

Sepsis severity predicts outcome in community acquired pneumococcal pneumonia

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Short title:

Severity and outcome of pneumococcal pneumonia

Abstract:

Easily performed prognostic rules are helpful for guiding the intensity of monitoring and treatment of patients. The aim of this study was to compare the predictive value of the sepsis score and the CRB-65 score in 105 patients with community acquired pneumococcal pneumonia. In addition we investigated the influence of timing of the antimicrobial treatment on outcome. The sepsis score and the CRB-65 score were used to allocate patients to subgroups with low, intermediate and high risk.

Comparable, highly predictive values for mortality were found for both scores: low risk group: 0 vs. 0 % (sepsis score vs CRB-65), intermediate risk: 0 vs. 8.6 %, high risk: 30.6 vs. 40 %, AUC 0.867 vs. 0.845. Patients with ambulatory antibiotic pre treatment had less severe disease with a lower acute physiology score ($p = 0.02$), lower white blood count ($p = 0.002$) and a faster decline of CRP levels ($p = 0.03$). No pre treated patient died.

In summary, both scores performed equally well in predicting mortality. The prediction of survival in the intermediate risk group might be more accurate with the sepsis score. Prehospital antibiotic treatment was associated with less severe disease.

Keywords: antibiotic treatment, pneumococcal infection, pneumonia, risk classification, sepsis

Introduction:

Streptococcus pneumoniae remains the most frequent pathogen in adults with community-acquired pneumonia (CAP) and a leading cause of community-acquired sepsis [1]. Case fatality rates are high despite the availability of highly active antimicrobial agents, especially in the elderly and patients with risk factors [2]. The emergence of drug-resistant *S. pneumoniae* (DRSP) may further hamper the efficacy of treatment at least with some groups of anti-infectives [3].

An easily performed prognostic procedure which more accurately may predict outcome of patients at admission may be helpful for guiding the intensity of monitoring and treatment. In the past, multiple prognostic factors including age, co-morbidities, low body temperature and leucopenia [4] and more complex severity scores like the APACHE II score were described to be predictive for survival [5]. Alternatively, pneumonia severity scores like the PSI [6] or the recently developed CURB and CRB-65 scores [7] are applied in CAP. However, in a recent analysis of the PORT study, > 50% of hospitalized CAP patients developed severe sepsis during the course of disease [8] indicating that systemic infection is frequent. Therefore, to date it is not clear whether a pneumonia severity score or a sepsis score according to the definition of Bone and coworkers [9] focusing on the systemic signs and sequelae of infection has the highest potential to predict outcome.

In addition to host factors which are measured by the above mentioned scores treatment related factors may influence the outcome. Time between admission and the first antibiotic dose (TFAD) and combination therapy in severe CAP were reported to be associated with a favourable outcome [10], but this finding has not been confirmed in other studies [11]. A possible explanation is that the major part of treatment delay may occur in the ambulatory setting, where timely diagnosis and treatment pose even greater problems. The impact of

prehospital treatment on the outcome of pneumococcal disease in hospitalized patients has not yet been evaluated.

Therefore, the aim of this study was to answer the following questions:

1. Is the sepsis score able to predict mortality of patients with pneumococcal pneumonia as accurate as the CRB-65 CAP score?
2. Does the timing of antibiotic treatment influence the outcome of this patient population?

Methods:

Case definition

A case of community acquired pneumococcal pneumonia was defined as a diagnosis of CAP in combination with isolation of *S. pneumoniae* from blood, the cerebrospinal fluid, other sterile sites or respiratory secretions of high quality ($\geq 10^4$ CFU/ml of *S. pneumoniae* in bronchoalveolar lavage [BAL], purulent sputum or tracheal secretions [only samples with > 25 PMN and < 10 squamous cells/high power field]). In addition, cases with positive urinary antigen test were included if the clinical diagnosis was CAP. The diagnosis of pneumonia was based on clinical symptoms (fever, respiratory symptoms, typical auscultatory findings), a new or progressive infiltrate on chest X-ray and laboratory signs of infection.

Patients

From December 1998 until November 2004, 105 adult hospitalized patients with community-acquired pneumococcal pneumonia, who were admitted at the university hospital Lübeck and two community hospitals from the same region were investigated in a prospective manner. Patients with defined immunodeficiencies (hematologic or solid neoplasia, glucocorticoid or cytotoxic therapy, HIV-infection or immunoglobulin deficiency) were excluded from the study.

Data on the influence of genetic polymorphisms on the clinical course of disease have been described previously [12,13]. The study was approved by the institutional ethics committee. Written informed consent was obtained from patients or their relatives.

Laboratory and clinical data:

Demographic data, comorbidities, complications and previous antibiotic therapy were prospectively assessed. Seventy (66,7 %) of the 105 pneumococcal isolates were available for serotyping. The clinical status including the sepsis severity and the acute physiology score

(APS) was documented at day 1, 2 and 7. Assessment of the in house mortality included early and late death defined as death during the first week (early death day 1-7) and death during the second week or later (late death day 8 - X).

Antibiotic susceptibility testing

Antibiotic resistance of *S. pneumoniae* strains was determined according to the standards and guidelines from the Clinical and Laboratory Standards Institute (CLSI) [14]. Briefly, direct colony suspensions, equivalent to a 0.5 McFarland standard, were inoculated on Mueller-Hinton agar with 5% sheep blood and incubated at 35°C in a 5% CO₂ atmosphere for 24h. The panel of routinely tested antibiotics included penicillin G, clindamycin, erythromycin A, vancomycin, ceftriaxone and doxycycline. Resistance testing for fluoroquinolones was not routinely done, since resistance rates of respiratory fluoroquinolones in our region are < 1 % [15,16]. *S. pneumoniae* ATCC 49619 was used as a control strain. Current CLSI interpretive criteria were used to define antimicrobial resistance (CLSI).

Serotyping. Pneumococcal isolates were serotyped by Neufeld's Quellung reaction using type and factor sera provided by the Statens Serum Institut, Copenhagen, Denmark.

Sepsis score and CRB-65 score

The sepsis score (non-sepsis, sepsis, severe sepsis and septic shock) was made according to the definition given by the American College of Chest Physicians-Society of Critical Care Medicine Consensus Conference 1992, adapted by Bone [9]. In brief, sepsis was defined as two or more of the following criteria in combination with pneumococcal infection: (1) temperature > 38°C or < 36°C, (2) heart rate > 90 beats/ min, (3) respiratory rate > 20/ min or pCO₂ < 32 mmHg and (4) WBC > 12.000/ mm³ or < 4.000/ mm³ or > 10% band forms. Severe sepsis was defined as sepsis associated with organ dysfunction together with perfusion

abnormalities. One of the following criteria had to be met: pH <7.3, pneumonia associated confusion, acute renal failure, disseminated intravascular coagulopathy, systolic blood pressure <90 mm Hg, PaO₂/FiO₂ <200. Septic shock was defined as sepsis associated with sepsis induced hypotension despite adequate fluid resuscitation.

The CRB-65 score was done as described by Lim et. al [7], with one point for each of **C**onfusion, **R**espiratory rate ≥ 30 /min, low systolic (<90 mmHg) or diastolic (≤ 60 mmHg) **B**lood pressure and age ≥ 65 years.

In line with previous studies [17] the sepsis score and the CRB-65 score were divided into low, intermediate and high risk classes: Sepsis severity: *low risk class* = Non-sepsis; *intermediate risk class* = sepsis; *high risk class* = severe sepsis or septic shock

CRB-65 score: *low risk class* = 0; *intermediate risk class* = 1 or 2; *high risk class* = 3 or 4 on a five point scale.

Influence of antimicrobial treatment on outcome

To assess the impact of treatment related factors, we studied the influence of

- Pre-hospital antimicrobial treatment and
- In-hospital antimicrobial treatment

on clinical course, parameters of inflammation and patient outcome.

Inappropriate treatment was defined as discordant treatment (isolation of pneumococci with resistance against the drug used) or treatment with drugs not recommended for the treatment of pneumococcal pneumonia in current guidelines (e.g. ciprofloxacin).

Statistical analysis

Patients were grouped into low, intermediate and high risk classes according to the results of the sepsis score and the CRB-65 score [17]. The Cochran Armitage test was used for trend of category variables. Fisher's exact test (two tailed) was used for association of discontinuous

variables with mortality. Continuous variables were compared by the Mann-Whitney U test (values are given in mean and standard error). A p-value < 0.05 was considered statistically significant.

Results

Demographic data, risk factors and comorbidities

These data are presented in table 1. Most patients had at least one risk factor or comorbidity. The total in hospital mortality was 10.5%.

Diagnosis of pneumococcal infection was made by recovery of *S. pneumoniae* from blood (n = 64), cerebrospinal fluid (n= 2), BAL (n = 11), sputum or tracheal secretions (n = 16), pleural fluid (n =4), BAL and blood (n = 2), cerebrospinal fluid and blood (n = 1) and by urinary antigen test (n = 5).

Pneumococcal serotypes

Serotyping data were available in 70 patients and were comparable to recent data from Germany [18]. The leading serotypes were 3 (18,6%), 14 (17,1%) and 7F (10%): serotype 1 (n=3), 3 (n=13), 4 (n=6), 5 (n=1), 6B (n=2), 7F (n=7), 8 (n=4), 9A (n=3), 9L (n=1), 9V (n=2), 10A (n=1), 12 F (n=4), 14 (n=12), 17F (n=1), 19F (n=1), 19C (n=1), 23A (n=2), 23F (n=2), 33F (n=2) and 38 (n=1). According to this data 90% of the serotyped bacteria would have been covered by the 23 valent pneumococcal polysaccharide vaccine. The serotypes were equally distributed over all risk classes (data not shown).

Disease severity

Single variables (temperature, CRP levels, leucocytes, age, bacteremia and comorbidities) were not associated with mortality (data not shown).

The predictive values of the sepsis score and the CRB-65 score were excellent (figure 1 and 2). The sepsis score at day 1 was significantly related to mortality (Table 2). At admission 36 patients (34.3 %) were in the high risk class (severe sepsis or septic shock) with a mortality of 30.5 %, compared to 45 patients (42.9%) in the intermediate risk class with a mortality of 0 % and 24 patients (22.9%) in the low risk class with a mortality of 0% ($p < 0.0001$).

The CRB-65 score was also predictive for mortality: 16 patients in the high risk class had a mortality rate of 40.0%, 58 patients in the intermediate risk class a mortality rate of 8.6 % and 32 patients in the low risk class a mortality rate of 0% (Table 2).

Considering the different risk classes there is a trend for a better prediction of *survival* in the intermediate risk class as defined by the sepsis score: survival in this subgroup was 100 % (95% CI: 92.1-100.0 %) compared to 91.4 % (95% CI 81.0-97.1 %) with the CRB-65 score (not significant).

Early versus late death

All patients were observed until discharge. Death occurred after a mean period of 12.5 +- 13.7 days (range 1-40). Length of hospital stay in survivors was 19.1 +- 10.8 days (range 5-53).

Early death during the first week was seen in 6 patients (mean 2.7 +- 1.9, range 1-5 days) and was attributable to uncontrolled septic shock ($n = 2$), acute respiratory failure (ARDS) ($n = 2$) and meningitis ($n = 2$). Late death was seen in 5 patients (mean 19.1 +- 10.8, range 9-40 days) (Figure 3). Late death was observed after a transient recovery from sepsis in all patients and was attributable to secondary organ failures including secondary bacterial pneumonia with respiratory failure ($n=3$), hypoxic cerebral failure after meningitis ($n=1$) and ischemic cerebral insult ($n=1$).

At admission late death patients were less severely ill than early death patients: Late death was associated with a lower Acute Physiology Score (APS) at admission (late death 11 +- 2.45 vs. early death 16.33 +-4.6, $p=0.03$).

In addition we compared the performance of the two scores in predicting early or late death. Using the sepsis score all late death patients were classified as high risk patients at admission. In contrast, 3 out of 5 late death patients were initially grouped in the intermediate risk class using the CRB-65 score (table 2, figure 3).

Influence of drug resistant *streptococcus pneumoniae* (DRSP) on outcome

10/100 patients (10 %) in whom data on susceptibility testing were available had DRSP isolated: erythromycin (n = 9) and intermediate penicillin resistance (MIC 0.12-1; n= 1).

There was a trend towards less severe disease in patients with DRSP (mortality 0 vs 12.1 %, p=0.1; APS at admission 4.9 +- 3.3 vs. 8.7 +- 5.3, p=0.03, see table 1 of the electronic supplement).

Influence of antimicrobial treatment on outcome

Prehospital treatment

Thirteen patients (12.4%) were treated with oral monotherapy before hospitalization: ciprofloxacin (n = 4), levofloxacin (n = 1), macrolides (n = 3), cephalosporines (n = 3), penicillin (n = 1), amoxicillin/clavulanic acid (n = 1).

In spite of the fact that 38.5 % of these treatments were inappropriate (ciprofloxacin n=4) or discordant (macrolide resistance n = 1), patients with prehospital antibiotic treatment had less severe disease (Table 3) as evidenced by lower APS values at admission (p=0.02). In addition, in pretreated patients lower WBC counts at admission (p=0.002) and faster decline of CRP levels with lower values at day 7 were seen (p=0.03). A smaller proportion presented in the high risk groups (CRB and sepsis score at admission) and no patient died (0 vs 12.0 %, n.s.).

Inhospital treatment

A delay of antibiotic therapy > 8 hours after hospital admission was associated with a trend for better survival (delay > 8h: mortality 0/16 (0 %); delay < 8h: mortality 11/69 (15.9 %), p=0.1; (see table 2 of the electronic supplement).

4 out of 105 patients received inappropriate therapy with a drug not recommended for the treatment of pneumococcal pneumonia (mortality 9.9% vs 25 % in patients with appropriate treatment, p=0.4). No patient received discordant treatment after admission.

Combination therapy was used in 52.4 % of all patients (mostly a betalactam with a macrolide or fluoroquinolone). No association of the use of combination therapy with outcome was seen (see table 3 of the electronic supplement).

Discussion

The main finding of our study is that the sepsis score at admission has a high predictive value for the outcome of community acquired pneumococcal pneumonia. Using the presence of severe sepsis +/- septic shock (high risk class) as cutoff, 30.5 % of these patients died compared to 0 % of the patients in the intermediate and low risk categories. The CRB-65 score showed also an excellent overall performance but appeared less discriminative with a survival rate of 91.4 % in the intermediate risk class compared to 100 % when using the sepsis score (table 2).

Furthermore, our data show that prehospital antimicrobial treatment is associated with a favourable clinical course in patients with pneumococcal pneumonia in spite of the fact that 38.5 % of ambulatory treatment courses were inappropriate or discordant (table 3).

For community acquired pneumonia, including pneumococcal infection, severity scores like the PSI and the CRB-65 score are successfully used. The CRB-65 score performed equally well for predicting outcome as the CURB and the CURB-65 score [19]. Recently an association between the CURB-65 score and mortality in patients with bacteremic pneumococcal pneumonia was demonstrated [20]. Conditions like pneumococcal infection carry a high risk of systemic dissemination and septic shock. Even in CAP due to different aetiologies the frequency of severe sepsis may exceed 50% [8]. Septic shock is a known risk factor for mortality from pneumococcal infection [21]. Therefore, scoring the severity of sepsis may add prognostic information in these patients. To our knowledge this study is the first that demonstrates a high predictive value of the sepsis score in patients with pneumococcal pneumonia. Our data are in line with a study of Ewig et al who found a high predictive value of the sepsis score in hospitalized CAP patients (mortality in low or intermediate risk class 1%). In addition, the authors observed an increased mortality rate of 8% in the intermediate risk class by using the CURB score [17]. The predictive value of the CURB score has been evaluated in several studies. Recently Spindler et al demonstrated an increasing mortality risk in patients with bacteremic pneumococcal pneumonia according to the CURB-65 score [20]. In that study patients with intermediate risk had a high mortality rate of 15 to 20% . For clinical pathways, an intermediate risk class with increased mortality may be useful for the decision of hospital admission, but is less useful for in hospital management. The sepsis score with its more discriminative prediction of mortality (low and intermediate vs high risk class) may be helpful to decide which patients need more intensive monitoring in the hospital (e.g. ICU). A possible disadvantage of the sepsis severity score compared to the CRB-65 lies in the need of some additional laboratory and clinical investigations. However, these data should be known by the clinician caring for hospitalized CAP patients (e.g. septic encephalopathy, septic shock, respiratory insufficiency, acute renal failure, disseminated intravascular coagulopathy, low blood pressure or acidosis)

It has been observed previously [4] that about half of the deaths in CAP patients are observed during the first 7 days due to direct septic complications and half of the deaths are seen later. We confirm this observation for pneumococcal disease: 55 % of the patients died during the first week and 45 % of the deaths occurred later after transient recovery due to secondary organ failures (figure 3). Patients with early death had initially more severe disease with a higher APS. Interestingly the weaker discriminative power of the CRB-score was more evident in patients with late death: The majority of these patients were initially grouped in the intermediate risk class with the CRB-score, whereas the sepsis score correctly predicted the high risk in all late death patients (table 2).

None of the patients with intermediate or low risk class of the sepsis score deteriorated to severe sepsis (high risk class) during hospitalisation confirming the stability of this scoring system (figure 3). The fact that “simple” sepsis or SIRS has a low predictive potential for the development of more severe disease has been described previously and has served as an argument against the specificity of the sepsis score [8]. In our opinion the associated high predictive value for survival in these risk groups makes the sepsis score an useful instrument for assessing the risk of patients with serious pulmonary infections.

Several risk factors for pneumococcal infection have been described. Although this study was not designed to study the incidence of pneumococcal infection, we found in 90% at least one risk factor or one comorbidity (table 1). The influence of comorbidities on outcome are under debate [4]. In our analysis single risk factors and comorbidities were not associated with sepsis severity or mortality, but all patients who died had at least one risk factor or comorbidity.

As expected, pneumococcal serotype analysis did not show any clear association to the outcome. In Germany, vaccination with 23 valent polysaccharide vaccine is recommended for patients older than 60 years and for all patients with comorbidities [22]. 94% of the recovered serotypes would have been covered by the vaccine. Thus a considerable part of the invasive pneumococcal infections observed could have been avoided by vaccination of risk groups. In line with other German cohorts [18] we found a low incidence of pneumococcal resistance (macrolide resistance 9 %, intermediate penicillin resistance 1%). The role of bacterial resistance, especially discordant treatment (e.g. receipt of an antimicrobial drug inactive against *S. pneumoniae in vitro*) is questionable [23]. In our study all patients with pneumococcal resistance received concordant in hospital treatment (e.g. receipt of at least one antibiotic with *in vitro* activity). We found a trend towards less severe disease in patients with isolation of drug resistant pneumococci (Table 1 supplement).

Hospitalization despite prior ambulatory antimicrobial treatment was seen in 12.4% of our patients. It was associated with antibiotic resistance in a minority of cases. Interestingly, we found a less severe course of disease and no deaths in pretreated patients, in spite of the fact that pneumococci were isolated in all cases at admission and 38.5 % had been treated either with inappropriate drugs, e.g. ciprofloxacin, or with macrolides in case of resistance. Pretreated patients had lower CRP and leucocyte values together with a lower acute physiology score (table 3). In addition less patients were in the high risk group of the sepsis score and none of the pretreated patients died. This suggests that prehospital antibiotic treatment, although suboptimal in many cases, had a beneficial effect on the course of disease, possibly by modulating the inflammatory response. In line with our data Ruiz et al demonstrated a protective effect of prior ambulatory antimicrobial treatment in patients with severe CAP [24]. Thus, rapid empiric treatment seems to be of importance for the course of CAP.

In contrast, we were not able to confirm an influence of treatment delay in the hospital, combination therapy or inappropriate treatment on outcome (table 2 and 3 supplement). Of note, these data are observational and are open to multiple biases. For instance, critically ill patients may receive immediate attention at the emergency room leading to faster initiation of treatment and to the institution of combination therapy., This could lead to underestimation of the effect of treatment intensity and speed. Indeed, patients receiving early therapy and combination therapy seemed to be more severe ill at admission (table 1 and 2 in electronic supplement). On the other hand, a treatment delay of a few hours in hospital may be less important for the course of than a delay in the prehospital phase which may comprise days [11].

In conclusion, the sepsis severity assessment and pneumonia scoring with CRB65 showed overall comparable performance in predicting mortality. There was a trend for a more accurate discrimination with sepsis assessment in patients with intermediate risk which has to be confirmed in larger cohorts. In hospitalized patients with community acquired pneumococcal pneumonia, both instruments may be complementary for evaluating disease severity. Regarding modifiable factors, prehospital antimicrobial treatment was associated with less severe disease. Controlled studies may be warranted to elucidate the role of earlier initiation of treatment in the prehospital setting.

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Table 1:
Demographic factors, comorbidities and risk factors in 105 patients with community acquired pneumococcal pneumonia.

Table 2:
Mortality including early and late death according to the risk class in the Sepsis score and the CRB-score (Cochrane Armitage Trend Test for mortality).
Sepsis score: Low risk class = Non-Sepsis, Intermediate risk class = Sepsis, High risk class = severe sepsis or septic shock.
CRB-65 score: Low risk class = 0 points, Intermediate risk class = 1 or 2 points, High risk class = 3 or 4 points.

Table 3:
Influence of pre-hospital treatment on the disease severity and the outcome of hospitalized patients with pneumococcal pneumonia

Figure 1:
Receiver-operator-characteristics (ROC) curve of predicting mortality for patients with community acquired pneumococcal pneumonia with the sepsis score. AUC=area under the curve; SE=standard error; CI=confidence interval.

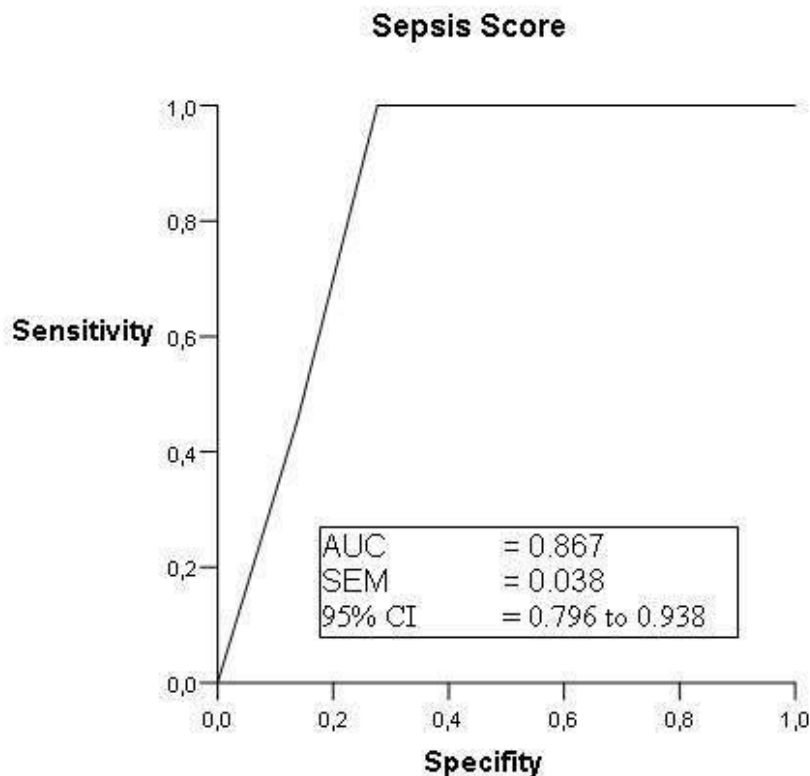


Figure 2:

Receiver-operator-characteristics (ROC) curve of predicting mortality for patients with community acquired pneumococcal pneumonia with the CRB-65 score. AUC=area under the curve; SE=standard error; CI=confidence interval.

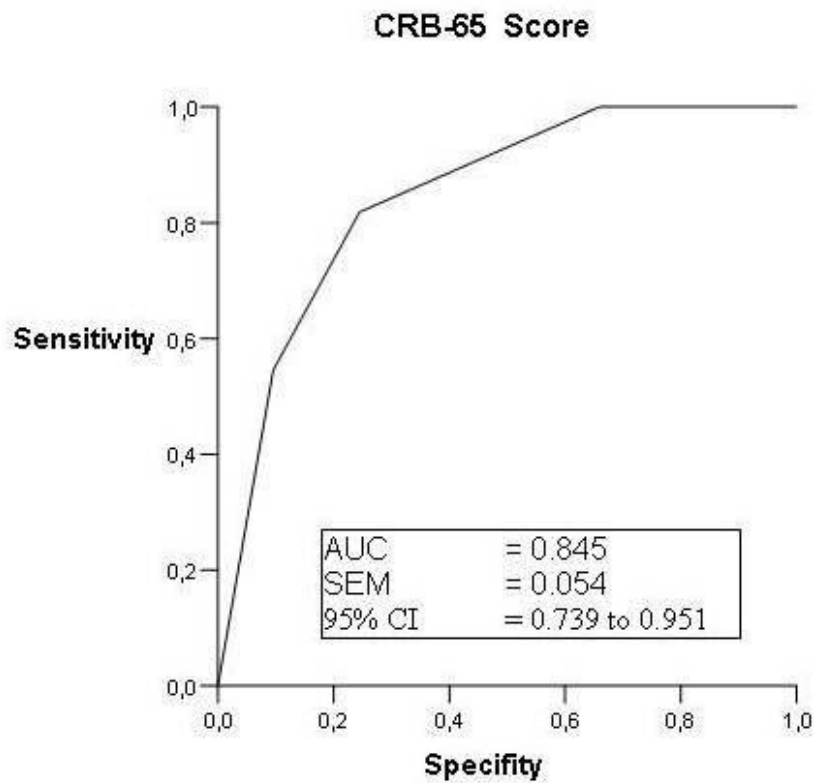


Figure 3:

Course of the disease in patients with community acquired pneumococcal pneumonia according to the risk class in the sepsis score at admission. Low risk class = Non-Sepsis, Intermediate risk class = Sepsis, High risk class = severe sepsis or septic shock.

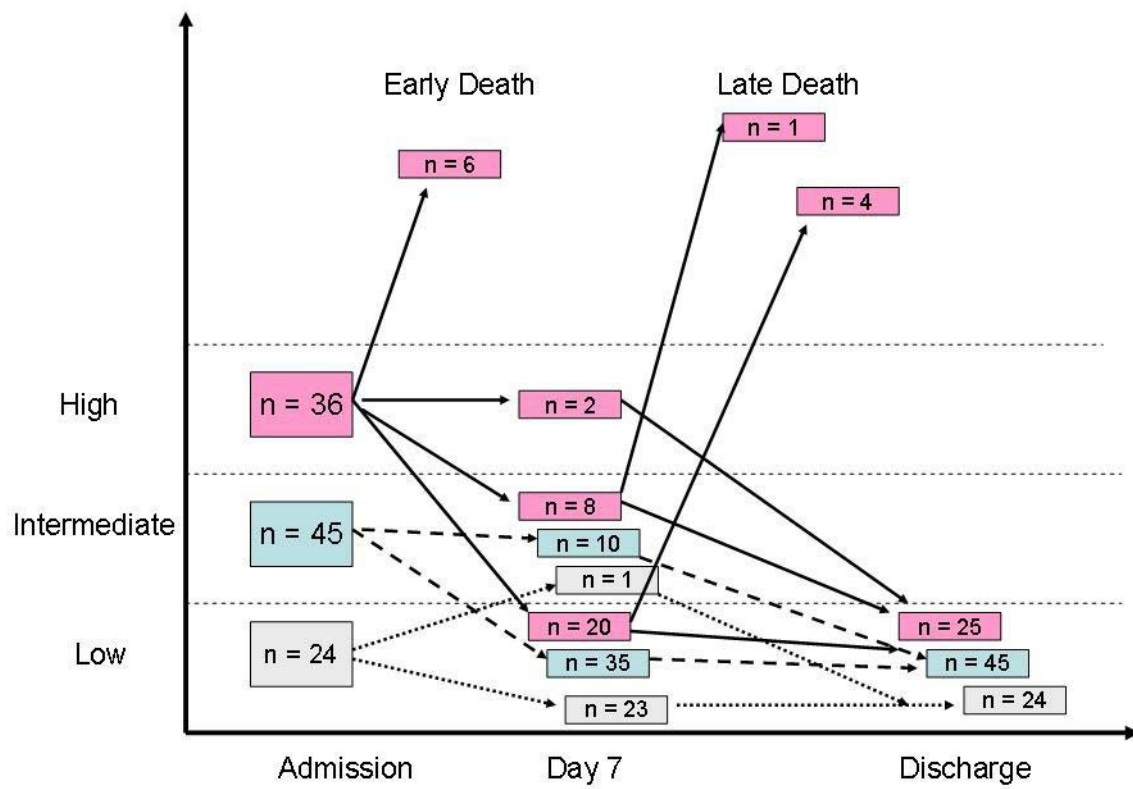


Table 1:

Age, mean	(range)	64.9 (24-96)
male	(%)	57.2
Risk factors (≥ 1)	(%)	84.8
Age > 65 years	(%)	54.3
Smokers	(%)	43.8
Alcohol abuse	(%)	17.1
Comorbidities (≥ 1)	(%)	61.9
Chronic lung disease	(%)	36.2
Chronic heart disease	(%)	30.5
Diabetes mellitus	(%)	20.0
Chronic liver failure	(%)	1.9
Chronic renal failure	(%)	19.0
≥ 1 Risk factor or Comorbidity (%)		89.5

Table 2:

	Alive		Dead		OR	95% CI	Early death	Late death
	N	%	N	%			N	N
Sepsis Score								
Low (Non-Sepsis)	24	100	0	0			0	0
Intermediate (Sepsis)	45	100	0	0	6.580*	1.91-35.86	0	0
High (Severe Sepsis + Septic Shock)	25	69.4	11	30.6	43.3*	3.66-128.6	6	5
						*P<0.0001		
CRB-65 Score								
Low (Score 0)	32	100	0	0			0	0
Intermediate (Score 1 + 2)	53	91.4	5	8.6	8.48*	2.34-38.25	2	3
High (Score 3 + 4)	9	60.0	6	40.0	71.83*	5.49-146.32	6	2
						*P<0.0001		

Table 3:

		Pre-hospital antibiotic therapy		
		Yes (n = 13)	No (n = 92)	P
CRP at admission	mg/dl	185 (+-181)	263 (+-178)	0.1
Leucocytes at admission	/ μ l	12.2 (+-4.6)	18.3 (+-7.8)	0.002
CRP at day 7	mg/dl	47 (+-46)	98 (+-85)	0.03
APS at admission		5,2 (+-4.1)	8.6 (+-5.2)	0.02
Sepsis high risk (Severe Sepsis or Shock)	%	23.0	35.9	0.53
CRB-65 high risk (Score 3 + 4)	%	7.7	15.2	0.70
Mortality	%	0	12.0	0.35

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Table 1 electronic supplement:

Influence of antibiotic resistance on the disease severity and the outcome of hospitalized patients with pneumococcal pneumonia. 5 patients with urinary antigen excluded.

Table 2 electronic supplement:

Influence of the timing of inhospital treatment on the disease severity and the outcome of hospitalized patients with pneumococcal pneumonia. Patients with prehospital treatment were excluded. Data for timing of antibiotic treatment is missing in 6 patients.

Table 3 electronic supplement:

3a: Antibiotic therapy used in 105 patients with pneumococcal pneumonia

3b: Influence of in-hospital combination therapy on the disease severity and the outcome of hospitalized patients with pneumococcal pneumonia

Table 1 electronic supplement

		Antibiotic resistance		
		Yes (n =10)	no (n = 90)	P
CRP at admission	mg/dl	212 (+-143)	257 (+-186)	0.57
Leucocytes at admission	/μl	14 (+-4.9)	18.2 (+-8)	0.087
CRP at day 7	mg/dl	55 (+-57)	96.2 (+-85.8)	0.1
APS at admission		4.9 (+-3.3)	8.7 (+-5.3)	0.03
Sepsis high risk (Severe Sepsis or Shock)	%	22.2	36.3	0.49
CRB-65 high risk (Score 3 + 4)	%	11.1	15.4	1.0
Mortality	%	0	12.1	0.59

Table 2 electronic supplement

		Delay of antibiotic therapy		
		< 8 hours (n =69)	> 8 hours (n = 16)	P
CRP at admission	mg/dl	286 (+-179)	210 (+-156)	0.1
Leucocytes at admission	/μl	18.4 (+-7.7)	20.9 (+-7.6)	0.18
CRP at day 7	mg/dl	98.8 (+-82.0)	106.7 (+-102.3)	0.84
APS at admission		9 (+-5.2)	7.6 (+-5)	0.41
Sepsis high risk (Severe Sepsis or Shock)	%	40.6	25	0.4
CRB-65 high risk (Score 3 + 4)	%	14.5	18.8	0.7
Mortality	%	15.9	0	0.1

Table 3 electronic supplement
3a:

Combination therapy 55 pts. (46.7%)	N	No Combination therapy 50 pts. (53.3%)	N
Betalactam + Macrolide	48	Betalactam	40
Betalactam + Aminoglycoside	6	Betalactam + Nitroimidazol	4
Betalactam + Fluoroquinolon	1	Fluoroquinolon	5
		Lincosamid	1

3b:

		Combination therapy		P
		Yes (n=55)	no (n = 50)	
CRP at admission	mg/dl	269 (+-197)	237 (+-172)	0.5
Leucocytes at admission	/μl	17.9 (+-6.2)	16.8(+-8.9)	0.18
CRP at day 7	mg/dl	74.3 (+-70.2)	100.6 (+-84.6)	0.1
APS at admission		9 (+-5.7)	7.1 (+-4.4)	0.13
Sepsis high risk (Severe Sepsis or Shock)	%	43.6	24	0.04
CRB-65 high risk (Score 3 + 4)	%	18.2	10	0.27
Mortality	%	14.5	6	0.2