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PROGNOSTIC ASSESSMENT IN COMMUNITY ACQUIRED PNEUMONIA

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Listen to your patient, he is telling you the diagnosis.
Sir William Osler

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ABSTRACT

Community acquired pneumonia (CAP) is the most commonly occurring infectious disease that requires hospital admission. CAP affects mainly, the youngest, the oldest, the poorest and the sickest. Annual incidence is 5-12 per 1000 adults. Between 20% and 40% of patients with CAP need in-hospital treatment. Mortality is below 1% among those who are treated in the community, however in-hospital mortality can be as high as 50% in patients who are critically ill due to CAP. In Europe the annual costs from pneumonia is estimated to be more than €10 billion. Streptococcus pneumonia is the main aetiology of CAP, as well as it carries the highest fatality rate. In the pre-antibiotic era the observed death toll from bacteraemic pneumococcal pneumonia could reach, and even exceed, 80%. Today, with access to effective antibiotics the observed fatality rate from bacteraemic pneumococcal pneumonia usually varies between 5% and 25%.

In paper 1, 460 patients were included, from five centres in five countries, in a prospective multicentre study. All patients had pneumococcal bacteraemic disease and 12% of the patients died during period of hospitalisation. Independent prognostic factors of death present on admission were age >65 years, chronic pulmonary disease, nursing home residency, high Acute Physiologic and Chronic Health Evaluation (APACHE II) score, and $\geq$2 lung lobes affected. Need for mechanical ventilation after admission was also an independent prognostic risk factor for death.

In paper 2, 340 patients with pneumonia, included in paper 1, were analysed. Aim of the study was to examine if the combination of β-lactam and macrolide antibiotics could reduce the case fatality rate (CFR) in patients with bacteraemic pneumococcal pneumonia. Despite use of univariate, as well as multivariate analysis, we were unable to find any reduction in fatality rate among patients, with bacteraemic pneumococcal CAP, who received antibiotic combination therapy.

Paper 3 included 375 patients who all suffered from bacteraemic pneumococcal pneumonia and were enrolled during two periods of time, 1993-1995 and 1999-2000. Patients enrolled during the first time period were identical with the Swedish patients who took part in the studies described in paper 1 and 2. In paper 4, 1172 patients were included from one hospital during 16 months. All patients in paper 4 had pneumonia of

different microbial aetiology. In both papers the proposed, and modified new scoring system, DS CRB-65, proved to be significantly more accurate, than CRB-65, to predict 30-day mortality in patients with bacteraemic pneumococcal CAP, as well as in patients with CAP of different microbial aetiology.

Keywords: β-lactam, macrolide, pneumonia, prognosis, scoring system, Streptococcus pneumoniae,

Men of good fortune

Often cause empires to fall

While men of poor beginnings

Often can´t do anything at all

Lou Reed

LIST OF PUBLICATIONS

I. Kalin M, Ortqvist A, Almela M et al. Prospective study of prognostic factors in community-acquired bacteremic pneumococcal disease in 5 countries. J Infect Dis. 2000 Sep;182:840-7.

II. Dwyer R, Ortqvist A, Aufwerber E et al. Addition of a macrolide to a β-lactam in bacteremic pneumococcal pneumonia. Eur J Clin Microbiol Infect Dis. 2006 Aug;25:518-21.

III. Dwyer R, Hedlund J, Darenberg J et al. Improvement of CRB-65 as a prognostic scoring system in adult patients with bacteraemic pneumococcal pneumonia. Scand J Infect Dis. 2011 Jul;43:448-55.

IV. Dwyer R, Hedlund J, Henriques-Normark B, Kalin M. Improvement of CRB-65 as a prognostic scoring system in adult patients with community acquired pneumonia. Manuscript.

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LIST OF ABBREVIATIONS

APACHE II	Acute Physiologic and Chronic Health Evaluation
APS	American Thoracic Society
AUC	Area Under Curve
B.C.	Before Christ
BP	Blood Pressure
BTS	British Thoracic Society
CAP	Community Acquired Pneumonia
CI	Confidence Interval
CFR	Case Fatality Rate
CRF	Case Report Form
CT	Computed Tomography
Hb	Haemoglobin
HIV	Human Immunodeficiency Virus
ICD-10	International Classification of Diseases 10^{th} revision
ICU	Intensive Care Unit
IV	Intravenous
kPa	Kilopascal
µmol /l	Micromoles per litre
mmol/l	Millimoles per litre
NIV	Non-Invasive Ventilation
PO_2	Partial Pressure of Oxygen
PSI	Pneumonia Severity Score
ROC	Receiver Operating Characteristic
SaO_2/SpO_2	Peripheral oxygen saturation measured by pulse oximetry with a pulse oximeter
UK	United Kingdom
USA	United States of America

1 INTRODUCTION

1.1 HISTORY

Man has known pneumonia for thousands of years and it is believed that Hippocrates (400 B.C.) has described pneumonia and its treatment (1). Hepatisation of lung tissue is described in an ancient Egyptian mummy (1). In 1819, and 1820 Laennec made the first "modern" characterisation of the disease, depicted the physical signs and pathologic changes of pneumonia, and was able to distinguish between "pneumonia" and "pleurisy" (1). Most of the main bacterial causes of pneumonia were defined by the late 1930s (1). Streptococcus pneumoniae, that was first isolated in 1881, by Pasteur (2, 3) and Sternberg (4, 5) was then, and is still today, the leading microbiological cause of pneumonia, found to account for two thirds of all 7000 cases with an established aetiology in a meta-analysis of 122 reports between the years 1966 and 1995 (6). In the pre-antibiotic era approximately 700 cases of pneumonia occurred in 100 000 young adults each year (1), and due to the seriousness of the disease with an observed case fatality rate CFR of more than 80% in patients with bacteraemic pneumococcal lobar pneumonia (1), many different remedies were tried such as alcohol, caffeine, strychnine, epinephrine, quinine, hydrotherapy, flaxseed poultice, serum therapy. Of these different therapies, treatment with specific antiserum in patients with serious pneumococcal pneumonia, was probably the most beneficial therapy, and could in some series of patients half the CFR (1). With optochin, a quinine derivative, the first attempt to treat pneumococcal infections with an antimicrobial chemotherapeutic agent was made. Morganroth and Levy showed that optochin inhibited growth of pneumococci in vitro (7). Unfortunately pneumococci rapidly became resistant (8). In addition optochin demonstrated optic toxicity (9) and was therefore abandoned from clinical use (10).

The second antimicrobial chemotherapeutic drug to be used in the treatment of patients who suffered from pneumococcal disease was sulphanilamide. As the pneumococcus was not as highly susceptible to sulphanilamide as Streptococcus pyogenes, search for a chemical compound related to sulphanilamide, however less toxic and more efficient began. Whitby (11) found in 1938, after undertaking systemic research the chemical compound pyridine or sulphapyridine. Only five weeks after Whithby´s work Evans and Gaisford (12) reported in The Lancet that treatment with sulphapyridine reduced the CFR among patients with lobar pneumococcal pneumonia from 27% to 8%.

Pyridine seemed to be the drug of choice for patients with pneumococcal infections; however, in 1943 sulphonamide-resistant strains were reported (13).
Though penicillin, when compared with sulphanilamid, possessed greater potency per unit, lack of interference by breakdown products, minimal interference of inoculum size on effectiveness, and no resistant pneumococcal strains, it took several years after the discovery of penicillin before it could replace the sulphonamide antibiotics. In the early 1940s it became possible to synthesise larger quantities of penicillin for the treatment of pneumococcal infections (14).

1.2 EPIDEMIOLOGY

Pneumonia is a very common clinical disorder. Community acquired pneumonia (CAP) in Western countries has an estimated annual incidence between 5 and 12 cases per 1000 persons (15-18). In the United States of America (USA) it is the second most common cause of hospitalisation after hospital admission due to childbirth (19), the sixth leading cause of death in those 65 years or older, and the most common cause of infection related mortality (20). The annual financial burden of pneumonia in Europe was in 2003, as estimated by the European Respiratory Society, €10.1 billion, including costs for hospitalisation accounting for €5.7 billion (21). In a study by Welte and colleagues (22), this year, the costs for absences from work in Europe, due to CAP, was estimated to be €3.6 billion.
Age is a factor that has great impact on annual incidence of CAP. This was well demonstrated in the study by Jokinen et al. (16) where the annual incidence in age group 16-59 was 6/1000 persons, for those aged 60 and over, it was 20/1000 persons and for age 75 years and over, it was 34/1000. The proportion of adults with CAP who required in-hospital treatment in the Finnish prospective longitudinal population study was 42% (16). In two British studies it was reported that between 22% and 42% of patients with CAP needed hospital care (15, 23). Patients with CAP who required intensive care unit (ICU)-management was 5% in a multicentre study by the British Thoracic Society (BTS) (24), and 10% in a Spanish study (25).
Mortality in patients treated for CAP is low among non-hospitalised patients in the community and the CFR is usually below 1% (26-28). Among patients admitted for hospital treatment in Europe the CFR has been observed to vary between 2.6% (29) and 14% (30). In an international cohort study that included more than 13 000 patients, published in May this year (31), mortality at 30 days was 8%. The 30-day mortality

among Swedish CAP-patients admitted to hospital, and treated in infectious diseases departments, was 2.6% in a study by Strålin et al. (29). In another Swedish study Johansson et al. (32) reported a CFR during hospitalisation of 3.8%. Many factors have been proposed, as well as discussed, that increase the risk of developing or dying from CAP. In the prognostic scoring systems, used for initial assessment of CAP, included and discussed in this thesis, risk factors associated with mortality in pneumonia are listed. However, in western countries old age is a most important (perhaps the most important) risk factor for both developing and dying of CAP (33). Many underlying, or concomitant diseases, prognostically unfavourable for patients with CAP, are age dependant and infrequently observed in the young and middle aged.

Today, as in the pre-antibiotic era, the leading bacterial cause of pneumonia, meningitis, and acute otitis media is the ubiquitous Gram-positive diplococcus, Streptococcus pneumoniae. Though pneumococcal disease affects people of all ages, it is the youngest and the oldest who are most often affected by pneumococcal infections. Pastor et al. (34) reported in a study from the USA an annual incidence of invasive pneumococcal disease of 136/100 000 persons under two years of age, as well as 80/100 000 persons over 65 years of age (overall annual incidence was 22/100 000 persons). In the same study Pastor additionally reported an increased incidence of invasive pneumococcal disease among low-income groups, as well as in the black community. As penicillin, and other antibiotic compounds, became accessible to patients with infectious diseases after the Second World War it was believed that pneumococcal disease was no longer a major problem among the infectious diseases. However, Austrian and Gold (35) revealed in 1964 that bacteraemic pneumococcal disease was still to fear. In their study they reported that the CFR of all patients with bacteraemic pneumococcal pneumonia was almost 20%, CFR in patients with pneumococcal meningitis was above 60%, and the CFR nearly reached 30% among patients with bacteraemic pneumococcal pneumonia who were 50 years of age or older. In the USA invasive pneumococcal disease still is a major infectious disease issue and a CFR exceeding 35% has been noted (36-41). The CFR among patients with bacteraemic pneumococcal pneumonia has in Sweden during the last three decades been observed to range between 5% and 11.5% (37-40).

1.3 ANTIBIOTIC COMBINATION THERAPY OF BACTERAEMIC PNEUMOCOCCAL PNEUMONIA

In many guidelines for the management of patients with severe CAP, therapy with a β-lactam antibiotic combined with a macrolide, or a "respiratory tract quinolone" (levofloxacin, moxifloxacin), has been recommended to cover atypical pathogens as Legionella species, as well as Mycoplasma pneumoniae (42, 43). Some studies, most of them retrospective, have shown that combination therapy also has a beneficial effect on CFR in patient with bacteraemic pneumococcal pneumonia, and this issue has become a matter of debate among medical researchers (44-46). The mechanism, or mechanisms, that mediate the alleged favourable effects in patients with bacteraemic pneumococcal pneumonia have not yet been found or explained. However, many explanations have been proposed for this effect such as concomitant infection with an atypical bacterial pathogen, particularly Legionella species (47, 48), pulmonary anti-inflammatory and immunomodulatory effects (49, 50), as well as effects regarding difference in killing rates among antimicrobial drugs, antibiotic synergism, antibiotic tolerant pneumococci, or pneumococci adherent to respiratory epithelial cells (51, 52). However, none of these proposed explanations have yet proved to be clinically important, and a mouse peritonitis model has demonstrated antagonism between penicillin and erythromycin (53, 54). Excessive use of antibiotics always increases the risk of resistance developing in microorganisms, as well as other adverse effects. The macrolide antibiotics are known for their cardiotoxic, pro-arrhythmic, effects that in some patients have led to sudden death (55-59).

1.4 PROGNOSTIC SCORING SYSTEMS FOR THE ASSESSMENT OF PATIENTS WITH PNEUMONIA

Community acquired lower respiratory tract infections are common, observed and handled at all levels of the health care system. Patients with CAP can be managed in many different ways due to the seriousness of the disease: as outpatients, sometimes provided with ambulatory care, in the hospital after admission, or on the ICU in severe cases. Due to the frequency and complexity of CAP many prognostic scoring systems for the initial assessment of CAP-patients have been created and tested.
A multicentre prospective survey of aetiology, mortality, prognostic factors, and outcome including 453 patients with CAP from 25 British hospitals was performed by the BTS and the Public Health Laboratory during the years 1982-1983 (60). The study was published in 1987. One of the main result of this study (the BTS rule) was that

included study patients had a 21-fold increased risk of death if 2 of the 3 following signs were observed on hospital admission: respiratory rate ≥30/minute, diastolic blood pressure (BP) ≤60 millimetres of mercury (mmHg), serum urea >7 millimoles per litre (mmol/l). Nine years after the BTS rule was published Neill, and colleagues, in New Zeeland, published their study of 255 prospectively collected patients with CAP (61). Neill et al. modified the BTS rule (mBTS) by adding the sign confusion present on hospital admission. If two, or more signs (tachypnea, low diastolic BP, elevated urea, confusion) were present on hospital admission patients had a 36-fold risk of death. The BTS and mBTS rules lay the ground for CURB-65, as well as the CRB-65 (62), as more than 1000 patients with CAP from the United Kingdom (UK), the Netherlands, and New Zeeland were prospectively studied. The two latter scoring systems proposed by the BTS (63) to be used for initial assessment of patients with CAP. The CURB-65 score contains 5 parameters, giving a 6-point score: **C**onfusion, **U**rea ≥7 mmol/l, **R**espiratory rate ≥30/minute, **B**lood pressure <90 mmHg systolic, or ≤60 mmHg diastolic, age ≥**65** years. The CRB-65, studied in over 6000 patients (63), and originally intended to be used in the outpatient setting, does not require any laboratory measurements, and is therefore simple to use as a bedside tool when assessing the CAP-patient. Though, the CRB-65 contains only clinical parameters, the CURB-65, and the CRB-65 have performed equally well at discriminating patients into mortality risk groups (63). The Swedish Society of Infectious Diseases (Svenska Infektionsläkarföreningen) recommends the use of CRB-65 for initial assessment of patients with CAP, as the scoring system is well studied and easy to use (42).
Developed in the USA, by Fine and colleagues, the Pneumonia Severity Index (PSI) (also called PORT score, as well as Fine score) (64), is the most widely studied predictive model in the management of CAP. The PSI is based on 20 variables, with different weight, that are used to derive a score. Based on 30-day mortality the score enables patient to be stratified into five risk classes, or categories. The PSI was developed to identify patients who were at low risk of death and who could be safely managed outside the hospital, and it is in the outpatient setting where the PSI has best been evaluated. The PSI has been studied worldwide in over 50 000 patients, and it is probably the best validated scoring system for identifying patients at low risk of death from CAP (64, 65).
As life expectancy is rising, the western worlds population is aging, and as people become older the number of persons who are medically compromised will increase, many of whom will require treatment for CAP (66). The PSI emphasis on age and

underlying medical conditions, two parameters that in the future probably will become of even greater importance than today when deciding sites of care in patients with CAP. Hypoxaemia is, as well one of the parameters included in the PSI. Several studies have found that low oxygenation on admission is an unfavourable prognostic factor in CAP (64, 67, 68). Sanz et al. (69) revealed that in patients with a low CURB-65 score (0-1), decreased oxygenation on admission was independently associated with adverse outcome. However, the PSI is cumbersome and time consuming to use with its 20 parameters, even when web based calculators are used for computation of the score. A scoring system for initial assessment of patients with CAP that include comorbidity, as well as oxygenation, both parameters included in the PSI, may have potential to help physicians and health care personnel who need to assess patients with CAP.

The PSI, CURB-65, and CRB-65 are still the most thoroughly evaluated scoring systems for initial prognostic assessment of patient with CAP in regard to 30-day mortality (63). Other prognostic scoring systems as A-DROP (70), SMART-COP (71), and SCAP (72) have been tested and evaluated in patients with pneumonia. These three scoring systems require at least one laboratory analysis, radiography, or some other nonclinical parameter to be measured before the scores can be calculated, and employed. The Acute Physiologic and Chronic Health Evaluation (APACHE II) (73) scoring system, common in the ICU-setting has, as well been used to measure severity of illness in patients with CAP (74-76) and in patients with bacteraemic pneumococcal disease (37). However, the APACHE II scoring system includes several laboratory parameters that require chemical analysis before the total score can be calculated.

2 AIMS

2.1 GENERAL AIMS

To investigate underlying prognostic factors impact on CFR in community acquired Streptococcus pneumoniae bacteraemia with especial emphasis on pneumonia. Analyse if a β-lactam-macrolide combination reduces CFR in patients with bacteraemic pneumococcal pneumonia. To evaluate and improve prognostic scoring systems that are easy to apply for initial assessment in patients with CAP.

2.2 SPECIFIC AIMS

PAPER 1

To identify and define the influence of risk factors in patients ≥18 years old with community acquired pneumococcal bacteraemia.

PAPER 2

To analyse if the addition of a macrolide to a β-lactam reduces mortality in patients with bacteraemic pneumococcal CAP.

PAPER 3

In adult patients with bacteraemic pneumococcal CAP compare the accuracy of three well established scoring systems (PSI, CURB-65, CRB-65) used for the initial assessment of patients with CAP, and to investigate the potential to improve CRB-65, while retaining its simplicity.

PAPER 4

To test and to further improve a modified CRB-65, as a prognostic scoring system in adult patients with CAP of different microbial aetiology, as well as to specify a scoring point level to facilitate the decision which patients, with CAP, that might safely be treated as outpatients, or may benefit from inpatient care.

3 MATERIALS AND METHODS

3.1 PATIENTS AND MATERIALS

3.1.1 Paper 1

From five cites in five countries (Sweden, Spain, Canada, England, and the USA) a total of 460 patients were prospectively included in the study during two years, from September 1993, through August 1995. All patients were admitted to hospital, had not been hospitalised during the preceding 30 days before admission, had pneumococcal bacteraemia, and were aged 18 years and above. An identical case report form was used for all patients in the study.

3.1.2 Paper 2

Of the 370 patients who participated in the first study (paper 1), and suffered from bacteraemic pneumococcal pneumonia, 340 patients who were treated with a ß-lactam antibiotic, with or without the addition of a macrolide, were studied. All patients had a new radiographic shadowing on chest x-ray, consistent with pneumonia. Antibiotics received by the patients during the two first days in hospital were defined as initial antibiotic therapy. The study was observational.

3.1.3 Paper 3

All 233 patients who were enrolled at the Swedish study centre, in paper 1, and suffered from bacteraemic pneumococcal pneumonia were included in paper 3. In order to increase the number of participants in the study another 142 patients with community acquired bacteraemic pneumococcal pneumonia were retrospectively recruited from Karolinska University Hospital and Södersjukhuset, from January 1999 through December 2000, by use of the same case report form (CRF) and inclusion criteria, as the patients enrolled in paper 1 and 2.

3.1.4 Paper 4

From Södersjukhuset, an inner city teaching hospital, patients were retrospectively enrolled during a 16-month period, from December 2008 through March 2010. A total of 1172 patients were recruited, of which 830 patients were admitted for inpatient

treatment, and 342 patients were assigned to ambulatory treatment after their visit at the emergency department (ED). Patients had not been hospitalised during the preceding two weeks before enrolment, and all patients, except 144 outpatients, had a new radiographic finding on chest x-ray, or chest computed tomography (CT), consistent with pneumonia. All admitted patients had a principal diagnosis of pneumonia, or a principal diagnosis of sepsis due to Streptococcus pneumonia, Haemophilus influenzae, or Klebsiella pneumoniae plus a secondary diagnosis of pneumonia according to the International Classification of Diseases 10th revision (ICD-10) codes. The patients who received ambulatory treatment all had a first-listed diagnosis of pneumonia based on ICD-10 codes. Clinical charts as well as laboratory parameters were recorded and analysed in order to calculate the different scoring systems used for initial assessment of patient with community acquired pneumonia.

3.1.5 SUMMARY

Patients in paper 1-3 all had growth of Streptococcus pneumoniae in blood cultures, and were prospectively recruited between September 1993 and August 1995. However, in paper 3 were as well 142 patients retrospectively included between January 1999 and December 2000. Patients in paper 4 suffered from community acquired pneumonia of different aetiology and were enrolled between December 2008 and March 2010, from one hospital. Studies 2-4 were observational, and antibiotic treatment received by each patient was at the discretion of the responsible physician.

3.2 METHODS

3.2.1 Prognostic factors

In all patients the following were to be recorded on admission – age, sex, nursing home living, smoking, alcohol, as well as intravenous (IV) narcotic abuse known by medical care, chronic disease (cardiac disease – hypertensive and/or arteriosclerotic with or without heart failure, pulmonary disease, liver disease, renal disease, diabetes mellitus, cancer, autoimmune disease, steroid treatment, human immunodeficiency virus (HIV)-infection, “other chronic diseases”) date of onset of symptoms, APACHE II score at admission (paper 1 and 2), weight and height, serum levels of albumin and C-reactive protein, peripheral oxygen saturation measured by pulse oximetry (SpO_2). In paper 1 clinical presentation was recorded as pneumonia, meningitis, endocarditis, arthritis or

osteomyelitis, peritonitis, “no focal infection”, as well as combinations of these clinical manifestations of bacteraemic pneumococcal disease.
In all patients need for intensive care unit treatment, and mechanical ventilation were recorded, and in paper 1, as well as in paper 2, antibiotic treatment, including treatment time and doses, were also recorded. Occurrences, as well as, type of nosocomial infections, were recorded in paper 1. In paper 2, in-hospital mortality was compared between the study group of patients who received a β-lactam alone, or in combination with a macrolide antibiotic, for initial antibiotic therapy. Initial antibiotic therapy was defined as the antibiotic therapy received by the patient during the two first days in hospital after admission.
In paper 1, and in paper 2, mortality during hospital stay served as endpoint, while in paper 3 and 4 mortality within 30 days of admission was set as endpoint.

3.2.2 Microbiology

Patients admitted for hospital treatment with suspected bacteraemia or sepsis had blood cultures taken. If growth of Streptococcus pneumonia was detected, the study person at the site was immediately informed about the finding, and the patient was enrolled in the study if inclusion criteria were fulfilled (paper 1).

3.2.3 Severity scores

In paper 1, and in paper 2, the APACHE II score was used for assessment of disease severity. The APACHE II score provides a general measure of severity of disease and it is widely used in ICUs. In paper 3 and 4 three well established scoring systems for the initial assessment of patients with CAP, the PSI, CURB-65, and CRB-65 were used. Severity scores often serve as tools to the clinician to determine the individual patients risk of dying and level of care needed. The scoring systems are also often used in medical research (studies) involving patients with pneumonia. Clinical findings and laboratory results used for the computation of the different scoring systems were, with only few reservations, the results found during first contact at the ED.
The four severity scores were, with few exceptions, calculated in accordance with the original publications. When calculating the APACHE II, and the PSI scores, the corresponding level of haemoglobin replaced haematocrit. As serum creatinine, instead of serum urea, is used in the hospitals were patients were enrolled, cut off values for serum urea when PSI was calculated (>11 mmol/l), as well as CURB-65 (>7 mmol/l)

were replaced by serum creatinine ≥130 micromoles per litre (μmol/l) corresponding to the higher serum urea level in accordance with a study by Spindler et al. (38). Coexisting conditions (see below), and a low oxygen blood level were of independent importance for predicting the case fatality rate (CFR) in the study by Fine et al. (64). Therefore in paper 3, and in paper 4, we analysed if adding information concerning coexisting conditions, as well as peripheral oxygen saturation <90% measured by a pulse oximeter (abbreviated as SaO_2 in paper 3 and SpO_2 in paper 4), or partial pressure of oxygen ($PaO_{2)}$ <8 kilopascal (kPa) (paper 3), to CRB-65, could easily improve its accuracy of predicting the CFR, without adding any laboratory measures. We let the existence of ≥1 coexisting medical condition increase the scores with 1 point, as well as letting the finding of SaO_2 <90%, or PaO_2 <8 kPa in paper 3 and SpO_2 <90% in paper 4 increase the scores with further 1 point.

3.2.4 Statistics

Computer software used for statistical analysis were SAS JMP 5.0.1, and SAS 9.0 (SAS Institute, Cary, NC, USA), SPSS 16.0 (IBM SPSS, Chicago, IL, USA). For the construction of receiver operating characteristic (ROC) curves, as well as for the comparison of the different ROC-curves, area under the curves (AUCs), the software NCSS 07.1.1 was used.

For estimation of individual factors prognostic importance in paper 1 the Cochran-Mantel Haenszel method was used to neutralise imbalance between centres. In paper 1-4 for comparisons of binary type the chi-square, t-test, or Fisher´s exact test were used. The Wilcoxon/Kruskal-Wallis rank sum test was used for continuous variables. For the estimation of independent risk factors found in univariate analysis to have significant, or near significant statistical impact on risk of death, multivariate regression models were used. In paper 3 and 4 the AUCs of the ROC-curves were measured for the comparison of the different scoring systems accuracy to predict 30-day mortality. To find an appropriate cut off value for DS CRB-65 in paper 4 the Youden Index was applied. For all analyses a two-sided p-value of less than 0.05 was considered to indicate statistical significance.

3.2.5 Ethics committee approval

The studies included in this thesis were approved by the local ethics committee at Karolinska Institutet, Karolinska University Hospital. Registration Number: 93:187, 328:02, 2011/1:3.

The CURB-65 score adapted from the original publication by Lim et al. (62)

One point for each element that is present, maximum score is 5 (0-5)

Confusion - new disorientation in person, time or place

Urea - blood urea nitrogen (BUN) level >7 mmol/l

Respiratory rate >30/minute

Blood pressure <90 mm Hg systolic and/or ≤60 mm Hg diastolic

Age ≥**65** years

30-day estimated mortality data by risk class

Risk class	Treatment	Risk mortality	Mortality %
0	Outpatient	Low	0.7
1	Outpatient	Low	2.1
2	In- or outpatient	Intermediate	9.2
3	Inpatient	High	14.5
4	Inpatient	High	40
5	Inpatient	High	14 (1/7 patients)

The Acute Physiologic and Chronic Health Evaluation (APACHE II) score

adapted from the original publication by Knaus et al.(73)

Physiologic variable	**+4**	**+3**	**+2**	**+1**	**0**	**+1**	**+2**	**+3**	**+4**
Temperature, rectal (^{0}C)	≥41	39-40.9		38.5-38.9	36-38.4	34-35.9	32-33.9	30-31.9	≤29.9
Mean arterial pressure, (mmHg)	≥160	130-159	110-129		70-109		50-69		≤49
Heart rate	≥180	140-179	110-139		70-109		55-69	40-54	≤39
Respiratory rate	≥50	35-49		25-34	12-24	10-11	6-9		≤5
If FIO2 >0.5 O_2 (kPa)	≥67	47-66	27-46		<27				
If FIO2 <0.5 PaO_2 (kPa)					≥9.3	8.1-9.3		7.3-8.0	<7.3
Arterial pH	≥7.7	7.6-7.69		7.5-7.59	7.33-7.49		7.25-7.32	7.15-7.24	<7.15
S-Sodium (mmol/l)	≥180	160-179	155-159	150-154	130-149		120-129	111-119	≤110
S-Potassium (mmol/l)	≥7	6-6.9		5-5.9	3.5-5.4	3-3.4	2.5-2.9		<2.5
S-Creatinine (µmol/l) **Double points if acute renal failure**	≥600	300-599	180-299	130-179	50-129		≤49		
Haematocrit (%)	≥60		50-59.9	46-49.9	30-45.9		20-29.9		<20
White blood count (10^9/l)	≥40		20-39.9	15-19.9	3-14.9		1-2.9		<1
Glasgow Coma Score (GCS)		See specified below							
Chronic Health Evaluation		See specified below							
Age		See specified below							

Glasgow Coma Scale (GCS):

GCS	15	14	13	12	11	10	9	8	7	6	5	4	3
APACHE II	0	1	2	3	4	5	6	7	8	9	10	11	12

Chronic Health Evaluation (CHE)

One point assigned for each of the following co-morbidities (0-5 points, see original publication for definitions);

1. Liver disease. 2. Circulation disorder. 3. Respiratory disease. 4. Renal disease. 5. Immune deficiency.

For non operative or emergency postoperative patients +5 points

For elective postoperative patients +2 points

Age

Age	≥75	65-74	55-64	45-54	≤44
APACHE II	6	5	3	2	0

The Pneumonia Severity Index (PSI) adopted from the original publication by Fine et al. (64)

Step 1. If patient is at low risk, class I (≤50 years old, no history of coexisting conditions or abnormalities on physical examination), outpatient treatment recommended.

Step 2. If any condition according to step 1 is not fulfilled go to step 2.

Step 2

Characteristics	**Points assigned**
Demographic factors	
Age in years	
Male	Age
Female	Age-10
Nursing home resident	+10
Coexisting conditions	
Neoplastic disease	+30
Liver disease	+20
Congestive heart failure	+10
Cerebrovascular disease	+10
Renal disease	+10
Physical-examination findings	
Altered mental status	+20
Respiratory rate ≥30/minute	+20
Systolic blood pressure <90 mm Hg	+20
Temperature 35^0C or ≥40^0C	+15
Pulse ≥125/minute	+10
Laboratory and radiographic findings	
Arterial pH <7.35	+30
Blood urea nitrogen ≥11 mmol/l	+20
Sodium <130 mmol/l	+10
Glucose ≥14 mmol/l	+10
Haematocrit <30%	+10
Arterial blood gas PaO_2 <60 mmHg (<8 kPa) or SaO_2/SpO_2 <90%	+10
Pleural effusion	+10
Score, total points	…..

Score	**Risk Class**	**Treatment**	**Estimated Mortality**
Step 1 none score	I	Outpatient	0.1%
≤70	II	Outpatient	0.6%
71-90	III	Outpatient	0.9%
91-130	IV	Inpatient	9.3%
>130	V	Inpatient	27.0%

4 RESULTS AND DISCUSSION

4.1 PAPER 1

4.1.1 Underlying conditions

A total of 460 patients with bacteraemic pneumococcal disease were prospectively enrolled from five centres during two years (Stockholm 290 patients, Barcelona 75 patients, Huntington West Virginia 49 patients, Manchester 30 patients, Halifax Nova Scotia 16 patients). The mean, and median ages were 62 and 65 years respectively, and 54% of the patients were male (P = 0.16). HIV-infection as well as intravenous narcotic use, alcoholism and liver disease were more prevalent among the Spanish patients. Chronic diseases were less common among the Swedish and British patients. Nursing home living, insulin-requiring diabetes mellitus, chronic cardiac as well as chronic lung diseases were more frequently seen in patients from the USA. For details see Table 1.1.

4.1.2 Presentation on admission

Pneumonia was the most common diagnosis in all five centres and occurred, as did meningitis, with nearly similar incidence in all centres. Mean APACHE II score was highest in Barcelona. However, in the remaining centres the APACHE II score was almost similar. ICU-admissions were also similar among the centres; however, mechanical ventilation was more than twice as common in Barcelona. The CFR was more than twice as high in Spain and in the USA, when compared with Stockholm. In patients with meningitis 9/34 died, and among patients diagnosed with both meningitis and pneumonia 5/10 died. Among patients with pneumonia who had two, or more, lung lobes affected 21/109 (19%) died, compared with patients who had one affected lung lobe where 18/245 died (7%), (P = 0.0016, Fisher´s exact test). Twelve (26%) of the 46 patients who died from pneumonia, died within 24 hours of hospital admission, further details are accounted for in Table 1.1.

4.1.3 Factors of prognostic importance

Table 1.2 demonstrates factors significantly correlated to the CFR in univariate analysis by the Cochran-Mantel-Haenszel method. Two-thirds of deaths were recorded in patients more than 65 years old, and the CFR was associated with a threefold increase in nursing home residents. Among underlying chronic conditions pulmonary disease as

well as cardiac disease with heart failure were the conditions most clearly correlated to a high CFR. As shown in Table 1.1 a high APACHE II score was well correlated to the CFR. The mean APACHE II score was 12.4 in the 456 patients who had their score calculated. In patients with a score $\geq$12 the CFR was 21%, and with a score <12 the CFR was 2.6%, for details, see Table 1.2. The CFR rapidly increased in correlation with an increasing APACHE II score, and at a score of 28 the CFR was approximately 50%. Mechanical ventilation, as well as nosocomial infections were well correlated to an increased CFR in univariate analysis, for further details, see Table 1.2.

4.1.4 Comparison between centres

Fisher´s exact test was used for univariate statistical analysis. A clear significant statistical difference could be demonstrated when Swedish patients were compared with patients from the USA regarding nursing home living, any chronic disease, chronic cardiac disease, chronic pulmonary disease, as well as total CFR. When the Swedish study centre was compared with the Spanish, the factors that differed significantly were: any chronic disease, chronic cardiac disease with, and without heart failure, chronic renal disease, APACHE II score $\geq$12, as well as the CFR, for details see the original paper (Table 5).

4.1.5 Antibiotic therapy

Cephalosporin therapy seemed initially by Cochran-Mantel-Haenszel univariate test to be significantly correlated with an increased CFR. This result was probably due to statistical imbalances between the different centres, as when multivariate analysis was performed no such difference could be observed regarding type of antibiotic treatment. The increase in CFR was probably due to the association between cephalosporin therapy and high APACHE II scores.

4.1.6 Mortality predictors

Multivariate analysis of prognostic factors present on admission in relation to the CFR revealed that age, nursing home living, chronic pulmonary disease, and a high acute physiology score (APS) were independent predictors of death. Prognostic factors associated with in-hospital mortality are demonstrated in Table 1.3.
When adding factors occurring during hospital stay, to factors present on admission, as need for mechanical ventilation and nosocomial infection: age, chronic pulmonary

disease, high APACHE II scores, as well as mechanical ventilation were independently associated with mortality, see Table 1.4.

4.1.7 Discussion

Important prognostic factors determining mortality in community-acquired bacteraemic pneumococcal disease, in five centres, located in five different countries, were prospectively examined during 2 years.

The virtually identical rate of pneumococcal meningitis cases in the different study centres supports the assumption that that these cases of pneumococcal bacteraemia are almost always admitted to hospital, have blood cultures taken, and are accurately diagnosed. This also supports that the indications for having blood cultures drawn are most probably, similar in all five sites. Other studies, where patients with bacteraemic pneumococcal disease were studied, have presented rates of pneumococcal meningitis practically identical with the results of paper 1 (34, 77-80). Additionally, the CFR in paper 1 does not differ from results of previous studies (35, 41, 77, 78, 80-85), including as well the difference in CFR between the centres in Stockholm and Huntington, West Virginia (40).

Older age, in accord with previous studies (35, 78, 80, 82, 84-88), as well as pulmonary disease, were independent risk factors for death. In a large meta analysis by Fine et al. (6), of patients with CAP of different origin, chronic pulmonary disease had no impact on mortality (OR. 1.0), whereas neurologic disease (OR. 4.6) as well as neoplastic disease (OR. 3.8) and congestive heart failure (OR. 2.4) had a clear significant influence on mortality. The results reported in the study by Fine et al. (6) are not completely in accordance with the observations made in paper 1. This may be due to the fact that Fine´s study included patients with CAP of different microbial aetiology, not only CAP caused by Streptococcus pneumoniae.

Nursing home living; however, not smoking or alcohol abuse, were independently important regarding prognosis. These findings were in agreement with a study by Watanakunakorn, and colleagues (80). Furthermore, patients infected with HIV had a good prognosis, which corresponds to studies by Hibbs et al. (89), and Feldman et al. (90).

As noted in two studies (78, 91), need for mechanical ventilation indicated a serious prognosis; however, ICU-admission without need for mechanical ventilation did not. An APACHE II score >14, as well as the APACHE II score component APS score >9,

implied an immediate rise in the CFR. Thus, both scoring systems worked very well as prognostic predictors of mortality. When multivariate analysis was performed (data not shown) APS plus age and underlying disease could not predict death as well as APACHE II. Therefore, a conclusion that can be drawn from this study is that the APACHE II scoring system can be used as the sole prognostic index for patients admitted with suspected bacteraemic pneumococcal disease. Two other studies have both concluded that an APACHE II score >15 often goes together with an increased CFR in patients with severe pneumonia (92), as well as bacteraemic pneumococcal pneumonia (80). Additionally, consistent with the findings in paper 1 is that radiographic extension of pneumonia well correlates with mortality, noted in previous studies (80, 92).

The CFR of the study populations in the USA, and in Spain was more than twice as high as in Sweden. By univariate analysis factors, such as age, nursing home residency any chronic disease, cardiac disease, heart failure, pulmonary disease, mechanical ventilation, high APACHE II score, and nosocomial infections, were significantly less prevalent in the Swedish study populations, when compared to the studied patients from the USA and Spain. Though, these differences in CFR could not be confirmed when comparable patients from the USA, Spain, and Sweden were weighed against each other by multivariate statistical analysis. Difference in mortality between the study populations from the USA, and Sweden is in accordance with the CFR of patients in a previous study (40), of patients with bacteraemic pneumococcal disease. The cause or causes for this difference between study centres in regard to CFR, remains unexplained. Higher prevalence of nursing home residency, as well as underlying morbidity, may be of importance.

4.1.8 Conclusion

In 460 prospectively enrolled patients from five centres, in five countries, with bacteraemic pneumococcal disease the APACHE II score accurately and excellently predicted the fatality risk. Independently associated with risk of death, were: mechanical ventilation (OR, 4.4), nursing home living (OR, 2.8), chronic pulmonary disease (OR, 2.5), and age over 65 years (OR, 2.2). Two or more affected lung lobes, on chest x-ray, was independently associated with an increased CFR for patients who had pneumonia. The in-hospital CFR was significantly higher among patients treated at the study centres in the USA and in Spain, when compared to the patients treated at the

Swedish study centre. However, no independent significant factors for these differences were identified.

Table 1.1. Demographic and clinical characteristics for 460 patients with bactearaemic pneumococcal disease at five study centres.

	Stockholm	**Barcelona**	**Huntington**	**Manchester**	**Halifax**	
Characteristics	**Sweden**	**Spain**	**WV, USA**	**UK**	**Canada**	**Total**
	N = 290	**N = 75**	**N = 49**	**N = 30**	**N = 16**	**N = 460**
Age median, years	66	65	65	50	66	65
Age mean, years	62	60	64	53	63	62
Male (%)	147 (51)	43 (57)	32 (65)	19 (63)	6 (38)	247 (54)
Nursing home (%)	15 (5)	6 (8)	7 (14)	1 (3)	3 (19)	32 (7)
Smoking currently (%)	90/260(51)	31/72 (41)	19 (39)	15/29 (50)	4 (25)	159/126(37)
Smoking recently (%)	14 (5)	9 (12)	4 (8)	4 (13)	1 (6)	32 (7)
Alcoholism (%)	20/274 (7)	17/73 (23)	6 (12)	3/29 (10)	1 (6)	47/441(11)
IV narcotics (%)	4/276 (1.5)	14 (19)	2 (4)	1/29 (3)	1 (6)	22/445 (5)
Chronic disease						
Cardiac	98 (34)	12 (16)	25 (51)	5 (17)	5 (31)	145 (32)
Cardiac+heart failure	44 (15)	2 (3)	12 (24)	2 (7)	1 (6)	61 (13)
Pulmonary	49 (17)	15 (20)	21 (43)	7 (23)	7 (44)	99 (22)
COPD	20 (7)	11 (15)	15 (31)	3 (10)	3 (19)	52 (11)
Liver	12 (4)	14 (19)	4 (8)	1 (3)	2 (13)	33 (7)
Renal	8 (3)	6 (8)	3 (6)	0	1 (6)	18 (4)
Diabetes mellitus	13 (4)	8 (11)	7 (14)	1 (3)	1 (6)	30 (7)
Active cancer	19 (7)	7 (9)	4 (8)	2 (7)	0	32 (7)
HIV-infection	10/211 (5)	18/72 (25)	1 (2)	0	0/15	29/376 (8)
Prednisolone >5 mg/day	15 (5)	4 (6)	6 (12)	4 (13)	2 (13)	31 (7)
Any chronic disease	192 (66)	63 (84)	40 (82)	17 (57)	13 (81)	325 (71)
Diagnosis						
Pneumonia	236 (81)	62 (83)	40 (82)	24 (80)	13 (81)	375 (82)
≥2 lobes affected,%	30	32	41	5	38	31
No focus found	27 (9)	4 (5)	5 (10)	2 (7)	1 (6)	39 (8)
Meningitis	21 (7)	7 (9)	3 (6)	2 (7)	1 (6)	34 (7)
Arthritis	8 (3)	1 (1)	0	2 (7)	1 (6)	12 (3)
Peritonits	0	2 (3)	1 (2)	1 (3)	1 (6)	5 (1)
Endocarditis	0	0	0	1 (3)	0	1 (0.2)
APACHE II score mean	11.6	15.3	12	13.2	13.2	12.4
ICU-treatment	51 (18)	21 (28)	9 (18)	3 (10)	4 (25)	88 (19)
Mechanical ventilation	21 (7)	19 (25)	5 (10)	3 (10)	3 (19)	51 (11)
Died	23 (8)	15 (20)	10 (20)	4 (13)	1 (6)	53 (12)

More than 1 disease may have been diagnosed. Number of lobes was determined in 354 patients.

Table 1.2. Different factors effect on CFR in 460 patients with bacteraemic pneumococcal disease.

	Patients who died		**Prognostic influence of factor**		
Factor	**+ factor**	**- factor**	**OR**	**95% CI**	**P-value[a]**
Age >65 years	35/224(16)	18/235 (8)	2.4	1.3 - 4.4	0.004
Nursing home living	9/32 (28)	44/428(10)	3.2	1.4 – 7.5	0.007
Pulmonary disease	21/99 (21)	32/359 (9)	2.6	1.4 – 4.9	0.003
APACHE II score $\geq$12	47/222(21)	6/234 (2.6)	10.7	4.9 – 23.1	0.001
ICU- treatment	26/88 (30)	27/372 (7)	5.3	3.0 – 9.5	0.001
Mechanical ventilation	23/51 (45)	30/409 (7)	8.9	4.9 – 16.3	0.001
Nosocomial infection	11/34 (32)	42/426(10)	3.7	1.7 – 8.0	0.001
Cephalosporin treatment	44/276(16)	9/184 (5)	3.1	1.5 – 6.5	0.003

[a]Cochran-Mantel-Haenzel test.

Data are, number of patients/ number of patients with = + or without factor = - (%)

CFR, case fatality rate; OR, odds ratio; CI, confidence interval; ICU, intensive care unit

Table 1.3. Impact of admission factors associated with in-hospital mortality by multivariate analysis.

Admission factor	**Odds Ratio**	**95% CI**	**P-value**
Age >65 years	2.2	1.1-4.4	0.026
Nursing home living	2.8	1.0-7.3	0.043
Chronic pulmonary disease	2.5	1.2-5.1	0.014
Acute physiology score (APS)			
5-8	3.1	0.9-15	0.10
9-14	7.6	2.4-33	0.002
15-17	22	5.8-112	<0.0001
≥18	41	12-194	<0.0001
Treatment study centre, USA	2.5	0.94-6.4	0.058
Treatment study centre, Spain	2.1	0.96-4.7	0.057

CI, confidence interval

Table 1.4. Impact of admission factors plus factors occurring during hospital stay associated with in-hospital mortality by multivariate analysis.

Factor	Odds Ratio	95% CI	P-value
Age >65 years	2.3	1.1-5.0	0.033
Nursing home living	2.5	0.83-6.9	0.093
Chronic pulmonary disease	2.2	1.0-4.7	0.048
Acute physiology score (APS)			
5-8	2.1	0.9-1.3	0.35
9-14	3.6	0.73-2.2	0.14
15-17	6.8	1.1-5.2	0.049
$\geq$18	11	1.8-7.6	0.013
Need for mechanical ventilation	4.4	1.1-22	0.045
Nosocomial infection	1.9	0.70-5.1	0.19

CI, confidence interval

4.2 PAPER 2

4.2.1 Underlying conditions

From paper one 370 patients with bacteraemic pneumococcal pneumonia were retrospectively analysed in this paper. Of the 370 patients enrolled in the first paper, 340 received a β-lactam antibiotic, with or without the addition of a macrolide antibiotic. Table 2.1 demonstrates the demographic characteristics, and Table 2.2 the clinical characteristics of the 261 patients who received a β-lactam without a macrolide (M-), and of the 79 patients who received a β-lactam plus a macrolide (M+). Univariate statistical analysis revealed no difference regarding time to admission, age, smoking alcohol abuse, gender, cardiac disease with heart failure, pulmonary disease as well as chronic obstructive pulmonary disease (COPD) between the M+ and M- patients. However, intravenous drug abuse, cardiac disease except heart failure, and liver disease were more common among the M+ patients, for further details see Tables 2.1 and 2.2.

4.2.2 Presentation on admission

The APACHE II score as well as the APS were significantly higher in the M+ patients. Need for ICU-therapy did not differ between the two groups while a higher proportion of M+ patients required mechanical ventilation.

4.2.3 Antibiotic therapy, mortality, and mortality predictors

In-hospital CFR among the M+ patients was 19.0%, and among the M- patients 10.7%. The difference in CFR between the two groups was not statistically significant (P = 0.08). Clinical characteristics of the M-, and M+ patients are presented in Table 2.2. As antibiotic therapy may not have had the time to alter the CFR in the 13 patients who died within two days of hospital arrival, statistical analysis without these patients was performed, as was statistical analysis performed in the severely ill patients with APACHE II score $\geq$12. Patients who for initial antibiotic treatment only received one single β-lactam-antibiotic, with or without the addition of a macrolide, were as well analysed separately. No significant difference in CFR was noted between the different groups of M-, and M+ patients, when statistical analysis was performed, for details, see Table 2.3. We also examined if CFR varied between the different study years, or if CFR changed when only patients aged over 50 years were included in the statistical analysis. However, no differences between the two groups were discerned.

4.2.4 Mortality predictors

By use of a logistic regression model for statistical analysis we tested factors independently associated with the CFR such as age, APS for estimating disease severity, two or more lung lobes affected according to chest x-ray, chronic lung disease. We included β-lactam-macrolide combination treatment in this model. No significant reduction in CFR was observed with the addition of this antibiotic regimen, details are demonstrated in Table 2.4.

4.2.5 Discussion

Several studies (44, 93-95) have demonstrated a decreased CFR in patients with community acquired bacteraemic pneumococcal pneumonia who have received a combination of β-lactam and macrolide antibiotics for initial antibiotic treatment. In one study (44) a reduction of the CFR was observed in retrospectively analysed adult patients older than 50 years, collected in one American city between1978 and 1997. Moreover, in another study (93) where patients had been included during a ten-year period multivariate, but not univariate, statistical analysis showed that when initial antibiotic treatment included a macrolide agent, CFR was reduced. In a prospective observational study (95) the CFR was reduced in the 16% of the patients classified as "critically ill" who received any combination of two or more antibiotics.
In the present study we were not able to find a reduction in CFR among patients who received antibiotic combination therapy with a β-lactam and a macrolide. On the contrary univariate statistical analysis revealed a trend towards an increased CFR in patients who received antibiotic combination therapy. However, when previously independent risk factors for death such as age, nursing home living, chronic pulmonary disease, APS, and $\geq$2 affected lung lobes were included in a multivariate statistical regression model, no difference was observed regarding the use of different antibiotic treatment regimens. When statistical analysis was restricted to patients more than 50 years of age, severely sick patients, or those patients who survived two days after admission, no difference in CFR could be observed, regardless of the initial antibiotic regimen - β-lactam antibiotic therapy, with or without the addition of a macrolide.
Several explanations have been proposed for a mortality reduction in patients with bacteraemic pneumococcal pneumonia who receive antibiotic combination therapy - difference in killing rates by different antibiotics, bacterial pathogen tolerant to one antibiotic, co-infection with atypical microbiological agents such as Legionella species,

antimicrobial synergism, macrolide antibiotic effect on cytokine production, as well as effect on pneumococcal adherence to respiratory epithelial cells (48, 51, 52). However, the impact, of the above listed proposed explanations, has not yet been proved to be of clinical importance. In a mouse peritonitis model, as well as in vitro, antagonism or indifference, instead of synergism, was found between a macrolide antibiotic (erythromycin) and β-lactam (penicillin, cefotaxime) (53, 54).

There is still need for prospective randomised studies regarding the issue whether antibiotic combination therapy with a β-lactam and a macrolide is beneficial for patients with severe pneumococcal pneumonia. Excessive use of combination therapy in patients with suspected, or proven, bacteraemic pneumococcal pneumonia, risk to increase costs, adverse effects, as well as resistance to antibiotics.

Table 2.1. Demographic characteristics of the 340 patients with bacteraemic pneumococcal pneumonia that received ß-lactam antibiotics alone (M-), or combined with a macrolide (M+).

Characteristics	M- N=261	M+ N=79	P-value[b]
Age, years			
median	66	60	0.069
mean	63.0	58.5	
Male[a]	136 (52.1)	45 (57.0)	0.520
Nursing home living[a]	21 (8.0)	5 (6.3)	0.810
Smoking[a]			
Currently[a]	89 (34.1)	35 (44.3)	0.110
Recently[a]	20 (7.7)	5 (6.3)	0.810
Alcoholism[a]	24 (9.2)	12 (15.2)	0.145
IV drug abuse[a]	7 (2.7)	7 (8.9)	0.013
Chronic disease			
cardiac[a]	93 (35.6)	16 (20.2)	0.013
cardiac with heart failure[a]	43 (16.5)	6 (7.6)	0.066
pulmonary[a]	53 (20.3)	24 (30.4)	0.067
obstructive pulmonary disease[a]	27 (10.3)	15 (19.0)	0.051
liver[a]	14 (5.4)	10 (12.7)	0.042
renal[a]	10 (3.8)	1 (1.3)	0.468
insulin-treated diabetes[a]	16 (6.1)	7 (8.9)	0.443
active cancer[a]	17 (6.5)	3 (3.8)	0.585
HIV-infection[a]	14 (5.4)	7 (8.9)	0.286
Therapy >5 mg prednisolon/day[a]	15 (5.8)	3 (3.8)	0.774

[a]no. of patients (%)

[b]difference between groups M- and M+, Fisher's exact test for binary variables and the Wilcoxon rank sum test for continuous variables

Table 2.2. Clinical characteristics of the 340 patients with bacteraemic pneumococcal pneumonia that received ß-lactam antibiotics alone (M-), or in combination with a macrolide (M+).

Characteristics	**M-** **N=261**	**M+** **N=79**	**P-value**[b]
Days to admission			
median	3	3	0.293
mean	3,6	4,2	
≥2 lobes affected[a]	72 (27.6)	32 (40.5)	0.363
APACHE II score			
median	11	13	0.022
mean	12.1	13.8	
Acute Physiology Score APS			
median	6	8,5	0.0002
mean	7.4	9.6	
ICU treatment[a]	40 (15.3)	15 (19.0)	0.486
mechanical ventilation[a]	20 (7.7)	13 (16.5)	0.029
nosocomial infection[a]	20 (7.7)	6 (7.6)	1.00
Died[a]	28 (10.7)	15 (19.0)	0.080

[a]no. of patients (%)

[b]Fisher's exact test for binary variables and Wilcoxon rank sum test for continuous

Table 2.3. Case fatality rate in patients receiving ß-lactam alone (M-), or in combination with a macrolide (M+) for initial therapy.

Antibiotic options	**M-**	**M+**	**P-value**[a]
All patients	28/261(10.7)	15/79 (19.0)	0.080
Excluding 13 patients who died within 2 days of admission	21/254 (8.3)	9/73 (12.3)	0.336
Patients with APACHE II score ≥12	25/117(21.4)	15/48 (31.2)	0.230
Patients with APACHE II score ≥12, excluding 12 patients who died within 2 days of admission	19/111(17.1)	9/42 (21.4)	0.640
Patients with APACHE II score ≥19	13/34 (38.2)	9/17 (52.9)	0.378
Patients with APACHE II score ≥19, excluding 9 patients who died within 2 days of admission	9/34 (30.0)	4/12 (33.3)	1.00

[a]Fishers exact test

Table 2.4. Multivariate analysis of factors of possible independent importance for the risk of death in 340 patients with bacteraemic pneumococcal pneumonia.

Factors	**OR**	**95% CI**	**P-value**[a]
Aged >65 years	2.57	1.18 - 5.86	0.020
Nursing home living	2.53	0.786 - 7.55	0.104
Chronic pulmonary disease	1.89	0.797 - 4.40	0.141
$\geq$2 lung lobes affected	2.17	1.01 - 4.67	0.045
APS 5-8	3.94	0.894 - 27.4	0.098
APS 8-14	8.26	2.13 - 54.8	0.007
APS 14-17	23.8	4.77 - 180.3	0.0004
APS $\geq$18	53.8	11.8 - 395.0	<0.0001
Addition of a macrolide	1.09	0.414 - 2.70	0.844

APS, acute physiology score (i.e., APACHE II without age and chronic disease scores); OR, odds ratio; CI, confidence interval

[a]*p*-value testing the null hypothesis OR=1, OR estimate and two-sided 95% confidence interval for OR, multiple logistic regression analysis

4.3 PAPER 3 & 4

4.3.1 Underlying conditions

Univariate statistical analysis of the 375 patients in paper 3, who all suffered from bacteraemic pneumococcal CAP, revealed that older age, underlying medical conditions such as cerebrovascular and renal disease, as well as $\geq$1 coexisting disease defined according to the PSI-rule (in Table 3.1 called D) were significantly associated with an increased risk of death. Clinical and demographic data on patients are demonstrated in Table 3.1.
Among the 1172 patients, with CAP of different microbial aetiology, described in paper 4, older age, male sex, nursing home living, atherosclerotic heart disease, heart failure and any cardiac disease, cerebrovascular, renal and malignant disease were all conditions significantly associated with an increased CFR. For details of the univariate statistical analysis of clinical and demographic data, see Table 4.1.

4.3.2 Presentation on admission

In paper 3 associated with a statistically significant increase in CFR were altered mental status, respiratory rate $\geq$30/minute, measured by arterial blood gas analysis pH <7.35, serum creatinine $\geq$130 µmol/l, peripheral oxygen saturation <90% (abbreviated as SaO_2 in paper 3 and SpO_2 in paper 4), PaO_2 <8 kPa (<60 mmHg) measured by arterial blood gas analysis, need for ICU-treatment, mechanical ventilation, and number of lung lobes affected (visualised by chest x-ray or chest CT), for details, see Table 3.2.
In paper 4 a significant increase in CFR, was observed, as in paper 3, for altered mental status, respiratory rate $\geq$30/minute, pH <7.35, serum creatinine $\geq$130 µmol/l, need for ICU-treatment, and ventilator support. Furthermore in paper 4 a low blood pressure (systolic <90 mmHg, or diastolic $\leq$60 mmHg), SpO_2 $\leq$90%, and non-invasive ventilation (NIV) were all factors associated with increased mortality, see Table 4.2 for details.

4.3.3 Prognostic importance of severity criteria in relation to 30-day mortality

Table 3.4.3 demonstrates (paper 3, and paper 4) cut off values, sensitivity, specificity, positive and negative predictive values for CRB-65, as well as for the modified CRB-65 (DS CRB-65) in relation to 30-day mortality. We let the existence of one, or more, of the diseases (D) that are part of the PSI-score, add an extra point to the modified

CRB-65 score. If poor oxygenation (S) was noted, we also let this finding yield an extra point to the modified CRB-65. The accuracy of this modified score, DS CRB-65, is demonstrated in Table 3.4.3. In paper 3, 97/375 (26%) of the patients received score 0 (3 deaths), thus classified as low risk by CRB-65. In paper 4 were 376/1172 (32%) of the patients similarly classified (1 death). If, by use of DS CRB-65, score 0-1, in paper 3, would be defined as low risk 166/375 (44%) of the patients would be included (5 deaths), and with the same score would 596/1172 (51%) of the patients in paper 4 be so defined (2 deaths). If DS CRB-65 score $\leq$2 would define low risk in paper 3, 264/375 (70%) of the patients would be included (7 deaths). In paper 4, DS CRB-65 score $\leq$2 would include 835/1172 (71%) of the patients with 14/835 (2%) recorded deaths, 18% of all patients who died in paper 4.The AUC of the ROC curve for CRB-65, as well as DS CRB-65 in paper 3 (Fig 1) was 0.77 (CI 0.66-0.84), and 0.83 (CI 0.73-0.89), P = 0.01 for the difference. In paper 4 the AUC of the respective ROC curve for CRB-65, and DS CRB-65 (Fig 2) was 0.82 (CI 0.77-0.85), and 0.87 (CI 0.84-0.90), P <0.0001 for the difference. The ROC curves AUCs, Z-values, and confidence intervals for the different scoring systems are demonstrated in Table 3.4.4. For DS CRB-65 the Youden Index was applied to find an accurate cut off score for predicting 30-day mortality in paper 4. For score $\geq$3 (sensitivity 82%, specificity 75%) the highest value was calculated, 0.58. The second highest value, 0.52, was calculated for score $\geq$2 (sensitivity 98%, specificity 54%). Notably, score 0-1 identified 51% of patients as at low risk, with a mortality of 0.3% (2 deaths).

4.3.4 Discussion

When treating a patient with suspected or proven CAP the physician often has to decide whether the patient should be admitted for hospital treatment, or could be safely treated at home. If the patient can be treated at home, on an outpatient basis, costs are reduced, and risk for nosocomial infections are eliminated. In a study by Coley et al. (96) were patients who received outpatient treatment able to resume normal activity sooner than patients who were hospitalised. Severity scoring systems for patients with CAP may facilitate the site of care decision. The PSI is the most thoroughly evaluated severity scoring system for patients with low-risk CAP suitable for outpatient management (64, 65, 97). However, the PSI is rather cumbersome and time consuming to use, as 20 parameters with different weight are included. Though, the PSI was developed and advocated in North America (97), CURB-65 is now recommended by the Infectious

Diseases Society of America and the American Thoracic Society (98). As a laboratory parameter, urea, is included in CURB-65, the result of a laboratory analysis has to be awaited before the site of care decision can be made. CRB-65, originally advocated for use in outpatient settings, does not require results of any laboratory test. The CRB-65 has been studied in over 6000 patients (63), seen both in community and in hospitals, and is widely used in European countries. The Swedish Society of Infectious Diseases (Svenska Infektionsläkarföreningen) recommends that CRB-65 should be used to assess mortality risk in patients with CAP, since it has the advantage of not requiring venous blood samples (42).

When the PSI was developed underlying medical conditions (malignancy, liver disease, cerebrovascular disease, renal disease, and congestive heart disease), as well as low partial pressure of oxygen, or low oxygen saturation, were found to be independently associated with an increased mortality risk. Information regarding underlying medical conditions, as well as level of peripheral oxygen saturation by pulse oximetry (SpO2), can easily be obtained in the ED.

For the prognosis of CAP the importance of underlying medical conditions are in accordance with several recent studies (38, 72, 99-101), and can probably partly be explained by the independent prognostic importance of high urea and low serum albumin found in other studies (61, 62, 101, 102). In recent reports poor oxygenation has proved to be of independent prognostic importance in proposed new scoring systems, as A-DROP (70), SMART-COP (71), and SCAP (72). These recently described severity scoring systems for patients with CAP seem to perform as well, or even better, than previous systems used for assessing severity of patients with CAP. However these scoring systems are not independent of laboratory resources. The Pitt bacteraemia score, as well as the modified American Thoracic Society score have been found to be the most accurate scores for identifying need for ICU treatment in patients with bacteraemic pneumococcal pneumonia (103). However, in both scores the need for mechanical ventilation and septic shock are included (both conditions in most cases indications for referral to the ICU), so the indication for critical care would be expected. Moreover, none of these two studies are aimed to identify patients in the ED who could be suitable for outpatient treatment.

In paper 3 and in paper 4 our aim was to analyse the accuracy of a modified CRB-65 scoring system in patients with CAP. We found in paper 3, in accordance with previous results when the PSI scoring system has been employed (97), that the presence of one or more of the following conditions - malignant, hepatic, renal, cerebrovascular disease,

and cardiac failure, were independently associated with 30-day mortality. The calculations were simplified by letting the existence of one, or more, of these conditions increase the sum of the "DS CRB-65" with 1 point. In accordance with the PSI we found as well that independently associated with 30-day mortality was the presence of hypoxaemia (PaO_2 <8 kPa measured by arterial blood gas, or a peripheral oxygen saturation <90% measured by pulse oximetry). Other combinations of underlying diseases, or clinical parameters were tested, but did not improve the accuracy of the modified CRB-65.

ROC curves for CRB-65, and DS CRB-65 were constructed for the endpoint 30-day mortality. When the AUCs of the different ROC curves were compared for patients with bacteraemic pneumococcal CAP (paper 3), and patients with CAP of different aetiology (paper 4) a clear statistical significant difference between the scoring systems was observed (P = 0,01 in paper 3, and P <0.0001 in paper 4). For patients classified as at low risk of dying within 30 days of admission (for CRB-65, score 0, for DS CRB-65, score 0-1) both CRB-65 (paper 3, three deaths, paper 4, one death), and DS CRB-65 (paper 3. five deaths, paper 4, two deaths), had a satisfactory prognostic accuracy. However, in paper 4, CRB-65 classified only 32% of the patients as at low risk of death, while with DS CRB-65 51% of the patients could be so classified, while retaining a low CFR (0.3%). Thus, DS CRB-65 may be a more useful prognostic tool than CRB-65, while keeping its independency of laboratory tests.

Paper 3 and paper 4 were both retrospectively designed. In paper 3 only patients with bacteraemic pneumococcal CAP were included, However, Streptococcus pneumonia is the leading cause of bacterial CAP, as well as the leading cause of death due to CAP (104, 105). The CFR among the patients in papers 3 and 4 was almost similar, 9%, though the patients in paper 4 were unselected and suffered from CAP of different microbial origin. Thus, it seems possible that a majority of the patients in paper 4 who died suffered from CAP due to Streptococcus pneumonia, as it is the most commonly occurring pathogen in CAP, as well as it is the leading cause of death in CAP (6).

In paper 3 patients were enrolled during two time-periods 1993-1995, 1999-2000. It may be questioned whether results from a study that took place nearly 20 years ago can be relevant today? However, in paper 3 all patients who were included in the study, were diagnosed by identical criteria: Streptococcus pneumoniae bacteraemia, new radiographic finding consistent with pneumonia, hospital admission, and use of identical CRFs. As patients were enrolled during two periods of time we compared the data from an on-going surveillance study of invasive pneumococcal disease in Sweden

to assess the generalisability of paper 3. Since 2006 it has been mandatory to report all cases of invasive pneumococcal disease in Sweden to the Swedish Institute for Infectious Diseases Control (Smittskyddsinstitutet, SMI). From January 2007 through December 2009, questionnaires regarding clinical information about patients with detected bacteraemic pneumococcal disease were returned from clinicians in charge at sites with notified bacteraemic pneumococcal disease. Of these 529 reported patients, 430 patients had pneumonia, and 46 of these patients died (CFR 11%) within 30 days after blood culture samples were taken. As the CFRs in paper 3 were almost similar in patients enrolled during the years 1993-1995, 1999-2000, as well as in the on-going study at the Swedish Institute for Infectious Diseases Control, and in previous Swedish studies of patients with pneumococcal bacteraemic CAP (37, 38, 40), we do not believe that, though patients were recruited during the years 1993 to 1995, this has had any significant influence on the results in paper 3.

In both papers serum creatinine replaced serum urea, a modification that is in accordance with previous studies, and ATS guidelines (38, 106).

In paper 4, patients with CAP of different microbial aetiology were studied, and patients admitted to hospital, as well as patients treated on outpatient basis were included. All hospitalised patients had a new finding on chest x-ray or chest CT consistent with pneumonia. In 144 of the 342 (42%) patients treated as outpatients, no chest x-ray, or chest CT, was performed and two of these patients died within 30 days. However, as a clear majority of the patients in paper 4 had radiographic findings compatible with pneumonia, revealed by chest x-ray, or CT, and as 94% of all patients who died were admitted for hospital care, missing radiological examination could hardly have affected the comparison between CRB-65 and DS CRB-65, which was the main objective of this study. Moreover, the way patients were examined, assessed and finally diagnosed with CAP, without chest radiography, is part of how CAP-patients who do not need hospitalisation are handled in the ED. Lack of roentgen examination in 144 of the ambulatory treated patients may have had an impact on the calculation of the PSI score, as the finding of pleural effusion increase the PSI score by 10 points. However, the main objective of the study described in paper 4, was to compare CRB-65 with DS CRB-65 in patients with CAP.

4.3.5 Conclusion

Paper 3, and paper 4 indicate that by adding data on the existence of underlying health conditions, as well as the presence of hypoxaemia in patients with CAP, the uncomplicated prognostic score CRB-65 will improve its accuracy and precision in predicting 30-day mortality, while retaining its independence of laboratory tests. The improved score, DS CRB-65, can easily be used in the ED, as well as outside the hospital to facilitate the site of care decision for a patient with suspected CAP. New studies, preferably prospective, as well as re-analysis of data from previous studies are needed to further evaluate, and confirm, the role of DS CRB-65 as a scoring system for early risk assessment of patients with CAP.

Table 3.1. Clinical and demographic data for patients who survived and for those who[a] died. Paper 3.

Characteristics	Survived N=340	Died N=35	P-value
Age, years			
median[c]	62.0	75.0	0.002
mean	60.6	70.3	
range	18-98	38-93	
Female[b]	173 (51)	13 (37)	0.1
Nursing home living[b]	9 (3)	3 (9)	0.09
Smoking			
currently[b]	117 (34)	9 (26)	0.4
recently[b]	13 (4)	2 (6)	0.6
Alcoholism[b]	30 (9)	7 (20)	0.06
IV drug abuse[b]	10 (3)	2 (6)	0.3
Cardiac disease			
cardiac any[b]	98 (29)	14 (40)	0.2
heart failure[b]	48 (14)	7 (20)	0.6
hypertension[b]	33 (10)	6 (17)	0.2
atherosclerotic	63 (18)	7 (20)	0.8
Chronic disease			
cerebrovascular	11 (3)	4 (11)	0.04
pulmonary[b]	59 (17)	5 (14)	0.8
liver[b]	22 (6)	5 (14)	0.09
renal[b]	4 (1)	3 (9)	0.02
diabetes[b]	28 (8)	5 (14)	0.2
malignancy[b]	23 (7)	4 (11)	0.3
HIV[b]	13 (4)	1 (3)	1.0
immunosuppression[b]	25 (7)	4 (11)	0.3
Preexisting diseases ”D”[b]	93 (27)	18 (51)	0.006
Any other preexisting diseases[b]	183 (53)	25 (71)	0.05

[a]No. (%). [b]Fisher´s exact test used. [c]Wilcoxon/Kruskal-Wallis rank sum test used.

Preexisting disease, ”D”,coexisting disease defined according to the PSI rule – malignant disease, liver disease, congestive heart failure, cerebrovascular disease, renal disease.

Any other preexisting disease, ”D” plus chronic lung disease (obstructive, restrictive e t c), diabetes mellitus (insulin and non-insulin dependent), chronic heart disease(congestive, atherosclerotic, hypertensive, valvular, arrythmic e t c).

Table 3.2. Physical examination, laboratory findings and ICU-treatment in patients who survived, and in patients who died[a]. Paper 3.

Findings	Survived N = 340 N (%)	Died N = 35 N (%)	P-value
Altered mental staus	34 (10)	16 (46)	<0.0001
Respiratory rate >30/min[a]	86 (25)	19 (54)	0.0006
Systolic BP <90 mmHg or diastolic BP ≤60 mmHg[a]	95 (28)	13 (37)	0.2
Body temperature <35 or >40°C[a]	23 (7)	2 (6)	1.0
Pulse ≥125[a]	56 (16)	10 (29)	0.1
pH <7.35[a]	13 (4)	11 (31)	<0.0001
Creatinine ≥130 µmol/l[a]	85 (25)	25 (71)	<0.0001
Sodium <130 mmol/l[a]	48 (14)	7 (20)	0.3
Glucose ≥14 mmol/l[a]	19 (6)	3 (9)	0.4
Haematocrit <30% or Hb <100 g/l[a]	25 (7)	6 (17)	0.06
Pleural effusion[a]	72 (21)	8 (23)	0.8
SaO_2 <90% or PaO_2 <60 mmHg[a] (8 kPa)	92 (27)	25 (71)	<0.0001
ICU-treatment[a]	54 (16)	19 (54)	<0.0001
Ventilator[a]	17 (5)	15 (43)	<0.0001
Affected lung lobes[b]			
median	1.0	2.0	
mean	1.4	2.0	0.001

Data are presented as No. total (%).

ICU, Intensive Care Unit PSI; Pneumonia Severity Index; BP, blood pressure.

[a]Fisher´s exact test used, [b]t-test used

Table 4.1. Clinical and demographic data for patients who survived, and for those who died. Paper 4.

Characteristics	Survived N= 1092	Died N=80	P-value[a]
Age, years			
Median	66.0	82.5	<0.0001
Mean	63.7	80.3	
Range	18-100	45-99	
Male, *n* (%)	532 (49)	49 (61)	0.04
Nursing home residence, *n* (%)	11 (1)	9 (11)	<0.0001
Cardiac disease, *n* (%)			
Hypertensive	287 (26)	25 (31)	0.4
Atherosclerotic	165 (15)	20 (20)	0.02
Heart failure	112 (10)	31 (39)	<0.0001
Cardiac any[b]	481 (44)	53 (66)	0.0002
Chronic disease, *n* (%)			
Cerebrovascular	119 (11)	25 (31)	<0.0001
Pulmonary	296 (27)	23 (29)	0.8
Liver	35 (3)	1 (1)	0.5
Renal	76 (7)	17 (21)	<0.0001
Diabetes mellitus	136 (12)	15 (19)	0.1
Malignancy	66 (6)	10 (12)	0.03
HIV	11 (1)	0	1

[a]Fisher´s exact test was used, except for continuous data, as age, where the Wilcoxon/Kruskal-Wallis rank sum test was used.

[b]Cardiac any = hypertensive, atherosclerotic, congestive, valvular, arrhythmic e t c

Table 4.2. Physical examination, laboratory findings and ICU-treatment in patients who survived, and in patients who died. Paper 4.

Findings	Survived, N=1092, N (%)	Died N=80, N (%)	P-value[a]
Altered mental status	53 (5)	14 (18)	<0.0001
Respiratory rate ≥30/min	229 (21)	45 (56)	<0.0001
Systolic BP <90 mmHg +/-diastolic BP ≤60 mmHg	149 (4)	31 (39)	<0.0001
Body temp. <35° or ≥40°C	26 (2)	3 (4)	0.4
Pulse ≥125/min	67 (6)	18 (22)	<0.0001
pH <7.35	34 (3)	9 (11)	0.002
Serum creatinine ≥130 µmol/l[b]	123 (11)	34 (42)	<0.0001
Serum sodium <130 mmol/l	30 (3)	2 (3)	1
Serum glucose ≥14 mmol/l	47 (4)	6 (8)	0.2
Hb <100 g /l	20 (2)	3 (4)	0.2
SpO_2 <90%	323 (30)	62 (78)	<0.0001
ICU-treatment[b]	67 (9)	14 (19)	0.01
Ventilator[b, c]	12 (2)	5 (7)	0.01
NIV[b, d]	23 (3)	9 (12)	0.001

BP, blood pressure; Hb, haemoglobin; ICU, intensive care unit; SpO_2, peripheral oxygen saturation measured by pulse oxymetri

[a]Fishers´s exact test.

[b]Only the 830 patients who were admitted were analysed.

[c]Ventilator = ventilatory support with patient intubated or tracheostomised.

[d]NIV = non-invasive ventilatory support with patient not intubated or tracheostomised.

Table 3.4.3. Sensitivity, specificity, positive and negative predictive values of 30-day CFR of the different prediction rules[a] in paper 3 and in paper 4.

30-day CFR		Cut-off	Sensitivity	Specificity	PPV	NPV
CRB-65, paper 3						
0	3/97 (3)	≥0	100	0	9	NA
1	6/140 (4)	≥1[b]	91	28	12	97
2	10/100 (10)	≥2	74	67	19	96
3	14/36 (39)	≥3	46	94	42	94
4	2/2 (100)	4	6	100	100	90
CRB-65, paper 4						
0	1/376 (0)	≥0	100	0	7	NA
1	18/471 (4)	≥1[b]	99	34	10	100
2	35 247 (14)	≥2	76	76	19	98
3	24/74 (32)	≥3	32	95	33	95
4	2/4 (50)	4	2	100	50	93
DS CRB-65, paper 3						
0	0/65 (0)	≥0	100	0	9	NA
1	5/101 (5)	≥1	100	19	11	100
2	2/98 (2)	≥2	86	47	14	97
3	9/67 (13)	≥3	80	76	25	97
4	11/32 (34)	≥4	54	93	43	95
5	8/12 (67)	≥5	23	99	67	92
6	0/0	6	NA	NA	NA	NA
DS CRB-65, paper 4						
0	0/295 (0)	≥0	100	0	7	NA
1	2/301 (1)	≥1	100	27	9	100
2	12/239 (5)	≥2	98	54	14	100
3	19/195 (10)	≥3	82	75	20	98
4	30/106 (28)	≥4	59	91	33	97
5	16/34 (47)	≥5	21	98	47	94
6	1/2 (50)	6	1	100	50	93

[a]Data are presented as No. total (%).

PPV, positive predictive value; NPV, negative predictive value; NA, not applicable.

CFR, case fatality rate.

[b]Cut-off points accepted as threshold to define high-risk groups according to original study design. [62, 63]

Table 3.4.4. Results of receiver operating characteristic (ROC) curves, of severity scores, in association with 30-day mortality for paper 3, and paper 4.

	AUC	**SE**	**Z-value**[a]	**95% CI**
PSI Class[b]	0.84	0.03	11.3	0.77 – 0.89
CURB-65[b]	0.81	0.04	8.4	0.73 – 0.87
CRB-65[b]	0.77	0.05	5.8	0.66 – 0.84
DS CRB-65[b]	0.83	0.04	8.4	0.73 – 0.89
PSI Class[c]	0.84	0.02	19.6	0.80 – 0.87
CURB-65[c]	0.83	0.02	15.8	0.79 – 0.87
CRB-65[c]	0.82	0.02	15.4	0.77 – 0.85
DS CRB-65[c]	0.87	0.02	22.6	0.84 – 0.90

[a]to test AUC >0.5

[b]Paper 3

[c]Paper 4

AUC, area under curve; SE, standard error; CI, confidence interval.

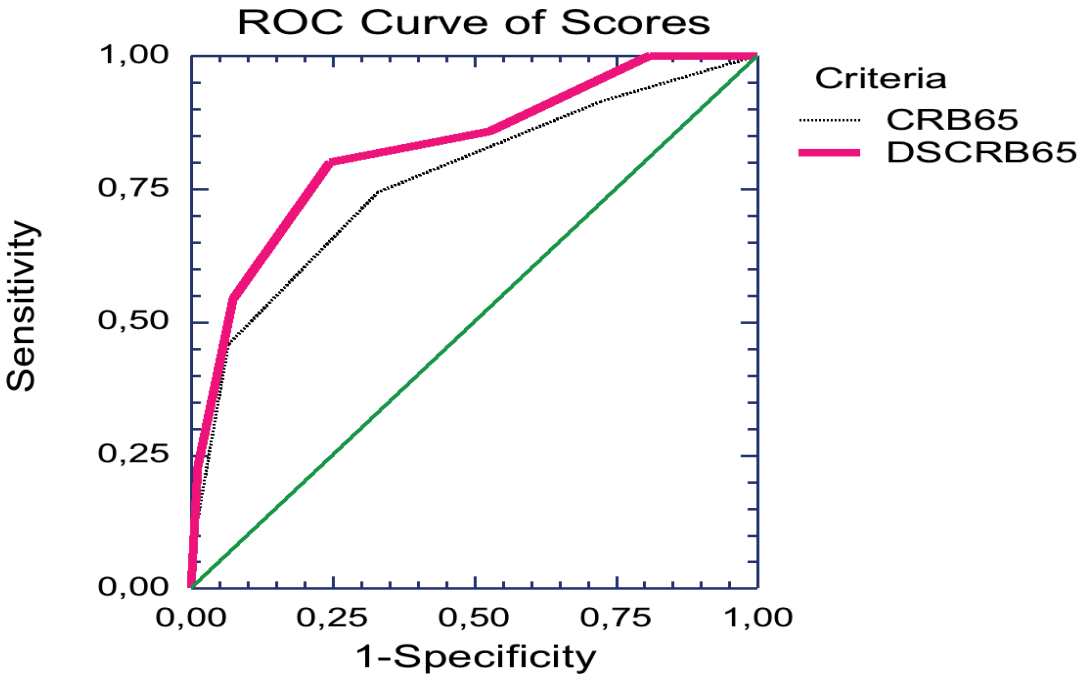

Figure 1. Comparative receiver operating characteristic (ROC) curves for severity scores CRB-65 and DS CRB-65 in association with 30-day mortality. Paper 3. For details, see Table 3.4.4.

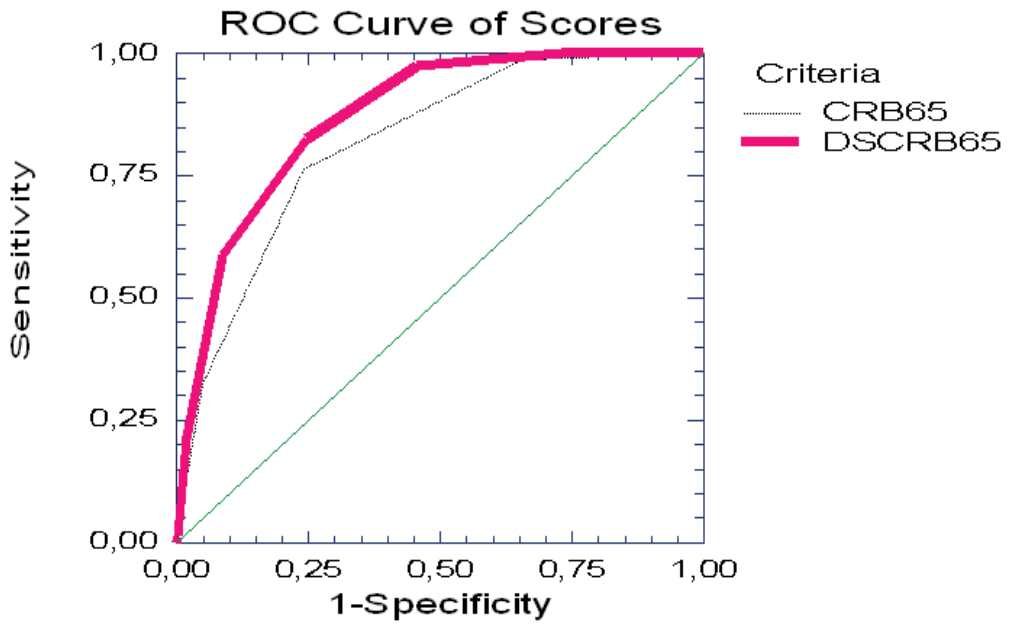

Figure 2. Comparative receiver operating characteristic (ROC) curves for severity scores CRB-65 and DS CRB-65 in association with 30-day mortality. Paper 4. For details, see Table 3.4.4.

5 GENERAL SUMMARY AND DISCUSSION

The first paper was a two-year prospective multicentre study that included 460 patients with community acquired bacteraemic pneumococcal disease from five centres, in five countries. The main aim of the study was to define prognostic factors that contribute to in-hospital mortality, as well as to analyse underlying and prognostic factors that may affect outcome in patients with bacteraemic pneumococcal disease. The scoring system APACHE II, a severity of disease classification system, often used in ICUs, predicted in-hospital CFR excellently and accurately. Independent risk factors for death, present on admission to hospital by multivariate analysis, were living in a nursing home, presence of chronic pulmonary disease, age over 65 years. Need for mechanical ventilation during hospital stay, was as well, a mortality risk factor found by multivariate analysis. Patients with pneumonia who had more than one lung lobe affected, revealed by chest x-ray, ran as well a significantly increased risk of death during hospital stay. Incidence of pneumonia and meningitis was almost similar between the participating centres. However, there was a great difference regarding the fatality rates. In the USA and in Spain, 20% of the studied patients died, while in Sweden 8% of the participating patients died. This significant difference in mortality between patients with bacteraemic pneumococcal pneumonia was demonstrated in a previous study (40). No plausible explanations for this difference between the participating centres were found. Interestingly, in paper 1, factors that were statistically significant regarding risk of death revealed by univariate, though not by multivariate, statistical analysis, such as old age, nursing home living, and heart failure, are prognostic factors included in the pneumonia severity index, created by Fine and colleagues (6). Age >65 years, revealed by both univariate and multivariate statistical analysis to be an important prognostic risk factor, is included in the recommended scoring systems for the assessment of CAP, CURB-65 and CRB-65 (62).

In paper 2 prospectively collected data on 340 patients with bacteraemic pneumococcal pneumonia were studied. Patients in paper 2 participated in the multicentre study described in paper 1. The aim of the study was to investigate if the addition of a macrolide antibiotic to a ß-lactam for initial antibiotic treatment could improve in-hospital survival. Neither univariate, nor multivariate statistical analysis could detect any significant decrease in CFR among patients who received antibiotic combination-therapy, not even when taking into consideration age, severity of illness or early deaths could any difference be discerned.

The aim of the studies described in paper 3 and in paper 4 was to improve the accuracy of the scoring system CRB-65 as a prognostic tool to predict 30-day mortality in patients with bacteraemic pneumococcal pneumonia (paper 3), as well as in patients with pneumonia of different microbiological aetiologies. An additional purpose of the study (paper 4) was to find a suitable scoring point level to facilitate the decision which CAP patients who might safely be treated as outpatients, or benefit from inpatient care. Paper 3 included 375 hospitalised Swedish patients. In paper 4 a total of 1172 patients (830 inpatients, 342 outpatients) with pneumonia of different aetiologies were retrospectively enrolled during 16 months, from one teaching hospital in Stockholm, Sweden. By letting the existence, of one or more of the underlying medical conditions, that are an important part of the PSI, increase CRB-65 with one point as well as letting hypoxaemia, in accordance with the PSI, also increase CRB-65 with one point, we could design a scoring system that could easily be managed without any need for laboratory tests or results. We choose to call this scoring system DS CRB-65 (D for disease, S for oxygen saturation). From the data in paper 3 and in paper 4 ROC curves were constructed for the outcome, death within 30 days of hospital admission, and a clear significant statistical difference was observed between the AUCs of the two scoring systems, in favour of DS CRB-65 ($P = 0.01$, and $P < 0.0001$, respectively). To find an appropriate cut off value for DS CRB-65 the Youden Index was applied. For score ≥ 3 (sensitivity 82%, specificity 75%) the highest value was calculated, 0.58. For score ≥ 2 (sensitivity 98%, specificity 54%) the second highest value, 0.52, was calculated. DS CRB-65, score 0-1, identified half of the patients in paper 4, as at low risk with 2 deaths (CFR, 0.3%), while among the 20% of the patients with score 2, the CRF had risen to 5%.

6 CONCLUSIONS

The APACHE II score worked exceptionally well and accurately as a prognostic instrument for predicting mortality risk in patients with bacteraemic pneumococcal disease. In-hospital mortality differed considerably between the centres, and was more than twice as high in the USA and in Spain when compared to Sweden. Independent predictors of death present on hospital admission were age over 65 years, nursing home residency, presence of chronic pulmonary disease, and a high APACHE II score. Risk factor for death after hospital admission was need for mechanical ventilation. Patients with pneumonia who on chest x-ray had two, or more, lung lobes affected, also had a significantly increased case fatality risk.

When ß-lactam and macrolide antibiotics were combined for initial antibiotic treatment in patients with bacteraemic pneumococcal pneumonia, no in-hospital decrease in CFR could be observed among all participating patients, or in different subgroups of patients (survived first 2 days of hospitalisation, high APACHE II score on hospital admission, 50 years of age or older, received ß-lactam and macrolide antibiotics only).

The accuracy of CRB-65 as a prognostic tool for the prediction of mortality within 30 days of hospital admission was significantly enhanced when underlying diseases, as well as hypoxaemia, both in accord with the PSI-rule, were added to the scoring system. The proposed new scoring system DS CRB-65 performed excellently well in patients with CAP due to Streptococcus pneumoniae, as well as in patients with CAP of different microbial aetiology. The DS CRB-65 can easily be used in hospitals EDs, or outside the acute hospital, as no laboratory tests are needed.

7 ASPECTS FOR THE FUTURE

The fatality rate is still high in bacteraemic pneumococcal disease, despite access to efficient antibiotics, intensive care, as well as mechanical ventilation for the critically ill. Our knowledge regarding underlying chronic diseases and their impact on patients who present with acute pneumococcal disease, is increasing. However, socioeconomic factors such as income, occupation, education, mental status, social network, gender e t c, are all factors difficult to measure in relation to infectious diseases. Research regarding these matters in relation to pneumococcal disease is an issue of great importance.

In many severe infections that require antibiotic treatment for weeks, or even many months, e.g. osteomyelitis, tuberculosis, endocarditis, or infections associated with foreign material, have combinations of antibiotics proven more successful than single antibiotic treatment. In CAP due to pneumococci different antibiotic combinations have been tested, however not yet been proven beneficial in decreasing the CFR. Hopefully, future studies can cast some light regarding if, or which antibiotic combinations, that may benefit patients who suffer from serious pneumococcal disease.

Scoring systems to grade seriousness of acute medical conditions are often used in hospitals EDs to facilitate safe and effective treatment, as well as to decide level of care. The new scoring system proposed to be used in patients with CAP, DS CRB-65, needs to be tested in future, preferably prospective studies with sufficient statistical power.

8 SWEDISH SUMMARY

Bland infektionssjukdomar är samhällsförvärvad lunginflammation den vanligast förekommande infektionssjukdomen som leder till vård på sjukhus. Det är en sjukdom som i första hand drabbar de yngsta, de äldsta, de fattigaste och de sjukaste i samhället. Insjuknande i samhällsförvärvad lunginflammation hos befolkningen (incidens) uppskattas hos vuxna i västvärlden uppgå till 5-12 personer per 1000 personer och år (0,5-1,2 %). Mellan 20 % och 40 % av de personer som drabbats av samhällsförvärvad lunginflammation behöver läggas in på sjukhus för vård. Dödligheten är under 1 % för personer som kan vårdas i hemmet. Hos sjukhusvårdade patienter med samhällsförvärvad lunginflammation kan dödligheten stiga till 50 % hos de allra sjukaste. I Europa beräknas den årliga kostnaden för samhällsförvärvad lunginflammation uppgå till över 10 miljarder Euro.
Den vanligaste mikrobiella orsaken till samhällsförvärvad lunginflammation är pneumokockbakterien (Streptococcus pneumoniae), som även ger upphov majoriteten av alla dödsfall i samhällsförvärvad lunginflammation. Innan antibiotika fanns tillgängligt för att behandla infektionssjukdomar kunde dödligheten i samhällsförvärvad lunginflammation, där patienter led av blodförgiftning med pneumokocker, ibland överstiga 80 %. Vid lunginflammation där pneumokocker har hittats i blodet på patienten kan man idag med hjälp av verksamma antibiotika och tillgång till intensivvård sänka dödligheten till mellan 5 % och 25 %.

I denna avhandling finns fyra delarbeten i form av forskningsstudier presenterade.

I den första forskningsstudien deltog 460 patienter från fem länder i en prospektiv multicenterstudie. Alla patienter hade pneumokockbakterier i blod och 12 % av alla patienter dog under tiden de var inlagda på sjukhus. De vanligast förekommande diagnoserna var samhällsförvärvad lunginflammation, bakteremi (bakterier i blod) utan funnet focus och hjärnhinneinflammation. Då patienterna lades in på sjukhus noterades flera oberoende prognostiska riskfaktorer som var kopplade till risken att dö under vårdtiden. Dessa riskfaktorer för död var – ålder över 65 år, kronisk lungsjukdom, vårdhemsboende, minst två lunglober infekterade (visar hur utbredd lunginflammationen är med hjälp av röntgen) samt behov av respiratorhjälp för att syresätta blodet.

I den andra forskningsstudien deltog 340 patienter som hade samhällsförvärvad lunginflammation och samtidigt pneumokocker i blodet. Målet med studien var att undersöka om man med kombination av två olika antibiotikasorter (β-laktamantibiotika som t ex penicillin eller cefalosporin i combination med med makrolidantibiotika, till exempel erytromycin, klaritromycin), kunde minska dödligheten i svår lunginflammation med pneumokocker som växer i blodet. Trots omfattande statistisk analys kunde vi inte påvisa att kombination av antibiotika, enligt ovan, minskade dödligheten jämfört med om man behandlade med β-laktamantibiotika, som t ex penicillin, vilket är förstahandsbehandling vid infektion med pneumokocker.
I den tredje och i den fjärde delstudien deltog patienter med samhällsförvärvad lunginflammation. Målet med studie tre och fyra var att på ett enkelt, men säkert sätt, bedöma patienters behov av vård på sjukhus med hjälp av ett poängbaserat bedömningssystem. Forskningsstudie tre inkluderades 375 patienter där alla patienter hade samhällsförvärvad lunginflammation och pneumokockbakterier i blodet. I delstudie fyra deltog 1172 patienter (830 patienter blev inlagda på sjukhus och 342 patienter kunde vårdas i hemmet). Patienterna i delstudie fyra hade samhällsförvärvad lunginflammation orsakad av olika sorters bakterier och virus.
Det behövs inga blodprover eller rtg-undersökningar för att kunna använda bedömningssystemet, som vi valt att kalla DS CRB-65. Varje bokstav och siffrorna 65 anger en parameter. Nödvändiga uppgifter om eventuella underliggande sjukdomar (D) erhålls via patienten, anhöriga, eller journalsystem. Mängden syre i blodet (S) kontrolleras med”en klämma på fingret”och med hjälp av några enkla frågor bedömer om patienten är förvirrad (C). Man kontrollerar även andningsfrekvens (R), blodtryck (B) och ålder (65) där ålder 65 år, eller äldre ger 1 poäng. Varje mätt parameter som uppfylls ger 1 poäng (0-6 poäng). Om patienten har låga poäng och inget talar däremot kan patienten vårdas i hemmet, vid höga poäng (minst 3) vårdas patienten bäst på sjukhus.

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