excluded from the study.

The analyzed patient group of 1517 outpatients presented initially at emergency departments of hospitals (n=804) or at private practices (n=713) and were included in the study if treated initially in an outpatient setting. Patients remaining in ambulatory care throughout the study formed group A (n=1403) and were compared with outpatients who were subsequently hospitalized, group B (n=114). The data recorded in both groups were from the first clinical presentation at the emergency room or at the general practitioner. The patients were recruited from the unselected population of Germany including male and female patients of all adult age groups and backgrounds.

Treatment failure

Hospital admission of an outpatient was defined as a surrogate of treatment failure in the outpatient setting.

Data collection and evaluation

A Personal Tutor (PT) recruited new CAP cases on the basis of defined diagnosis criteria as described above. Data of the recruited cases were entered by the PT on-time using a standardized electronic report form (case report form) in a central database. Validity and consistency checks were performed by an independent monitor prior to data analysis. This concept allows the patient recruitment process to be followed continually, the identification of problems on-time and data quality (for more information, see also http://www.capnetz.de). All patients were assessed at first presentation and during follow-up according to a standardized data sheet. The following parameters were recorded: date of presentation, age, gender, alcohol habits, defined comorbidities, residence in nursing home; duration of symptoms, clinical symptoms at admission (body temperature, respiratory rate, heart rate, arterial systolic and diastolic blood pressure, pneumonia-associated confusion, i.e. disorientation with regard to person, place or time that is not known to be chronic, chest radiograph; laboratory parameters (hemoglobin, haematocrit, leukocyte count, band forms, serum-creatinine, sodium, blood glucose, C-reactive protein). Antimicrobial treatment was documented prospectively. After 14 days all patients or relatives were contacted either personally or via telephone for a structured interview on outcome parameters (e.g. resolution of symptoms, length of antibiotic therapy, death). This interview was repeated for all patients at 30 days and after 180 days. 28-day mortality was measured from the day of first diagnosis of CAP.

Determination of CRB-65

The CRB-65 score consists of four variables: confusion, respiratory rate ≥30/min, systolic blood pressure ≤90 mmHg or diastolic blood pressure ≤60 mmHg, and age ≥65 yrs [11]. One point is given for each parameter present, which results in CRB-65 scores of 0–4. The CRB-65 score was calculated with patient data obtained at presentation.

Diagnostic microbiology

Diagnostic microbiology was done as described by Welte et al. [15]. Briefly, validated sputum samples, blood culture samples, pleural fluid, transthoracic needle aspiration samples, and undiluted and serially diluted Tracheo Bronchial Aspirates (TBAS), Protected Specimen Brush (PSB) And Broncho Alveolar Lavage Fluid (BALF) samples were plated on the following media: blood-sheep agar, MacConkey agar, chocolate agar as well as Sabouraud agar. Undiluted PSB and BALF samples were also cultured on charcoal–yeast extract agar. Urine was tested for the presence of *Streptococcus pneumoniae* and *Legionella* antigen. Identification of microorganisms and susceptibility testing was performed according to standard methods. PCR from respiratory samples was done for italics.

Statistical analysis

All data were analyzed and processed on Statistical Package for Social Sciences (SPSS) Version 13.0 on a Windows XP operating system. Demographic and clinical data of outpatients and secondarily hospitalized outpatients with CAP were compared. Risk factors for hospitalization and 28 days mortality were further evaluated by univariate and multivariate analysis. Results are expressed as frequencies and percentage or as mean ± standard deviation, unless indicated otherwise. The chi-square test was used to compare categorical variables and Fisher`s exact test was performed when appropriate. Continuous variables were compared by Student's t-test. The 95% confidence intervals were reported for all comparisons and exact intervals for single proportions were estimated according to Newcombe {Newcombe, 1998 4355 /id}. Effects on subsequent hospitalization were assessed by stepwise forward logistic regression analyses (largest p-value for entering variables 0.05; smallest p-value for removing variables 0.10) for the following variables: age, comorbid conditions, residence status, and initial antibiotic treatment, risk class assignment (confusion, respiratory frequency and blood pressure

(CRB-65 score) The standardised expected β coefficient, 95% CI and level of significance are reported. All tests were explorative and two-sided and the significance level was set at 5%.

Results

Patient characteristics

Study period: 1517 patients were recruited through the network that were primarily diagnosed and treated in an outpatient setting. The proportion of patients without and with subsequent hospitalization were 1403 (91.9%, group A) and 114 (8.1%, group B), respectively.

	group A n=1403	group B n=114	p-value
Mean age, years	50.9 ± 16.4	56.7 ± 24.8	0.05
Male / female, n	648 / 755	56 / 58	0.54
Body mass index, kg/m²	25.3 ± 4.9	25.3 ± 5	0.61
Initial presentation n (%)			
Emergency Room	765 (55)	39(34)	0.01
General practitioner	638 (45)	75 (65)	0.01
Body temperature, °C	37.5 ± 1.1	37.7 ± 1.1	0.32
Dyspnea, n, (%)	902 (64.3)	79 (69.0)	0.04
Purulent sputum, n (%)	824 (58.8)	62 (55.3)	0.05
Cough, n (%)	1346 (96)	106 (93)	0.54
Pleuritic pain, n (%)	653 (46.6)	51 (45.1)	0.73
Pleuritic effusion, n (%)	74 (5.3)	13 (11.9)	0.2
Respiratory rate/min	18.6	19.5	0.045
Confusion, n (%)	20 (1.4)	4 (3,5)	0.045
Blood pressure, mmHg			
Systolic	125.7 ± 18.56	127.87 ± 21.56	0.06
Diastolic	77.8 ± 10.75	76.36 ± 13.56	0.12
CRB-65-score (mean value)	0.4	0.6	0.01
Leucocytes, 1000/µl	10.0 ± 5.3	16.5 ± 9.4	<0.001
Thrombocytes, 1000/µl	294.7 ± 106	296.1 ± 120.6	0.22
Hemoglobin, g/l	8.65 ± 0.9	8.59 ± 1.09	0.01
C-reactive protein, mg/l	66.2 ± 81.6	100.3 ±105.5	0.01
Sodium, mmol/l	138.2 ± 6.2	137.17 ± 5.1	0.84
Urea, mmol/l	4.79 ± 2.1	5.5 ± 2.8	<0.001
Glucose, mmol/l	4.97 ± 1.77	7.07 ± 4.7	<0.001

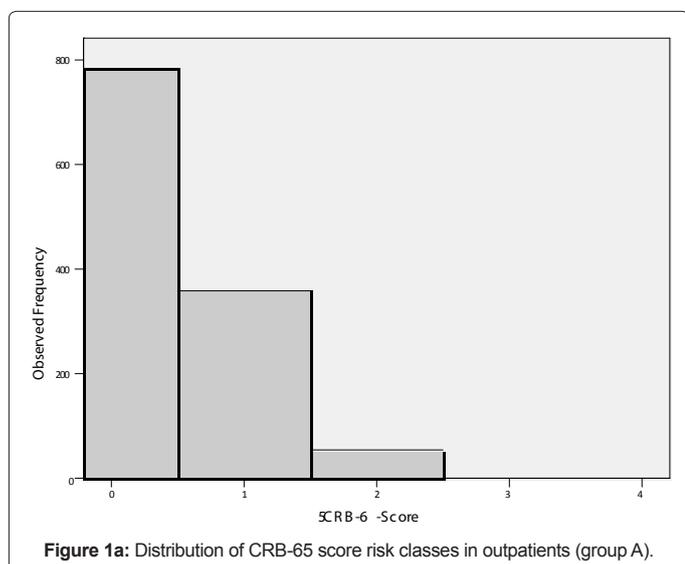**Table 1:** Demographic and clinical data of the study population.

Figure 1a: Distribution of CRB-65 score risk classes in outpatients (group A).
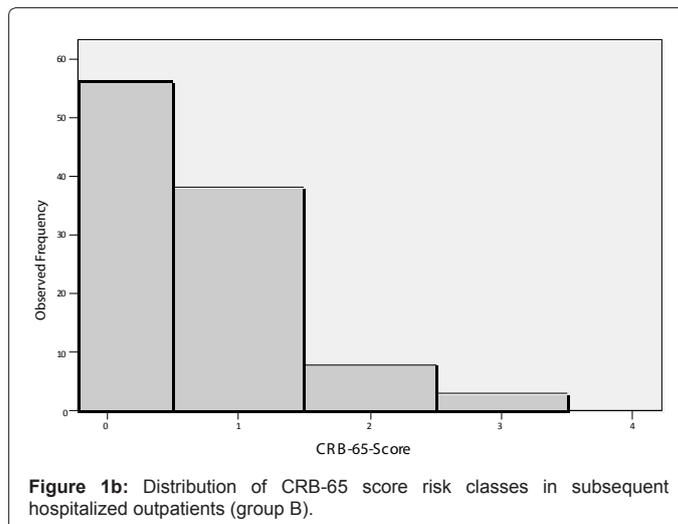

Figure 1b: Distribution of CRB-65 score risk classes in subsequent hospitalized outpatients (group B).

Table 1 displays demographic and clinical data in both subgroups. No significant differences were found regarding sex and body mass index. Patients from group B had a higher mean age. On clinical examination, they revealed a slightly higher respiratory rate and proportion of dyspnea and confusion. Regarding the laboratory parameters major differences included elevated values for blood urea nitrogen, C-reactive protein, leucocyte count and glucose at first presentation.

Risk stratification

The CRB-65 score was used for risk stratification in ambulatory patients. Figures 1a and 1b show proportions of CRB-65 risk classes in group A and B. 1455 (96%) outpatients had a CRB-65 score of 0 or 1. 62 (4.0%) outpatients showed pathologic vital signs: 9 (0.6%) had pneumonia associated confusion, 14 (0.9%) tachypnea and 39 (2.5%) hypotension. 68% of the patients with age >65 years age was the only risk factor. 62 (4%) of the outpatients were scored in CRB group 2 and 3.

The mean CRB-65 score was significantly higher in group B (0.6 vs. 0.4, p<0.01), indicating more severe disease. However, >53% of patients from this subgroup had CRB-65=0, and in 68% of patients with CRB-65 =1 age >65 years was the only risk factor. Thus, only 4 (3.5%) of patients from group B with CRB-65=1 had pathologic vital signs as assessed by the CRB-65 score at first presentation.

Patients from group B showed a significantly higher prevalence of severe comorbidities like cerebrovascular disease (7.1 vs. 2.2%, p<0.01), chronic kidney disease (11.4% vs. 1.4%, p<0.01) and diabetes mellitus (11.5% vs. 6.3%, p<0.05). In contrast, chronic pulmonary diseases were not associated with hospitalization. More patients from this subgroup were nursing home residents (3.5% vs. 0.8%, p<0.05). Table 2 illustrates the relationship between CRB-65 risk classes and comorbidities in the two subgroups: in general no significant differences in comorbidities were observed between the CRB-65 classes and the presence of severe comorbidities was not reflected by an increase of the score with the exception of group B, who showed a higher prevalence of diabetes mellitus (16% vs. 10%, p=0.001) and cerebrovascular disease (25% vs. 7%, p=0.001) in CRB-65 class 2/3 compared to CRB-65 0/1. However, in a considerable proportion of patients these conditions were already present in the lower risk classes and may have influenced the site of care decision.

CRB-65	Comorbidities	group A	group B
0	COPD	30%	28%
	CHF	5%	11%
	CRF	1%	12%
	DM	5%	10%
	CVD	3%	7%
	CLD	0.5 %	0.5%
1	COPD	34%	34%
	CHF	4%	11%
	CRF	0.5%	12%
	DM	5%	9%
	CVD	3%	7%
	CLD	0.8%	2%
2/3	COPD	30%	29%
	CHF	5%	12%
	CRF	1%	12%
	DM	5%	16%*
	CVD	6%	25%**
	CLD	0.5%	1%

*$p < 0.01$ vs. CRB-65 0/1; **$p < 0.01$ vs CRB-65 0/1

COPD: chronic obstructive pulmonary disease, CHF: congestive heart failure, CRF: chronic renal failure, DM: diabetes mellitus, CVD: cerebrovascular disease, CLD: chronic liver disease

Table 2: Comorbidities of outpatients (group A) n=1403 and subsequent hospitalized outpatients (group B) n=114 dependent on CRB-65 risk classes.

	Group A n = 1403 (%)	Group B n = 114 (%)	p-value
Aminopenicillin ± BLI	365 (26.0)	17 (14.9)	0.001
Macrolide	279 (19.8)	22 (19.2)	0.98
Fluoroquinolone	569 (40.5)	41 (36.0)	0.086
Cephalosporin	168 (12.1)	32 (28.0)	0.001
Other	23 (1.6)	2 (1.7)	0.16
BLI: betalactamase inhibitor			

Table 3: Antimicrobial therapies of outpatients (group A) and subsequent hospitalized patients (group B).

Etiology

In 389 (25.6%) of outpatients respiratory pathogens were detected from respiratory samples (Group A n=361, Group B=28). *Streptococcus pneumoniae* was the main pathogen with 168 (43,1%) isolates (Group A n=153, 42%; Group B n=11, 39%). *Haemophilus influenzae* was found in 17 patients (Group A n=14, 4%; Group B n=3, 10%). *Legionella spp.* were detected in 49 patients (Group A=43, 12%; Group B n=6, 21%), *Mycoplasma pneumoniae* was found in 55 (Group A n=54, 15%; Group B n=1, 4%) and *Chlamydia pneumoniae* in 7 samples of Group A. Infections with respiratory viruses were observed in 48 (Group A n=47, 13%; Group B n=1, 4%) patients. Gram negative bacilli were found in 13 (Group A n=12, 3%; Group B n=1, 3%) cases as causative pathogen, *Staphylococcus aureus* was detected in 5 (Group A n=4, 1%; Group B n=1, 3%) patients. Mixed infections with two or more pathogens were found in 27 (Group A: n=25, 7%; Group B: n=2, 7%) patients. In 2 (7%) patients of Group B with hospital admission after ambulatory treatment *Stenotrophomonas maltophilia* was isolated. Overall, a definite microbial aetiology could be determined in 389 (25, 6%) cases. Most pathogens were equally distributed across both groups. The microbial aetiology allows for only imprecise effect estimation due to the small case number.

Antimicrobial treatment

Table 3 shows the initial antimicrobial treatment of both patient groups. Nearly all patients were treated with oral monotherapy. There were no significant differences between the local clinical centers in the choice of ambulatory treatment (data not shown). Patients from group B received more frequently oral cephalosporins (p<0.01) and less frequently aminopenicillin treatment. After hospitalization antimicrobial treatment was changed in all cases. Clinical failure was the main reason (103/114 patients, 90.3%), rarely intolerance or resistance were documented. In comparison, ambulatory treatment in group A was changed only in 14.7% as shown in Table 4.

Univariate and multivariate analysis of risk factors for hospitalization

Risk factors for hospitalization in ambulatory CAP patients are shown in Table 5. The CRB-65 score, age, nursing home residence, comorbid conditions, C-reactive protein concentration and choice of initial treatment were associated with hospital admission after initial outpatient management. Table 6 displays the results of logistic regression analysis of the 14 selected variables included in the multivariate model. Age, CRB-65 index, nursing home residence, cerebrovascular disease, diabetes mellitus, chronic kidney disease, and CRP-level and cephalosporin treatment remained significant risk factors for hospitalization.

Outcome

The 28 day mortality rate was significantly higher among group B

	Group A n = 1403	Group B n = 114	p - value
Overall, n (%)	206 (14.7)	114 (100)	0.001
ineffectiveness	130 (9.3)	103 (90.3)	0.036
sequential therapy	15 (1.1)	7 (6.7)	0.04
deescalation	42 (3.0)	0.0	0.001
intolerance	19 (1.5)	2(1.5)	1
resistance	0.0	2(1.4)	0.001

Table 4: Change of antibiotic therapy

	OR	95% CI	p-value
age	1.06	1.035-1.09	<0.001
nursing home	1.02	1.01-1.08	0.045
COPD	1.07	0.96-1.21	0.89
cerebrovascular disease	4.84	1.09-6.56	0.04
congestive heart failure	1.63	0.76 – 1.74	0.12
diabetes mellitus	1.93	1.04-3.59	0.03
chronic kidney disease	1.32	1.054-1.67	0.016
*CRB-65	2.07	1.7 – 2.44	<0.001
Leucocytes 10³/nl	1.01	0.98-1.1	0.054
CRP	1.00	1.00-1.008	0.05
Fluoroquinolones	1.37	0.75-2.52	0.29
Cephalosporins	2.77	1.48-5.20	< 0.001
Macrolides	1.78	0.96-3.31	0.065
Aminopenicillins	0.89	0.53-1.36	0.58

*univariate analysis for CRB-65 was performed as logistic regression, OR and 95% CI is shown per step

Table 5: Univariate analysis of risk factors for hospitalization in outpatients with CAP.

	β	OR	CI	p-value
age	0.02	1.02	1.00-1.038	0.003
nursing home	0.26	2.61	1.44-3.72	0.005
COPD	0.71	1.33	0.89-1.98	0.16
cerebrovascular disease	0.67	1.52	1.15-2.10	0.016
congestive heart failure	0.05	0.96	0.91-1.02	0.63
diabetes mellitus	0.31	1.93	1.04-3.59	0.033
chronic kidney disease	1.04	2.84	1.87 – 4.31	0.001
CRB-65	0.72	2.6	2.1-3.2	0.043
Leucocytes 10^3/nl	0.11	1.01	0.98-1.04	0.30
CRP	0.003	1.00	1.00-1.005	0.03
Fluoroquinolones	0.93	1.48	0.82-2.67	0.19
Cephalosporins	1.05	2.86	1.56-5.27	0.001
Macrolides	0.57	1.77	0.98-3.26	0.69
Aminopenicillins	0.03	1.02	0.49-2.14	0.94

Table 6: Multivariate analysis of risk factors for hospitalization in outpatients with CAP.

patients (4.3%) compared to group A (0.2%, p<0.001) and was further increased after 6 months (7.1% vs. 1.1%, p=<0.001). 8.1% of ambulatory treated CAP patients were subsequently hospitalized of whom 4.3% died during short term follow up.

Discussion

The majority of patients with pneumonia is treated in an outpatient setting and has a low risk of short-term mortality. Outpatient treatment is often preferred by low-risk patients [16] and costs are substantially less compared to inpatient treatment [1]. A small proportion of patients with CAP initially treated in the outpatient setting are subsequently hospitalized. There are few data on risk factors for hospitalization and outcomes in this patient group [8-11,16-18].

In this study, we identified patient characteristics that are independently associated with hospitalization after outpatient treatment. The prospective data acquisition in the CAPNETZ study including follow up of ambulatory patients in the hospital enabled us to analyze patient data and course of disease in a representative cohort. A comparatively high proportion (8.1%) of our ambulatory patients was subsequently hospitalized. In a cohort of 149 younger outpatients with CAP (mean age: 41 years) Marrie et al. reported an admission rate of 5.4% [19], and none of these patients died. Similarly, Capelastegui et al. described an admission rate of 4.4% in a study including inpatients and outpatients with CAP. The outpatient group had excellent outcomes with a 30-day mortality of 0.1%, and only one patient was admitted to the ICU [6]. Recently Majumdar et al. reported on a large cohort of ambulatory pneumonia patients showing a nearly identical admission rate as in our study, but a lower death rate (1% as compared to 4.3%) [20]. These differences may be due to variations in the proportion of elderly and comorbid patients as well as different thresholds of hospitalization in national health care systems. In addition a different study design may play a role since in the aforementioned studies patients presented initially at the emergency room whereas in our study the site of care decision was made by general practitioners in 50% of patients.

The CRB-65 risk score was independently associated with hospitalization in our study. However, the majority of hospitalized patients were initially placed in low risk classes showing a CRB-65 score of 0 or 1 with advanced age as the only risk factor. Thus, additional factors seem to be important for the site of care decision. In the original study and validation of the CURB score by Lim et al. only hospitalized patients were included [11]. In an interventional trial Atlas et al. used

the Pneumonia Severity Index (PSI) for site of care decisions. As in our study the authors found a high rate of subsequent admissions of 9%, which appeared to be partly pneumonia related [17]. In the study of Capelastegui et al. patients with a CURB-65 score=0 showed frequently other indicators of adverse prognosis as coexisting diseases, hypoxemia, arterial pH <7.35, multilobar radiographic involvement or pleural effusion [6]. Oxygen saturation <90% has been described recently as an important predictor of hospitalization and death independent from the PSI [20]. In our study a considerable proportion of patients with CRB-65=0 had comorbidities such as cerebrovascular disease, chronic kidney disease and diabetes mellitus which were independently associated with subsequent hospitalization. In contrast, chronic respiratory disease did not increase the hospitalization rate in our cohort although it has been shown to increase the risk of re-hospitalization [21]. Interestingly, the prevalence of most comorbid conditions did not show a clear relation to the CRB-65 score. To what extent hospitalizations were due directly to pneumonia or to deteriorating comorbidities is not clear from our data. However it seems reasonable to assume that short-term hospitalization and mortality are at least indirectly infection-related [20]. Apart from medical reasons social factors such as homelessness or absence of a stable home environment should also be taken into account [22,23]. Taken together our data indicate that judgment by the CRB-65 score alone underestimates the need of hospitalization in outpatients with CAP. A modification of the CRB65 score providing more accurate prediction of the hospitalization risk in terms of deterioration of functional status and relevant comorbidities [22] is desirable.

Taken together, our findings emphasize the importance of clinical judgment in addition to risk scoring when making the site of care decision. The risk factors for hospitalization identified in this study may be helpful in guiding the clinical approach.

Previous investigators have observed that choice and timing of antimicrobial treatment influence the outcome of pneumonia in hospitalized patients [24-26]. In contrast, a recent metaanalysis of randomized trials of CAP in outpatients did not show treatment related differences in outcome [5]. However, patients with risk factors were underrepresented in most of these trials, and rates of hospitalization were rarely reported. In our study therapy with oral cephalosporins was an independent risk factor for hospitalization. There are several possible explanations for this finding: first, failure of coverage for atypical pathogens could lead to treatment failure since a high proportion of atypical infections have been found in ambulatory patients [19]. Ineffective outpatient treatment with betalactams was associated with a threefold increased chance of finding atypical pathogens in a previous study [27]. However the need for atypical coverage is controversially discussed [28,29] and recommendations from international guidelines differ in this respect [30-34]. Since aminopenicillin therapy did not increase the risk of hospitalization, failure of atypical coverage is an unlikely explanation for the increased admission rate under cephalosporins in our study. Second, under-dosing and the variable bioavailability of oral cephalosporins may lead to ineffective treatment, particularly in elderly and comorbid patients [35]. In contrast, resistance rates of S. pneumoniae to oral cephalosporins were very low during the study period [36]. Lastly a prescription bias favoring treatment with cephalosporins in more severely ill patients could lead to confounding by indication. However our data do not support this possibility since cephalosporin treatment remained an independent risk factor after adjustment for CRB-65 class, age, residence status and comorbidities. Apart from efficiency issues it should be kept in mind that cephalosporin therapy may increase the selection of ESBL producing enterobacteriaceae and C. difficile.

Conclusions

(1) The majority of hospitalizations occurred in low CRB-65 risk classes.

(2) Cerebrovascular disease, diabetes mellitus and chronic kidney disease were predictive for hospital admission independent of initial risk classification.

(3) Apart from CRB-65 score and comorbid conditions initial treatment with oral cephalosporins was associated with an increased risk of hospitalization.

In summary the risk factors described in this study may help to identify CAP patients in the outpatient setting who have an increased risk of subsequent hospitalization and require special attention during the course of disease. Evidence based site of care decisions are helpful to optimize ambulatory management without increasing the rate of treatment failure and subsequent hospitalization. Our data suggest that the need of hospitalization is not fully predicted by the CRB-65 score but is associated with further patient- and treatment-related factors. More studies on the course of CAP in outpatients are warranted with a special focus on the reasons for hospital admission and on strategies to improve safe ambulatory treatment.

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Contribution of all Authors

Petra Creutz helped planning the study, performed data acquisition, processing, analysing and interpretation and wrote the manuscript. Klaus Dalhoff was involved in organizing of the CAPNETZ network, planning of the study, data analysis and interpretation and wrote parts of the manuscript. Henning Kothe helped with the statistical analysis and data analysis. Maike Braun was involved in data processing and statistical analysis. Thorsten Bauer helped with the manuscript-drafting the article and revising it critically for important intellectual content. Norbert Suttorp and Tobias Welte organized CAPNETZ network and data processing, planned the study and helped with the manuscript.

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