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Jaana Karhu

SEVERE COMMUNITY-ACQUIRED PNEUMONIA – STUDIES ON IMAGING, ETIOLOGY, TREATMENT, AND OUTCOME AMONG INTENSIVE CARE PATIENTS

UNIVERSITY OF OULU GRADUATE SCHOOL;
UNIVERSITY OF OULU,
FACULTY OF MEDICINE,
INSTITUTE OF CLINICAL MEDICINE,
DEPARTMENT OF ANAESTHESIOLOGY, DIVISION OF INTENSIVE CARE;
OULU UNIVERSITY HOSPITAL, DEPARTMENT OF INFECTION CONTROL;
MEDICAL RESEARCH CENTER OULU

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Academic Dissertation to be presented with the assent of the Doctoral Training Committee of Health and Biosciences of the University of Oulu for public defence in Auditorium 1 of Oulu University Hospital, on 19 September 2014, at 12 noon

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Abstract

Pneumonia is a common diagnosis for intensive care unit (ICU) admission. In 2012, 51% of the ICU-treated infections in Finland were of pulmonary origin. The ICU-treated pneumonias can be classified according to acquisition of infection as community-acquired (CAP) or hospital-acquired (HAP). Ventilator-associated pneumonia (VAP) is a subtype of HAP. Patients with severe community-acquired pneumonia (SCAP) require ICU treatment due to need of mechanical ventilation or hemodynamic support. SCAP is associated with high morbidity and high ICU and hospital mortality. The aim of this observational study was to evaluate the clinical characteristics and outcome of SCAP, with special interest on imaging, viral etiology, combination antibiotic treatment and long-term outcome.

The thesis comprises three retrospective studies with altogether 392 SCAP patients, median age 55 years, 55.9% of them male. The usefulness of early chest CT and β-lactam-respiratory quinolone (βQ) versus β-lactam-macrolide (βM) therapy for SCAP treatment was evaluated. The hospital and long-term outcomes of SCAP patients were compared with 66 HAP and 25 VAP cases. A prospective study included 49 mechanically ventilated SCAP patients. The frequency of viral etiology in SCAP was analyzed.

In SCAP patients, the chest CT as compared to the chest radiograph yielded new imaging findings for 58.5% of the SCAP patients. This information led to procedures or treatment changes in 43% of the cases. The severity of oxygenation disorder correlated to the extent of lung involvement. In prospective SCAP series ICU- mortality was 6.1% and hospital mortality was 12.2%. Viral etiology was found to be common in SCAP and viruses were demonstrated in 49% of patients. The outcome was similar whether SCAP patients were treated with βQ or βM combination. The type of pneumonia did not have a significant association with hospital mortality in ICU-treated SCAP, HAP and VAP patients. Among the hospital survivors, the long-term mortality was substantial, SCAP patients representing the best 1-year outcome.

In conclusion, early CT might be useful in SCAP diagnostics and treatment. Viral etiology is common in SCAP. Both β-lactam-respiratory quinolone and β-lactam macrolide combinations were equally good in SCAP treatment. Hospital mortality did not differ among ICU-treated pneumonia cases, but SCAP had the best long-term survival.

Keywords: community-acquired infections, intensive care, mortality, pneumonia, treatment outcome

Karhu, Jaana, Tehohoitoon johtava kotisyntyinen keuhkokuume – tutkimuksia kuvantamisesta, etiologiasta, antimikrobihoidosta ja ennusteesta.

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Tiivistelmä

Keuhkokuume on yleinen tehohoitoon johtava tulehdussairaus. Suomessa vuonna 2012 tehoosastolla hoidetuista infektioista 51 % oli keuhkoalkuisia. Keuhkokuume luokitellaan hankintapaikan mukaan kotisyntyiseksi (CAP) tai sairaalasyntyiseksi (HAP). Hengityslaitehoitoon liittyvä keuhkokuume (VAP) on sairaalasyntyisen keuhkokuumeen alatyyppi. Vakavalla kotisyntyisellä keuhkokuumeella (SCAP) tarkoitetaan vaikeaa keuhkoinfektiota, joka vaatii hengityslaitehoitoa tai verenkierron tukihoitoa teho-osastolla. SCAP:iin liittyy korkea sairastuvuus sekä tehohoito- ja sairaalakuolleisuus. Tässä havainnoivassa kliinisessä tutkimuksessa selvitettiin SCAP:n kliinistä kuvaa ja ennustetta. Erityishuomion kohteena oli varhaisvaiheessa suoritetun keuhkojen tietokonekerroskuvauksen (CT), keuhkokuumeen aiheuttajamikrobien ja antibimikrobihoidon vaikutus taudin hoitoon ja ennusteeseen sekä tehohoidettujen keuhkokuumepotilaiden pitkäaikaisennuste.

Väitöskirja koostuu kolmesta retrospektiivisestä osatyöstä, joissa oli yhteensä 392 SCAP-potilasta. Potilaiden mediaani-ikä oli 55 vuotta ja heistä 55,9 % oli miehiä. Varhaisvaiheen keuhkojen CT:n sekä beetalaktaami-kinoloni- ja beetalaktaami- makrolidi-yhdistelmähoidon vaikutusta keuhkokuumeen hoitoon arvioitiin retrospektiivisesti. SCAP-potilaiden sairaalakuolleisuutta ja pitkäaikaisennustetta verrattiin 25:n VAP- ja 66:n HAP-potilaan ennusteeseen. Prospektiivisessa tutkimuksessa oli 49 hengityskonehoidettua potilasta. Tutkimuksessa tarkasteltiin virusten osuutta ja merkitystä vaikeassa SCAP:ssa.

Keuhkojen CT havaitsi 58,5 %:lla SCAP-potilaista löydöksiä, joita ei todettu keuhkojen natiiviröntgentutkimuksessa. Löydökset johtivat toimenpiteisiin 43 %:lla SCAP-potilaista. Happeutumishäiriön vaikeusasteen ja CT:llä todettujen keuhkojen tulehdusmuutosten laajuuden välillä havaittiin yhteys. Virusetiologia on SCAP:ssa yleinen. Viruksia havaittiin 49 %:lla SCAP-potilaista. Beetalaktaami-kinoloni- ja beetalaktaami-makrolidi -yhdistelmähoidon välillä ei havaittu eroa SCAP-potilaiden ennusteessa. SCAP-, HAP- ja VAP-potilaiden ennustevertailussa keuhkokuumetyypin ei todettu vaikuttavan sairaalakuolleisuuteen. Paras yhden vuoden ennuste oli SCAP-potilailla.

Yhteenvetona todettakoon, että varhaisvaiheen keuhkojen CT on hyödyllinen SCAP:n hoidossa. Virukset ovat yleisiä SCAP:n aiheuttajamikrobeja. Molemmat tutkitut antimikrobiyhdistelmät todettiin hyviksi SCAP:n hoidossa. Sairaalakuolleisuus ei eroa keuhkokuumealatyyppien välillä, mutta SCAP- potilailla on paras pitkäaikaisennuste.

Asiasanat: avohoitoinfektiot, bakteerikeuhkokuume, hengityslaitehoitoon liittyvä keuhkokuume, hoidon vaikuttavuus, kuolleisuus, tehohoito

To three beautiful girls- Roosa, Saga & Alisa

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Oulu June 2014 Jaana Karhu

Abbreviations

AKI	Acute kidney injury
APACHE	Acute Physiology and Chronic Health Evaluation
ARDS	Adult respiratory distress syndrome
ATS	American Thoracic Society
BAL	Bronchoalveolar lavage
βM	Betalactam-macrolide
BMI	Body mass index
BPP	Bacteremic pneumococcal pneumonia
βQ	Betalactam-quinolone
BTS	British Thoracic Society
BUN	Blood urea nitrogen
CAP	Community-acquired pneumonia
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CRB-65	Confusion Respiratory rate Blood pressure age ≥65 years
CRP	C-reactive protein
CT	Computed tomography
CURB-65	Confusion Urea Respiratory rate Blood pressure age ≥65 years
FiO2	Fraction of inspired oxygen
HAP	Hospital-acquired pneumonia
HR	Hazard ratio
ICU	Intensive care unit
IDSA	Infectious Disease Society of America
IG	Immunoglobulin
IL	Interleukin
kPa	Kilopascal
LOS	Length of stay
LRTI	Lower respiratory tract infection
NIV	Non-invasive ventilation
NP	Nasopharyngeal swab
OR	Odds ratio
PaO2	Partial pressure arterial oxygen
PCR	Polymerase chain reaction
PCT	Procalcitonin

PF	Ratio of partial pressure of arterial oxygen and fraction of inspired oxygen
PIRO	Predisposition Insult Response Organ failure
PSI	Pneumonia Severity Index
RIFLE	Risk Injury Failure Loss End-stage
RRT	Renal replacement therapy
SaO2	Oxygen saturation
SCAP	Severe community-acquired pneumonia
SD	Standard deviation
SMART-COP	Systolic blood pressure Multilobar lung involvement Albumin Respiratory rate Tachycardia Confusion Oxygenation pH
SOFA	Sequential Organ Failure Assessment
suPAR	Soluble urokonase-type plasminogen activator receptor
TNF	Tumour necrosis factor
TUS	Thoracic ultrasound
VAP	Ventilator-associated pneumonia
WBC	White blood cell count

List of original publications

This thesis is based on the following publications, which are referred throughout the text by their Roman numerals:

I Karhu J, Ala-Kokko TI, Ahvenjärvi L, Rauvala E, Ohtonen P & Syrjälä H (2014) Early Chest CT scan compared to plain chest x-ray in acute severe community-acquired pneumonia. Manuscript.

II Karhu J, Ala-Kokko TI, Vuorinen T, Ohtonen P & Syrjälä H (2014) Lower respiratory tract virus findings in mechanically ventilated patients with severe community-acquired pneumonia. Clin Infect Dis 59(1): 62–70.

III Karhu J, Ala-Kokko TI, Ohtonen P & Syrjälä H (2013) Severe community-acquired pneumonia treated with β-lactam-respiratory-quinolone vs. β-lactam-macrolide combination. Acta Anaesthesiol Scand 57(5): 587–593.

IV Karhu J, Ala-Kokko TI, Ylipalosaari P, Ohtonen P, Laurila JJ & Syrjälä H (2011) Hospital and long-term outcomes of ICU-treated severe community-acquired, hospital-acquired and ventilator-associated pneumonia patients. Acta Anaesthesiol Scand 55(10): 1254–1260.

Table of contents

1 Introduction

In 2013 in Oulu University Hospital altogether 1,677 patients had pneumonia as a hospital discharge diagnosis. Pneumonia is a common diagnosis for intensive care unit (ICU) admission. In a Finnish single center study 60% of the community-acquired and 48% of the hospital-acquired infections necessitating ICU treatment were pneumonias (Ylipalosaari *et al.* 2006a). In a Finnish prospective multicenter sepsis study 43% of the ICU-treated infections were of pulmonary origin; in 2012 the corresponding figure was 51% (Karlsson *et al.* 2007, Poukkanen *et al.* 2013). The ICU-treated pneumonias are often classified as either community-acquired or hospital-acquired, depending on whether the infection is developed in an outpatient (i.e., outside hospital) or inpatient setting (Kollef *et al.* 2005). Community-acquired pneumonia (CAP) is an acute lower respiratory tract infection (LRTI) acquired from the community, with fever, cough, dyspnea, tachypnea, and pleural chest pain as typical symptoms. Diagnosis is confirmed with new opacity in the chest radiograph (Bartlett *et al.* 2000, Mandell *et al.* 2007, Lim *et al.* 2009, Woodhead *et al.* 2011). Patients with severe community-acquired pneumonia (SCAP) have single or multiple organ dysfunctions which require treatment in the ICU, typically mechanical ventilation or hemodynamic support (Mandell *et al.* 2007). Hospital-acquired pneumonia (HAP) is defined as a pneumonia occurring 48 hours after hospital admission, which was not incubating at the time of admission (Niederman *et al.* 2005, Rotstein *et al.* 2008). Ventilator-associated pneumonia (VAP) is a sub-type of HAP, which refers to pneumonia developing more than 48 hours post-endotracheal intubation and mechanical ventilation (Rello *et al.* 2002, Niederman *et al.* 2005, Rotstein *et al.* 2008).

Approximately 20–32%, in Finland up to 42–51%, of CAP patients are treated as inpatients, and 10–20% of them require treatment in ICUs (Jokinen *et al.* 1993, Guest & Morris 1997, Angus *et al.* 2002, Koskela 2013). HAP is the second most frequent cause of hospital-acquired infection, accounting for 13–18% of all nosocomial infections in the Western countries (Lynch 2001, Vallés *et al.* 2003). The incidence of HAP ranges from five to more than 20 cases per 1,000 hospital admissions (Niederman *et al.* 2005, Rotstein *et al.* 2008, Barbier *et al.* 2013). Almost 30% of HAPs are ICU-acquired, accounting for up to 90% VAP cases (Masterton *et al.* 2008, Rotstein *et al.* 2008). VAP is the most frequent ICU-acquired infection occurring in 9–40% of intubated patients (Rello *et al.* 2002, Vincent *et al.* 2009, Forel *et al.* 2012, Rosenthal *et al.* 2012). The incidences of VAP have varied between 2 and 19 per 1.000 ventilator days (Hubmayr 2002,

Ylipalosaari *et al.* 2006b, Lee *et al.* 2012, Rosenthal *et al.* 2012). Compared to mechanically ventilated patients without VAP, patients with VAP have significantly longer duration of mechanical ventilation, longer ICU and hospital stays (Rello *et al.* 2002).

The hospital mortality in SCAP has varied from 18% to 40% and the outcome is strongly influenced by manifested organ failures (Angus *et al.* 2002, Rodriguez *et al.* 2007, Georges *et al.* 2013). The hospital mortality in CAP is clearly lower, being 5–10% (Fine *et al.* 1996, Lim *et al.* 2009). Compared to non-ICU CAP patients, the mortality rates among ICU-treated SCAP patients are almost fourfold (Angus *et al.* 2002). Crude mortality rates of HAP resemble those of CAP, i.e., 10% (Craven & Chroneou 2010). Mortality is explicitly higher for VAP, with a range of 20% to 76%, and depending on the case mix, disease severity, specific microbiology and management (Rello & Diaz 2003, Melsen *et al.* 2011, Timsit *et al.* 2011, Forel *et al.* 2012).

While pneumonia is a common ICU-admission diagnosis, data comparing the clinical risk factors and long-term outcomes between ICU-treated pneumonia groups are sparse. Chest radiograph is required for verifying the pneumonia (Bartlett *et al.* 2000). There are some promising results concerning the use of CT also in CAP diagnosis (Syrjälä *et al.* 1998), although its real clinical significance remains open for the moment (Mandell *et al.* 2007). Viruses account for 11–55% of CAP cases among adults (Ruuskanen *et al.* 2011) but there are only few studies concentrating on viral etiology in SCAP (Choi *et al.* 2012, Wiemken *et al.* 2013). Combination antibiotic therapy is considered superior to single regimen options for treatment of SCAP patients, specifically patients in septic shock (Rodriquez *et al.* 2007, Martin-Loches *et al.* 2010). There is still debate as to the best antimicrobial combination for improving the outcome in SCAP (Sligl *et al.* 2014).

This single center study was carried out to obtain more information on the characteristics, diagnosis, etiology, treatment and outcome of SCAP in a mixed tertiary-level academic medical surgical adult ICU. We were interested in whether chest CT provides additional clinically important information to chest radiograph in the diagnosis and treatment decisions for SCAP patients. The frequency and importance of viral etiology in SCAP was assessed. The comparison of the antimicrobial combination therapy using either β-lactam quinolone or β-lactam-macrolide antibiotics also needed further characterization. Finally, to obtain perspective for long-term outcome, SCAP was compared with ICU-treated hospital-acquired and ventilator-associated pneumonia patients.

2 Review of the literature

2.1 Definition for severe community-acquired pneumonia

Community-acquired pneumonia (CAP) is an acute lower respiratory tract infection (LRTI) acquired from the community with fever, cough, dyspnea, tachypnea and pleural chest pain as typical symptoms. Diagnosis is confirmed with new opacity in chest radiograph (Fig. 1) (Bartlett *et al.* 2000, Mandell *et al.* 2007, Lim *et al.* 2009, Woodhead *et al.* 2011). Pulmonary infection develops as a consequence of a specific pathogenic organism, large inoculation of micro-organisms and compromised immune system of the host (Waterer *et al.* 2011). The inflammatory response, which is caused by the counteraction between micro-organisms and host, does not always remain localized. Severe community-acquired pneumonia (SCAP) is a progressive disease developing from a local pulmonary infection to a systemic infection manifesting as sepsis, severe sepsis, septic shock and multiorgan failure when inflammatory cytokines spread into systemic circulation (Fig. 2) (Rello 2008, Waterer *et al.* 2011).

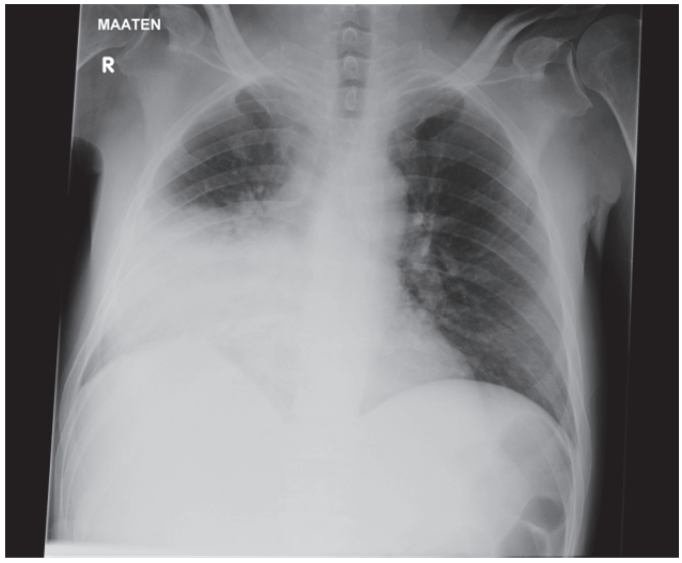

Fig. 1. A chest radiograph of a patient with severe community-acquired pneumonia showing lobar airspace opacity in the right inferior lobe.

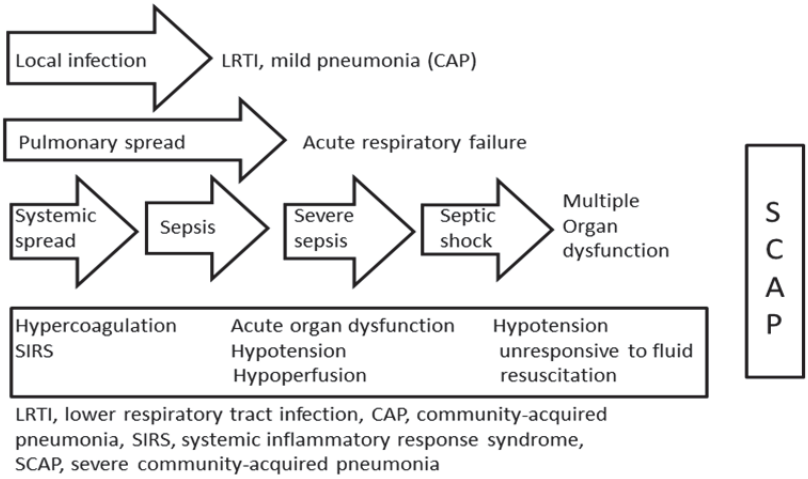

Fig. 2. The progression of CAP to SCAP. Modified from Rello, Critical Care 2008.

2.1.1 Pneumonia severity scores

The definition of SCAP lacks a golden standard. In many trials SCAP has been defined as disease necessitating admission to the ICU due to need for ventilatory or hemodynamic support (Oosterheert *et al.* 2003). Several scoring systems have been developed, firstly, to recognize the severity of illness, secondly, to reduce the expensive hospital costs of patients with low risk of mortality, and thirdly, to predict the likelihood of death and complicated disease course. None of them, however, include a precise definition of SCAP (Fine *et al.* 1997, Lim *et al.* 2003, España *et al.* 2006, Mandell *et al.* 2007, Charles *et al.* 2008).

Pneumonia Severity Index (PSI) (Appendices, Table 18) has been validated with large cohorts of CAP inpatients and outpatients. The tool consists of twenty variables and was primarily developed to predict low risk of death and to help select patients for outpatient treatment. It is not designed to define the need for ICU treatment. Based on the PSI score patients are divided into five risk classes, I–V. Patients in risk classes IV–V are considered to have severe CAP and should be hospitalized or admitted to ICU care (Fine *et al.* 1997). Studies have shown that the score cannot accurately predict hospital admission and the need for ICU care, and being heavily weighted by age, PSI score underestimates the severity of

disease in younger patients (Angus *et al.* 2002, Ewig *et al.* 2004, Carratala *et al.* 2005, Renaud *et al.* 2007).

CURB-65 score (C equals Confusion, U equals Urea, R equals Respiratory rate, B equals Blood pressure and 65 equals age ≥65 years) was introduced by the British Thoracic Society (BTS) (Appendices, Table 19) (Lim *et al.* 2003). The score is based on a 6-point scale and was developed to predict 30-day mortality. Patients with CURB-score ≥3 should be hospitalized or treated in ICU setting. CURB-65 has not been found useful for predicting ICU-admission (Capelastegui *et al.* 2006). The CRB-65 score is a simplified version of the CURB-65 score. The CRB-65 score has also been validated within large CAP inpatient populations and performs well in pneumonia severity and 30-day mortality prediction in the hospital setting (McNally *et al.* 2010).

In 2007 the Infectious Diseases Society of America and the American Thoracic Society (IDSA/ATS) revisited the ATS 10 scale criteria originally published in 1993 and further evaluated by Ewig (Ewig *et al.* 2004). The criteria comprise variables known to predict in-hospital death, and they were developed to define severe CAP and to predict ICU-admission. The IDSA/ATS criteria for SCAP and ICU admission consist of two major criteria: the need for mechanical ventilation and septic shock and nine minor criteria (Table 2). The patient has SCAP and should be considered for ICU admission when one major criterion or at least three minor criteria are met (Mandell *et al.* 2007). The IDSA/ATS score seems to perform well; one validation study found that the predictive rule had a sensitivity of 71% and specificity of 88% for determining the need for ICU admission (Liapikou *et al.* 2009). Another study observed that the IDSA/ATS minor criteria predicted hospital mortality and guided ICU admission among patients who did not need emergency mechanical ventilation or vasopressors (Phua *et al.* 2009). The IDSA/ATS definition is now widely accepted to define SCAP (Rello 2008).

SMART-COP is an acronym for systolic pressure, multilobar lung infiltrates, albumin level, respiratory rate, tachycardia, confusion, oxygenation and arterial pH. The scoring system consists of eight factors predicting the need for intensive respiratory and vasopressor support and is suggested to better define SCAP (Appendices, Table 20) (Charles *et al.* 2008). The need for respiratory and vasopressor support is regarded to be a more objective endpoint than admission to ICU, which is used in other scoring systems (Charles *et al.* 2008). The sensitivity and specificity of SMART-COP to predict the need for invasive ventilation and

hemodynamic support was found to be 92.3% and 62.3%, respectively (Charles *et al.* 2008).

The España rule or SCAP score, used to define severe CAP and need for ICU admission, has two major criteria (blood pressure <90 mmHg or arterial pH <7.30) and six minor criteria resembling those in the IDSA/ATS definition (Appendices, Table 21) (España *et al.* 2006). The PIRO (Predisposition, Injury, Response, Organ dysfunction) severity assessment tool was developed by Rello and colleagues to predict mortality among SCAP patients admitted to ICU (Appendices, Table 22). In a multicenter study the PIRO score was shown to perform well in 28-mortality prediction and was associated with increased healthcare utilization in ICU-admitted SCAP patients (Rello *et al.* 2009).

Table 1. Definitions of SCAP.

Score	Definition for SCAP
PSI (Fine *et al.* 1997)	PSI-class IV–V
CURB-65 (Lim *et al.* 2003)	CURB-score ≥3
IDSA/ATS (Mandell *et al.* 2007)	1 major criterion / 3 minor criteria
SCAP-score (España *et al.* 2006)	SCAP-score > 10 points or 1 major or ≥2 minor
SMART-COP (Charles *et al.* 2008)	SMART-COP ≥3 points

Table 2. The Infectious Diseases Society of America/ The American Thoracic Society criteria for SCAP and guidelines for intensive care unit admission. Mandell *et al.* 2007.

Major criteria (any one of)	Minor criteria (at least three of these)
Invasive mechanical ventilation	Respiratory rate ≥30 breaths/minute
Septic shock with the need for vasopressors	PaO_2/FiO_2 ratio ≤250 mmHg (33 kPa)
	Multilobar infiltrates
	New onset confusion/desorientation
	Uremia (BUN level, ≥20mg/dL)
	Leukopenia (WBC count, <4,000 cells/mm^3)
	Thrombocytopenia (platelet count, <100,000 cells/mm^3)
	Hypothermia (core temperature, <36°C)
	Hypotension requiring aggressive fluid resuscitation

2.1.2 The limitations of the scoring systems

Several limitations have been presented concerning the severity scores. None of them include an accurate definition of SCAP. PSI and CURB-65 are useful for excluding the need for hospital admission. SMART-COP and IDSA/ATS major

criteria guide the need for ICU admission. IDSA/ATS minor criteria may be useful in defining patients at high risk for complications (Pereira *et al.* 2012). The scores do not necessarily take into account all the aspects of SCAP, such as social factors and comorbidities (i.e., COPD, immune status). They may underestimate the the severity of disesase in younger, otherwise healthy patients, who would benefit from supportive care (i.e., oxygen and fluid therapy administration), respiratory and hemodynamic monitoring. Above all, these scores are fairly rigid and they have mainly been developed for use in the emergency department setting and they perform poorly in predicting the evolving SCAP (Niederman 2009). One of the main values of scoring is the opportunity to allow comparisons between different study populations. Clinical judgment combined with the knowledge of patients' clinical, hemodynamic, laboratory and imaging characteristics is still the most essential in SCAP treatment, and scoring systems act only as useful guides (Niederman 2009, Ewig *et al.* 2011).

2.2 Incidence of severe community-acquired pneumonia

The annual incidence of CAP among the adult ranges generally between 5 and 11 per thousand habitants, the incidence varying markedly with age (Lim *et al.* 2009, Vila-Corcoles *et al.* 2009). In Eastern Finland in 1981–82, the reported incidence of CAP was 13 per 1,000 habitants per year, increasing up to 34 per 1,000 for those over 75 years (Jokinen *et al.* 1993). Approximately 20–32% of CAP patients are treated as inpatients, but some higher rates have been reported from Finland (Jokinen *et al.* 1993, Guest & Morris 1997, Angus *et al.* 2002, Koskela 2013). A recently published Finnish register study showed that the incidence of CAP and also the need of hospital treatment are increasing especially among elderly (over 75 years) patients (Koskela 2013). The proportion of hospitalized adults with CAP requiring treatment in the ICU ranges between 5% and 20%, depending on the admission criteria and the availability and level of healthcare systems in different countries (Ruiz *et al.* 1999, Marrie & Shariatzadeh 2007, Charles *et al.* 2008). A British analysis of ICU admissions between the years 1995 and 2004 found that 5.9% of all ICU admissions were due to SCAP. During the study period there was a 128% increase in admissions for SCAP, from 12.8 per 1,000 to 29.2 per 1000 (Woodhead *et al.* 2006). In a US cohort with 1,339 CAP inpatients, 12.7% of the patients were admitted to ICU, admission rates ranging from 8.8% to 26.1% across participating centers (Angus *et al.* 2002). In the same

study it was calculated that ICU-treated SCAP patients accounted for 43% of the total hospital costs of CAP patients (Angus *et al.* 2002).

2.3 Risk factors to severe community-acquired pneumonia

The early identification of the patients at risk for SCAP is fundamental to optimize the treatment and level of care. Studies have found several risk factors predisposing to SCAP, and many of these risk factors are also included in pneumonia severity scores (Fine *et al.* 1997, Lim *et al.* 2003, España *et al.* 2006, Mandell *et al.* 2007, Charles *et al.* 2008, Rello *et al.* 2009). Advanced age (defined in many studies as age over 65 years) has been shown to increase the risk of CAP and adverse outcome, as well (Moine *et al.* 1994, Rello *et al.* 1996, Fine *et al.* 1996, Baik *et al.* 2000, Kaplan *et al.* 2003, Welte *et al.* 2012). However, despite the higher case fatality rate among elderly people, more than 50% of deaths from bacteremic pneumococcal pneumonia occur among patients aged 18 to 65 years (Feikin *et al.* 2000). Some studies have demonstrated that SCAP patients are younger than CAP patients treated in the ward (Marrie & Shariatzadeh 2007, Valencia *et al.* 2007). In different SCAP studies the mean age has varied from 45 to 73 years, mean age being approximately 60 years (Table 7). Male gender has also been considered as a risk factor in SCAP, the proportion of males ranging from 53% to up to 88% (Table 7) (Wilson *et al.* 2005, Restrepo *et al.* 2008).

Co-morbidities, including chronic obstructive pulmonary disease (COPD), kidney injury or need for hemodialysis, congestive heart failure, ischemic heart disease, diabetes, malignancy, chronic neurologic disease and liver disease have been found to predispose to SCAP. Of SCAP patients, from 60% to 83% had at least one chronic disease (Moine *et al.* 1994, Rello *et al*. 1996, Ruiz *et al.* 1999, Marik 2000, Angus *et al.* 2002, Rello *et al.* 2003, Yoshimoto *et al.* 2005, Marrie & Shariatzadeh 2007, Rodriguez *et al.* 2007, Restrepo *et al.* 2008, Welte *et al.* 2012, Torres *et al.* 2013). Alcoholism (as defined by a daily alcohol intake of ≥80 g/day) has been associated with defects of innate and adaptive immunity and represents an important independent risk factor for SCAP (Gamble *et al.* 2006). The risk for SCAP was increased in the alcoholic patients who were leukopenic at hospital admission (Ruiz *et al.* 1999, de Roux *et al.* 2006, Marrie & Shariatzadeh 2007). There is evidence that smoking increases the risk of CAP and SCAP (Marrie & Shariatzadeh 2007, Almirall *et al.* 2008). It has recently been shown

that smoking is an independent risk factor for 30-day mortality of CAP patients (Bello *et al.* 2014).

Treatment with low dose corticosteroids and immunosuppression has been associated with SCAP in previous studies (Rello *et al.* 1996, Ruiz *et al.* 1999). Underweight (body mass index, BMI <18.5 kg/m^2) has been shown to predispose to SCAP, whereas obesity (BMI >30 kg/m^2) has not been found to be a risk factor (Torres *et al.* 2013). No association between obesity and ICU transfer, need for mechanical ventilation or vasopressor utilization has been found, either (Kahlon *et al.* 2012, King *et al.* 2013). However, during the Influenza A (H1N1) pandemic 2009, obese and morbidly obese patients were more likely to be admitted to ICU due to severe influenza pneumonia compared to non-obese patients (Kok *et al.* 2013).

Conditions affecting specific innate immunity can increase the risk of developing SCAP (Waterer *et al.* 2001a). Substantially increased risk for CAP and invasive pneumococcal disease has been found among patients with mutations in the gene encoding mannose-binding lectin (Roy *et al.* 2002). Mannose-binding lectin acts as a key mediator of innate host immunity that activates the complement pathway and directly opsonizes infectious pathogens (Roy *et al.* 2002). Tumor necrosis factor-α (TNF-α) hypersecretor gene polymorphism has been found to be associated with the development of septic shock in CAP patients (Waterer *et al.* 2001a).

Table 3. Risk factors for SCAP.

Risk factors for SCAP
Age ≥65 years
Male gender
Co-morbidity
Alcoholism
Smoking
Immunosuppressive medication
Body mass index <18.5 kg/m^2
Factors affecting innate immunity

2.4 Clinical characteristics of severe community-acquired pneumonia

Cough, fever (>38°C), dyspnea (i.e., shortness of breath) and tachypnea (i.e., elevated respiratory frequency) and pleural chest pain represent the characteristic symptoms of pneumonia. Certain symptoms are not specific for pneumonia or are not conclusive for pneumonia diagnosis, neither are they characteristic of any pathogen (Lim *et al.* 2009). Approximately 70% of patients with SCAP and non-severe CAP presented cough on hospital admission (Ewig *et al.* 1998, Ruiz *et al.* 1999, Angus *et al.* 2002, Marrie & Shariatzadeh 2007). Dyspnea on hospital or ICU admission is a sign of severe disease. According to previous studies, up to 90% of SCAP patients have had dyspnea, compared to 65% of non-ICU patients with milder disease (Ewig *et al.* 1998, Ruiz *et al.* 1999, Angus *et al.* 2002). On the contrary, pleuritis chest pain, due to pleural inflammation or irritation, occurs less commonly among SCAP patients (Ewig *et al.* 1998, Ruiz *et al.* 1999, Angus *et al.* 2002, Marrie & Shariatzadeh 2007). Elderly patients present more frequently non-specific symptoms: 20–30% of them lack fever or other typical clinical symptoms. However, they show more often confusion or deterioration of the underlying disease as a sign of severe disease on hospital admission (Fernández-Sabé *et al.* 2003).

SCAP manifests most often as respiratory failure. Elevated respiratory rate (respiratory rate >30 breaths per minute), and hypoxia (i.e., PF ratio <33–40 kPa or PaO_2 <8kPa or SaO_2 <90%) are the most prevalent findings in up to 65% and 90% of the patients, respectively, in reported SCAP series (Ewig *et al.* 1998, Georges *et al.* 1999, Ruiz *et al.* 1999, Angus *et al.* 2002, Yoshimoto *et al.* 2005, Restrepo *et al.* 2008). Tachypnea and hypoxia develop due to inflammation-induced ventilation perfusion mismatching or are related to circulatory failure due to sepsis. A respiratory rate of over 30 breaths per minute has been found as a prognostic factor for a need of ventilatory or vasopressor support, ICU treatment and adverse outcome in several studies (Fine *et al.* 1997, Lim *et al.* 2003, Mandell *et al.* 2007, Charles *et al.* 2008).

SCAP patients need mechanical ventilation on or during ICU admission in 50% to up to 85% of the cases, whereas the presence of septic shock is reported to be somewhat lower, 16–64%, in previous studies (Table 7). Acute kidney injury (AKI) is a common complication of SCAP and many patients present AKI on ICU admission (Mongardon *et al.* 2012). Many pneumonia severity scoring systems

use blood urea as a surrogate for kidney injury and when AKI is defined by urea >10 mmol/L, reported frequencies have ranged from 30% to 55% (Georges *et al.* 1999, Angus *et al.* 2002, Yoshimoto *et al.* 2005, Restrepo *et al.* 2008). Confusion (assessed by Abbreviated Mental Test or disorientation to place or time) has been considered a sign of severe disease, and 17–57% of SCAP patients have been reported to present confusion on ICU admission (Ewig *et al.* 1998, Ruiz *et al.* 1999, Angus *et al.* 2002, Marrie & Shariatzadeh 2007, Restrepo *et al.* 2008). On the contrary, the rates among non-ICU CAP patients have ranged from 5% to 18% (Ewig *et al.* 1998, Marrie & Shariatzadeh 2007, Restrepo *et al.* 2008).

Most SCAP patients present also other abnormalities in vital signs and laboratory parameters on admission. Metabolic acidosis (pH <7.3) has been shown to increase the risk for SCAP and predict ICU admission, mechanical ventilation as well as the need for vasopressor support (Angus *et al.* 2002, Wilson *et al.* 2005, Yoshimoto *et al.* 2005, Mandell *et al.* 2007, Charles *et al.* 2008, Restrepo *et al.* 2008). Leukopenia (white blood cell count $<4.0\times10^9$/L), thrombocytopenia (platelet count $<100\times10^9$/L), tachycardia (heart rate >125 beats per minute) and hyponatremia (serum sodium concentration <130 mmol/L) have been found to be more prevalent in SCAP as compared to CAP in previous studies (Angus *et al.* 2002, Wilson *et al.* 2005, Restrepo *et al.* 2008). A US study showed that among non-diabetic CAP patients with pneumococcal pneumonia hyperglycemia, *per se*, was a marker of severe disease and increased mortality (Rueda *et al.* 2010). Similar studies concerning SCAP are not available.

2.5 Imaging

2.5.1 Chest radiograph

The chest radiograph is the primary radiological imaging study for patients with symptoms of acute respiratory tract infection and suspicion of pneumonia (cough, dyspnea and fever). The ATS guidelines recommend the chest radiograph for all patients with suspicion of community-acquired pneumonia to assess the extent of pneumonia and to diagnose complications such as parapneumonic effusions (Niederman *et al.* 2001). The chest radiograph has been considered as a reference standard for the diagnosis of pulmonary infection (Bartlett *et al.* 2000).

In a Finnish LRTI study the diagnostic accuracy of chest radiograph for pneumonia was 69.2% compared to high-resolution computed tomography

(Syrjälä *et al.* 1998). According to different studies, the inter-reader agreement for diagnosing pneumonia, evaluating the type of consolidation and the presence of pleural fluid has varied from 52% to up to 89% (Hopstaken *et al.* 2004, Campbell *et al.* 2005). Among severely ill patients the chest radiograph can usually only be taken in supine position as an anterior-posterior projection. It has been shown that the infiltrates located in the upper lobes may not be visualized and the liver, spleen, heart and vertebrae will cause superimposition, impairing the diagnostic accuracy (Syrjälä *et al.* 1998, Hansell *et al.* 2010a).

The basic radiological pneumonia patterns are lobar (non-segmental or airspace) pneumonia, bronchopneumonia (lobular pneumonia) and interstitial pneumonia. These patterns vary according to patient factors, underlying lung disease and the patients' immune status (Washington & Palacio 2007). The chest radiograph findings are not reliable for identifying different etiologies of pneumonia (Boersma *et al.* 2006).

In earlier studies, multilobar involvement has been associated with mortality, and this radiologic finding has been included in CAP severity scores (Ewig *et al.* 1998, Mandell *et al.* 2007, Rello *et al.* 2009). The presence of pleural fluid and bilateral occurrence has also been shown to be an adverse prognostic sign in CAP, but there are no studies concerning SCAP (Fine *et al.* 1997). In a large prospective study with 457 ICU-admitted SCAP patients the rapid progression of pneumonic infiltrates in chest radiograph during the first 48 hours was found as an independent predictor of adverse outcome with a threefold increase in the risk of death (Lisboa *et al.* 2009). A Turkish study showed that among SCAP patients the need for non-invasive ventilation was 2.4 fold when there was multilobar involvement in chest radiograph, and the need for invasive mechanical ventilation increased 8-fold with multilobar involvement in chest CT (Erdem *et al.* 2014).

2.5.2 Thoracic computed tomography

The thoracic computed tomography (CT scan) is defined as the gold standard test for lung imaging and its usefulness in immunocompromised patients for pneumonia diagnostics has been shown (Demirkazik *et al.* 2008, Franguet 2011). Chest CT has a crucial role among patients with non-resolving pneumonia and pneumonia complications such as empyema (Sharma *et al.* 2007). The usefulness of chest CT scan as an adjunct to the plain radiograph has been shown among CAP patients in selected cases. The CT scan allows better identification of

opacities compatible with pneumonia thanks to better tissue contrast and three-dimensional visualization of anatomic structures, especially among ICU patients (Romano *et al.* 2008). Hayden and Wrenn showed that pneumonia was demonstrated on the CT scan in 27% of the patients with suspicion of CAP whose chest radiograph was negative or non-diagnostic (Hayden & Wrenn 2009). In CAP high-resolution CT has been found more accurate in detecting pneumonia compared to plain chest radiograph. The accuracy was also better in showing bilateral infiltrations; 33.3% by chest radiograph compared to 61.5% by high-resolution CT (Syrjälä *et al.* 1998). Compared to the chest radiograph, the chest CT scan is more accurate in showing the pattern and distribution of pulmonary processes, atelectasis and pleural effusions (Tan Kendrick *et al.* 2002, Sharma *et al.* 2007, Brixey *et al.* 2010, Kitazono *et al.* 2010). However, similarly to chest radiograph, the applicability of CT scan to define the infective organism is poor, as has also been shown (Reynolds *et al.* 2010).

Chest CT has no routine role in SCAP diagnostics and only few studies have been published so far. The radiation dosage has also limited the wider use of chest CT in SCAP, but new low-dose techniques have been introduced (Börjesson *et al.* 2011, Neroladaki *et al.* 2013). In one study in the emergency department setting, patients with pneumonia in the chest radiograph underwent chest CT examination. CT was found useful in guiding therapy (antibiotic changes) and providing alternative diagnosis (Banker *et al.* 2007). Chest CT can also be useful in optimal lung segment guidance to obtain diagnostic specimens by bronchoscopy (Reynolds & Banerjee 2012).

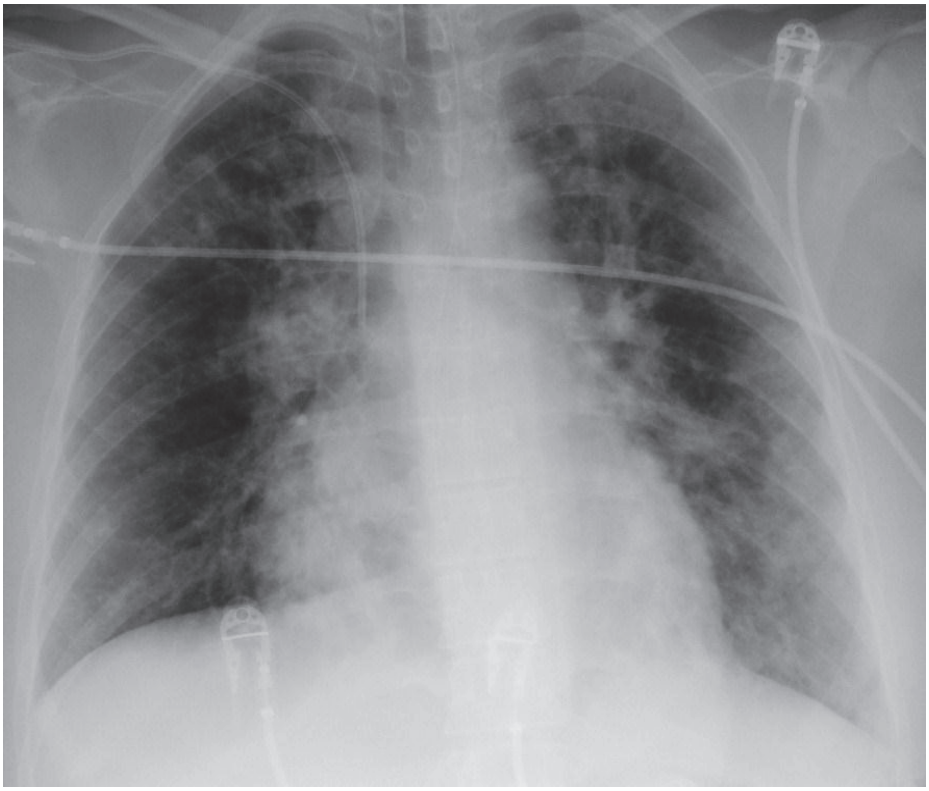

Fig. 3. A typical chest radiograph finding of a SCAP patient with bronchopneumonia showing bilateral diffuse opacities in all lung lobes.

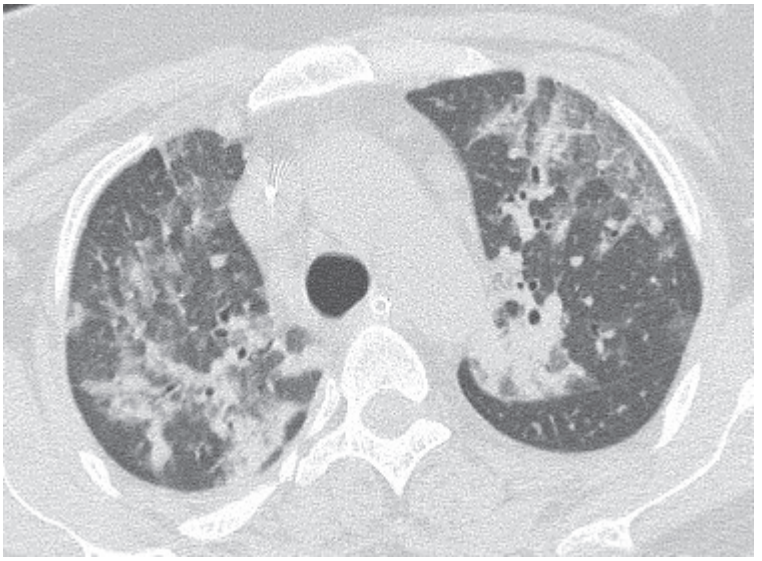

Fig. 4. A chest CT scan finding of the same patient with bronchopneumonia revealed more wide spread opacities.

2.5.3 Thoracic ultrasound

The role of the thoracic ultrasound (TUS) has traditionally been limited to the evaluation of pleural effusions and guidance of thoracocentesis (Reissig *et al.* 2012). In recent years the use of thoracic ultrasound to study pulmonary and pleural diseases has been of clinical interest especially in the emergency department and ICU. Easy execution at bedside, reproducibility, repeatability, low cost, and absence of radiation has been reported as the advantages of thoracic ultrasound (Sperandeo *et al.* 2011). Some studies have found TUS to be superior to chest radiograph for confirming pneumonia (Parlamento *et al.* 2009, Sperandeo *et al.* 2011, Reissig *et al.* 2012). One small study found TUS useful in the follow-up of CAP inpatients (Sperandeo *et al.* 2011). In the ICU setting, compared to chest radiograph, bedside lung ultrasound has shown better sensitivity, specificity and accuracy in revealing pulmonary consolidations, pneumothoracies and pleural effusions, and it has been suggested as an alternative for chest CT (Xirouchaki *et al.* 2011).

TUS seems to be a new promising adjunctive technique in community-acquired pneumonia, especially for patients in whom radiation should be avoided

(i.e., pregnant women and children). The technique requires an experienced operator, which has limited its wider implementation (Gardelli *et al.* 2012, Chavez *et al.* 2014). Thoracic radiograph still remains the primary investigation for CAP and SCAP.

2.6 Laboratory diagnostics

2.6.1 Leukocytes

Leukocyte levels $<4\times10^9$/L or $>14\times10^9$/L have been associated with pneumonia severity (Leroy *et al.* 1995, Fine *et al.* 1996, Mandell *et al.* 2007). The diagnostic value, however, has been shown to be inferior compared to other markers of inflammation (Melbye *et al.* 1992). One previous study investigated the diagnostic and prognostic accuracy of laboratory parameters in CAP. Leukocyte count was inferior compared to C-reactive protein (CRP), and especially to procalcitonin (PCT), in predicting non-radiologically and radiologically confirmed CAP, bacteremia and pneumonia severity (Müller *et al.* 2007a). Some studies have found leukopenia (leukocyte level $<4\times10^9$/L) associated with mortality in SCAP (Georges *et al.* 1999, Marik 2000) while others have not (Lim *et al.* 2000, Yoshimoto *et al.* 2005).

2.6.2 C-reactive protein

Plasma C-reactive protein (CRP) is an acute-phase protein synthesized predominantly by the liver, mainly in response to the inflammatory mediator interleukin-6 (IL-6). The level of CRP rises rapidly in response to several inflammatory stimuli, bacterial infection being one of the most potent. The secretion of CRP begins within 4 to 6 hours of the stimulus, doubling every 8 hours, and peaking at 36–50 hours. After the disappearance or removal of the stimulus, CRP concentration decreases rapidly with a half-life of 19 hours (Povoa *et al.* 2002). In general, among critically ill patients CRP level >100mg/L has correlated with organ failures and ICU length of stay, as well as mortality (Lobo *et al.* 2003). In CAP, CRP level >100mg/L has been regarded as an indicator of presence of pneumonia, marker of disease severity, trigger of inpatient care and predictor of pneumonia complications (Almirall *et al.* 2004, Hohenthal *et al.* 2009, España *et al.* 2012). One study found median CRP levels to be significantly

higher in patients with confirmed CAP (median 110.7 mg/L) compared to those with unconfirmed pneumonia (median 31.9 mg/L)(Almirall *et al.* 2004). On the contrary, in a study by Müller CRP was not shown to associate with the CAP severity (Müller *et al.* 2007a).

Literature of CRP in SCAP is sparse. In a prospective British study hospital admission CRP <100mg/L was associated with a reduced need for mechanical ventilation and/or inotropic support and a reduced risk for 30-day mortality. Furthermore, failure of CRP to fall by 50% or more at day 4 led to increased need for mechanical ventilation and/or inotropic support and the risk for 30-day mortality (Chalmers *et al.* 2008). Two studies have demonstrated that daily CRP measurement was useful in the identification (as early as day 2 or 3) of SCAP patients with poor outcome (Coelho *et al.* 2007, Nseir *et al.* 2013). The CRP level correlated with clinical course, organ failures and 30-day mortality. In Coelho's study a level of CRP higher than 50% of the initial level on the third treatment day was a marker of poor outcome (Coelho *et al.* 2007). In the second study a fractional decrease less than 25% in CRP levels at the second day was significantly associated with 30-day all-cause mortality in SCAP patients (Nseir *et al.* 2013). Higher CRP levels have been found in pneumococcal bacteremic SCAP compared to non-bacteremic patients (Pereira *et al.* 2013).

2.6.3 Procalcitonin

The procalcitonin (PCT) peptide is a precursor of calcitonin. It is normally synthesized in thyroid C cells. In healthy individuals serum PCT concentration is lower than 0.1μg/L (Boussekey *et al.* 2005). In severe systemic infection PCT is released from parenchymal cells, including liver, kidney and monocytes, in response to microbiological toxins and proinflammatory cytokines, such as IL-6 and TNF-α. PCT has been found to be a good early marker of infection (Christ-Crain & Opal 2010). PCT starts to increase 3–6 hours after the beginning of an infectious syndrome (Dandona *et al.* 1994). There are two commercially available assays for measuring the PCT levels. The LUMI test measures procalcitonin levels by the luminometer technique with a lower limit of detection of 0.30–0.50μg/L. The more sensitive Kryptor test is based on sheep polyclonal anti-C antibody and a monoclonal anti-kalcin antibody binding and is able to detect PCT levels as low as 0.06μg/L (Chirst-Crain *et al.* 2007).

When compared to CRP, PCT has been found more sensitive and specific in differentiating bacterial infection from non-infective causes of inflammation in

hospitalized patients (Simon *et al.* 2004, Tian *et al.* 2014). PCT seems to perform better than other infection markers in the diagnosis of CAP (Müller *et al.* 2007, Christ-Crain & Opal 2010). The utility of PCT measurement among patients with suspected LRTI was first shown by Chirst-Crain. PCT concentrations ≤0.25μg/L were able to identify the patients who did not have CAP (Christ-Crain *et al.* 2004). The sensitivity of PCT to differentiate between bacterial and viral CAP and SCAP has also been shown (Piacentini *et al.* 2011, Falsey *et al.* 2013).

Among ICU-admitted SCAP patients serum PCT levels were found to be higher in cases with microbiologically documented SCAP compared to those without defined etiology (median 49μg/L vs. 15μg/L) (Bousekkey *et al.* 2005). Bacteremic SCAP patients and patients with septic shock have been reported to exhibit higher PCT levels even on ICU admission (Bousekkey *et al.* 2005, Ramirez *et al.* 2011, Pereira *et al.* 2013). PCT has been shown to increase among those who develop infection-related complications during their ICU stay (Bousekkey *et al.* 2005). The correlation of PCT to organ failures (assessed by Sequential Organ Failure Assessment, SOFA score) and prognosis of SCAP has been addressed (Brunkhorst *et al.* 2002, Boussekey *et al.* 2005, Boussekey *et al.* 2006, Bloos *et al.* 2011). PCT-based algorithms for starting or de-escalating antibiotics in LRTI, CAP and ICU-treated all-cause septic patients have been introduced (Christ-Crain & Opal 2010, Schuetz *et al.* 2011). The cost-effectiveness of these algorithms and their impact on the length of ICU or hospital stay and antimicrobial-resistance has not been proved yet (Schuetz *et al.* 2012, Prkno *et al.* 2013).

2.6.4 Other biomarkers

Other biomarkers have been studied for their use in diagnostic and prognostic assessment, site-of-care decisions and follow-up. However, most of the studies concentrate on CAP and there are only few studies among SCAP patients.

The inflammatory cytokine IL-6 has been found promising in prognostic assessment. A correlation has been shown between elevated IL-6 to IL-10 ratio and the hospital and 1-year mortality risk in CAP patients (Marik 2000, Kellum *et al.* 2007, Yende *et al.* 2008).

Triggering receptor expressed on myeloid cells-1 is upregulated by microbial products, and among mechanically ventilated patients it could differentiate between bacterial and fungal pneumonia (Gibot *et al.* 2004). In one study with

SCAP patients triggering receptor expressed on myeloid cells-1 measured in plasma was shown helpful in guiding either etiology or outcome (Müller *et al.* 2007b).

Copeptin (arginine vasopressin), proadrenomedullin and atrial natriuretic peptide have mainly been studied among CAP patients. In a cohort study with 373 CAP patients copeptin levels were found to increase according to pneumonia severity and predicted outcome independently (Müller *et al.* 2007c). There is some evidence that compared to CRP and PCT, elevated proadrenomedullin and atrial natriuretic levels are better able to predict CAP severity at hospital admission as well as CAP outcome (Christ-Crain *et al.* 2006, Renaud *et al.* 2009, Claessens *et al.* 2010, Krüger *et al.* 2010, Bello *et al.* 2012, Courtais *et al.* 2013).

Activation of the coagulation cascade and downregulation of anticoagulant pathways are common features in severe sepsis. Higher baseline D-dimer levels have been found in association with mortality in patients with SCAP (Snijders *et al.* 2012).

2.7 Microbiological testing

2.7.1 Blood culture

The usefulness of the systematic use of blood cultures and their impact on treatment has been questioned in CAP patients (Waterer & Wunderink 2001). The number of positive findings from blood cultures is generally low and their impact on antimicrobial treatment has not been shown inconclusively (Waterer & Wunderink 2001, Campbell *et al.* 2003). One study found approximately 5% of the blood cultures as false positive findings leading to the use of broad spectrum antibiotics (e.g. vancomycin) and longer hospital stays (Metersky *et al.* 2004). Microbiological testing has been justified especially in patients with SCAP (Rello *et al.* 2003). The guidelines recommend obtaining two sets of blood cultures before antibiotic treatment of all hospitalized CAP patients with risk factors for bacteremia and especially of SCAP patients (Bartlett *et al.* 2000, Mandell *et al.* 2007, Strålin 2008, Lim *et al.* 2009, Woodhead *et al.* 2011). Some studies have considered bacteremia as a marker of CAP severity (Fine *et al.* 1996), while opposite results have also been presented (Campbell *et al.* 2003, Bordón *et al.* 2008). The reported rates of positive blood cultures among hospitalized CAP patients are low, from 5% to 15% (Waterer & Wunderink 2001, Campbell *et al.*

2003, Metersky *et al.* 2004). The number of positive blood cultures is halved by previous use of antimicrobials (Metersky *et al.* 2004). However, among patients with multiple risk factors for bacteremia (e.g. severe disease, liver disease and leukopenia), and especially among SCAP patients, the number of positive blood cultures has been reported to be higher ranging from 20% to 33% (Moine *et al.* 1994, Paganin *et al.* 2004, Laterre *et al.* 2005, Wilson *et al.* 2005). In SCAP, up to 15% of blood cultures are still found positive after initiation of antibiotic treatment (Mandell *et al.* 2007).

Isolation of bacteria from blood culture in patients with SCAP is highly definitive for pneumonia etiology (Marston *et al.* 1997). *Streptococcus pneumoniae* is yielded in two thirds of the positive blood culture findings among SCAP patients (Laterre *et al.* 2005, Moine *et al.* 2005, Wilson *et al.* 2005, Mongardon *et al.* 2012). SCAP patients may also be infected with bacteria other than pneumococcus, including *Staphylococcus aureus*, *Haemophilus influenzae* and gram-negative bacteria, which may not necessarily be covered by the empiric antibiotic therapy (Table 5).

2.7.2 Respiratory tract specimen

International guidelines recommend obtaining a respiratory tract specimen from all hospitalized CAP, and especially SCAP, patients before antimicrobial therapy to guide antimicrobial treatment whenever good quality purulent samples are available (Mandell *et al.* 2007, Lim *et al.* 2009, Woodhead *et al.* 2011). Respiratory specimens can be collected as deep cough-produced or induced sputum samples, endotracheal suction aspirates, transtracheal or transpulmonary needle punctures, or bronchoscopically assisted aspirates, bronchoalveolar lavage (BAL) or protected specimen brushes (Strålin 2008, Woodhead *et al.* 2011). The microbes cultured in sputum samples are indicative of probable or presumed etiology in CAP or SCAP (Marston *et al.* 1997). The yield of positive bacterial findings is influenced by the quality of the sample, adequate transportation and the use of cytological criteria and skill of interpretation (Bartlett *et al.* 2000, Mandell *et al.* 2007, Lim *et al.* 2009). Antimicrobial therapy before sample collection lowers the number of positive results and affects the reliability of the gram stain and culture (Miyashita *et al.* 2008). The adequacy of the sample is assessed by Gram-stain, with a high leukocyte-epithelial cell ratio indicating a good-quality lower respiratory tract sample (Musher *et al.* 2004, Miyashita *et al.*

2008). In a Spanish study with CAP patients only 14.4% of 1,669 sputum samples were of good quality, while other studies have shown higher rates ranging between 39% and 57% (Roson *et al.* 2000, García-Vázguez *et al.* 2004, Miyashita *et al.* 2008).

Endotracheal aspirate collection, obtained before antimicrobial treatment, is recommended for all ICU-admitted intubated SCAP patients. Bronchoscopically assisted specimen collection might be preferable (Rodriguez *et al.* 2001, Rello *et al.* 2003, Mandell *et al.* 2007). Endotracheal aspirate represents the lower respiratory tract specimen, and when obtained soon after intubation, is less likely to be contaminated by oropharyngeal bacteria or colonization (Liebrel & Markin 2000, Mandell *et al.* 2007). Compared to sputum samples the frequency of microbe detection is substantially higher with endotracheal aspirates both in CAP and SCAP. Up to 80% rates of detected microbes from endotracheal aspirates have been reported among patients without previous antibiotic treatment (Rodriguez *et al.* 2001, Rello *et al.* 2003).

The use of bronchoscopical sample collection for SCAP diagnostics has not been studied widely and the literature of BAL in acute care setting is sparse. Most investigations have suggested bronchoscopical studies when treatment failure occurs (van der Eerden *et al.* 2005). In a small study with 26 intubated SCAP patients pathogens were identified with BAL in 83.3% compared to 28.6% of the patients in the conventional group (Rodriguez *et al.* 2001). In a French study fiberoptic BAL was performed in 76% of SCAP patients resulting in a positive bacterial finding in 65% (Paganin *et al.* 2004) while in a Spanish study BAL revealed positive microbiology only in 21% and PSB in 24% (Rello *et al.* 2003). In a Korean study consisting of 64 patients with SCAP and 134 patients with healthcare-acquired pneumonia BAL revealed a bacterial diagnosis in 21.1%, while viruses were detected in 55.6% in the BAL fluid (Choi *et al.* 2012).

2.7.3 Pleural fluid diagnostics

Diagnostic thoracocentesis should be performed when a significant pleural effusion is present (Rahman & Munavvar 2009). Practice guidelines recommend biochemical analysis (i.e., pH, protein content, lactate dehydrogenase, glucose) in all sampled effusions with microbiological and cytological tests (Maskell *et al.* 2003, Sahn 2007). Purulent appearance and pleural fluid pH <7.20 indicate complicated parapneumonic effusions and require drainage (Heffner *et al.* 1995,

Sahn 2008). A positive culture of pleural fluid provides a definitive etiology of pneumonia (Marston *et al.* 1997).

2.7.4 Urine antigen tests

There are commercially available urine antigen tests for *Streptococcus pneumoniae* and the *Legionella pneumoniae* serogroup 1 detection. The *Streptococcus pneumoniae* antigen is detected by a urine immunochromatographic test, Binax NOW® (Binax, Inc., Portland, Maine). The test detects the C polysaccharide cell wall antigen (common to all *Streptococcus pneumoniae* strains) of 23 *Streptococcus pneumoniae* serotypes, which are responsible for 90% of all pneumococcal infections (manufacturer's information). The test is fast: the result can be obtained in 15 minutes. False positive results are caused by cross-reactions, as the cell wall C polysaccharide is also identified among other streptococci (*Streptococcus mitis* and *Streptococcus oralis*), *Staphylococcus aureus* and *Haemophilus influenzae* (Murdoch *et al.* 2001, Gutiérrez *et al.* 2003, Marcos *et al.* 2003). False positive findings have also been reported in children, in the case of earlier CAP within three months and among those with pneumococcal vaccination. Prior antibiotics have not been shown to affect test efficacy (Smith *et al.* 2003, Lasocki *et al.* 2006). Urine pneumococcal antigen remains positive for several days (Smith *et al.* 2003).

Studies mostly performed among CAP patients have found the sensitivity of urine pneumococcal antigen to be from 65.9% to 70.4% and specificity from 89.7% to 98% when positive pneumococcal findings from blood cultures and/or respiratory specimens have been used as the reference standard (Smith *et al.* 2003, Diederen & Peters 2007, Sordé *et al.* 2011, Sinclair *et al.* 2013). Similar findings have been shown among ICU-admitted SCAP patients (Lasocki *et al.* 2005). In CAP, combining the urine pneumococcal antigen test with conventional methods has raised the number of positive findings of pneumococcal pneumonia from 33% to 49% in one study and from 39.1% to 53.1% in another investigation (Gutiérrez *et al.* 2003, Genne *et al.* 2006). Guidelines recommend urine antigen testing for all patients with moderate or severe CAP (Mandell *et al.* 2007, Lim *et al.* 2009).

For *Legionella pneumophila* several urinary antigen assays are available, one of the most commonly used being Binax NOW® (Binax, Inc., Portland, Maine) (Shimada *et al.* 2009). Urine antigen test detects *Legionella pneumophila*

serogroup 1, which accounts for 80–95% of the community-acquired legionella pneumonias (Helbig *et al.* 2001, Shimada *et al.* 2009). Prior studies with culture proven legionella have indicated urine antigen sensitivity of 74% and specificity of up to 99%. The test has been found to be positive on day 1 of illness and stays positive for weeks (Diederen 2008, Shimada *et al.* 2009).

2.7.5 Serological tests

Serological assays are mainly used to detect atypical pathogens such as *Mycoplasma pneumoniae* and *Chlamydia pneumoniae*. These microbes are difficult to culture with a low yield (She *et al.* 2010a). Newer antigen and polymerase chain reaction tests have replaced serological methods for *Legionella pneumoniae* and viral diagnostics (Strålin 2008). For accurate diagnosis and the detection of seroconversion paired serum samples (acute and convalescent serum samples with a time interval of 7–14 days) are required (Hammerschlag 2001, Loens *et al.* 2010). It is thus a clear disadvantage of serological methods that for diagnostic purposes and treatment decisions the results are obtained with a delay (Mandell *et al.* 2007, Loens *et al.* 2010).

Many commercial tests are available for *Mycoplasma pneumoniae* diagnostics, but a universally agreed gold standard for the detection of *Mycoplasma pneumoniae* antibodies is lacking (Petitjean *et al.* 2002, Busson *et al.* 2013). With indirect enzyme immunoassays a better accuracy is achieved, and measuring immunoglobulin G (IgG) and IgM antibodies is possible separately (Loens *et al.* 2010). A 4-fold increase, or with the newer test, a 2-fold increase in the *Mycoplasma pneumoniae*-specific IgG antibodies or a seroconversion IgM antibodies between paired serums is used as a diagnostic criterion of *Mycoplasma pneumoniae* infection (Hammerschlag 2001, Waites & Talkington 2004, Loens *et al.* 2010).

Assays for *Chlamydia pneumoniae* detection are based on microimmunofluorescence enzyme-linked immunosorbent assay and enzyme immunoassay techniques (Kumar & Hammerschlag 2007). The Centers of Disease Control and Prevention and IDSA guidelines have defined the criteria for acute *Chlamydia pneumoniae* infection as a single IgM titer of ≥1:16 or a 4-fold rise in the IgG titer between paired serum samples (Dowell *et al.* 2001, Strålin 2008). In primary *Chlamydia pneumoniae* infections, IgM antibodies are detectable in 2–3 weeks and IgG antibodies in 6–8 weeks after infection, so for

optimal interpretation of serodiagnostics, the time when the symptoms began is thus required (Kumar & Hammerschlag 2007, Hvidsten *et al.* 2009).

2.7.6 Polymerase chain reaction methods

Polymerase chain reaction (PCR) or nucleic acid amplification techniques introduced in recent years have increased the diagnostic yield of pneumonia etiology (Templeton *et al.* 2005, Hohenthal *et al.* 2008, Johansson *et al.* 2010, Mustafa *et al.* 2011, Luchinger *et al.* 2013). According to previous studies, the reported rates of microbes identified with conventional methods have been from 21% to 49.6%, compared to 43–80% with PCR (Templeton *et al.* 2005, Johansson *et al.* 2010, Huijiskens *et al.* 2014). The PCR test result does not depend on the viability of the microbe and is less likely to be affected by previous antimicrobial treatment. Moreover, a PCR test provides the results earlier (in hours) than serological methods (Nolte 2008, Tiveljung-Lindell *et al.* 2009). Microbes can be tested from nasopharyngeal and oropharyngeal swabs, sputums, endotracheal aspirates and BAL fluid (Lieberman *et al.* 2009, Loens *et al.* 2009). Recently developed multiplex real-time PCR assays can simultaneously detect several bacteria or viruses in one analysis (Oosterheert *et al.* 2005, Tiveljung–Lindell *et al.* 2009, Brittain-Long *et al.* 2010). However, PCR techniques are still not widely used in clinical practice. The main reason is the high cost; in addition, some methods are not standardized for clinical use and the value of the results for clinical decision-making and treatment is inconclusive (Oosterheert *et al.* 2005, Nolte 2008).

Bacterial PCR diagnostics

Bacterial PCR methods have only been standardized for *Mycobacterium tuberculosis* and Legionella spp. (Strålin 2008). Techniques, including multiplex methods, have been developed for the detection of *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Mycoplasma pneumoniae, Chlamydia pneumoniae* and *Legionella pneumoniae* (Strålin *et al.* 2005, Strålin *et al.* 2006, Schmitt *et al.* 2013). The reported sensitivities and specificities of bacterial PCR tests depend on the test used and the specimen tested compared to the diagnostic method used as reference. When compared to standard cultures (i.e., sputum, nasopharyngeal swab and aspirate) the sensitivity of PCR for *Streptococcus pneumoniae* has been

92–96.2%, for *Haemophilus influenzae* 78–100%, for *Mycoplasma pneumoniae* 67–100% and for *Chlamydia pneumoniae* 100%; correspondingly, the specificities have been 42–96% for *Streptococcus pneumoniae*, 95.4% for *Haemophilus influenzae*, 93–97% for *Mycoplasma pneumoniae* and 100% for *Chlamydia pneumoniae* (Morozumi *et al.* 2006, Strålin *et al.* 2008, Strålin *et al.* 2014). Bacterial PCR techniques have not, thus far, been used for the identification of SCAP etiology.

Viral PCR diagnostics

Virus diagnostics in LRTIs was earlier based on the detection of virus antigen from nasopharyngeal aspirates or swabs and lower respiratory tract samples by culture, immunofluorescence microscopy or antibody detection in paired serum samples (Heikkinen *et al.* 2002, Östlund *et al.* 2004, Tiveljung-Lindell *et al.* 2009, Ruuskanen *et al.* 2010). PCR methods have increased the ability to detect respiratory viruses including those difficult to culture or detect with other methods, e.g. respiratory syncytial virus (Falsey *et al.* 2002, Talbot *et al.* 2010). Furthermore, PCR methods have revealed new viral etiologies for LRTI and pneumonia (Falsey *et al.* 2002, Falsey *et al.* 2005, Walsh *et al.* 2008, Talbot *et al.* 2010). PCR methods have been found to be two to five times more sensitive compared to conventional diagnostic methods (She *et al.* 2010b). During the past years, several multiplex PCR assays have been introduced, being able to detect simultaneously up to 16 respiratory viruses (e.g. Anyplex™ II RV16) (Tiveljung-Lindell *et al.* 2009, Talbot *et al.* 2010, Choi *et al.* 2012). According to recently published studies these assays have increased the rate of detected viruses in lower respiratory tract infections, especially in pneumonia (de Roux *et al.* 2004, Templeton *et al.* 2005, Angeles-Marcos *et al.* 2006, Charles *et al.* 2008, Diaz *et al.* 2007, Hohenthal *et al.* 2008, Jennings *et al.* 2008, Johnstone *et al.* 2008, Lieberman *et al.* 2009, Johansson *et al.* 2010, Choi *et al.* 2012, Luchsinger *et al.* 2013, Wiemken *et al.* 2013).

Viral pneumonia diagnostics has mostly been based on upper respiratory tract specimen (i.e., nasopharyngeal aspirate, washes or swabs, throat swabs, combined nasopharyngeal and throat swabs and sputum) collection (Loens *et al.* 2009). In adults nasopharyngeal swabs seem to have higher sensitivity compared to throat swabs (Lieberman *et al.* 2009). Transnasally taken nasopharyngeal flocked swabs have been shown to exhibit high virus detection rates in adults (Jennings *et al.* 2008, Lieberman *et al.* 2009, Johansson *et al.* 2010). The use of upper respiratory

tract specimens in viral pneumonia diagnostics has been questioned. Nasopharyngeal viruses may be the cause of an upper-respiratory tract infection or only a co-incidental finding, but not the etiological pathogen for CAP or SCAP (Ruuskanen *et al.* 2010, Choi *et al.* 2012). However, only few studies have used lower respiratory tract specimens (i.e., endotracheal aspirates, bronchoscopy or BAL fluid) for diagnosing viral LRTI and especially viral SCAP (Garbino *et al.* 2009, Choi *et al.* 2012).

2.8 Microbiological etiology of severe community-acquired pneumonia

2.8.1 The bacterial etiology of severe community-acquired pneumonia

The bacteriological etiology of SCAP differs from CAP (Mandell *et al.* 2007). The pathogens causing SCAP may also vary according to geographic area and underlying risk factors (Cillóniz *et al.* 2011). According to published studies, with the diagnostic methods available, the bacterial etiology of SCAP can be defined in 25–79% (Table 4). Higher yields are achieved via invasive diagnostic techniques, i.e., bronchoscopic sampling and BAL. The rate of antimicrobial pretreatment also influences the microbiological results (Cillóniz *et al.* 2011).

Almost all published studies, depending on the diagnostic method used, have reported *Streptococcus pneumoniae* as the most prevalent pathogen in SCAP (Table 5). Among SCAP patients pneumococcus has been detected in 16.3–60% of the positive blood cultures (Moine *et al.* 1994, Georges *et al.* 1999, Laterre *et al.* 2005, Marik 2000, Marrie & Shariatzadeh 2007, Mongardon *et al.* 2012). Only few SCAP studies have reported pneumococcal findings from respiratory specimens the reported rates ranging from 16.3% to 68% (Georges *et al.* 1999, Marrie & Shariatzadeh 2007, Mongardon *et al.* 2012).

As Table 5 shows, the second most common bacteria yielded in SCAP is *Staphylococcus aureus*. *Staphylococcus aureus* is typically related to influenza outbreaks (Mandell *et al.* 2007). *Haemophilus influenzae* infection is usually seen among patients with underlying diseases (Mandell *et al.* 2007) (Table 5). Severe chronic pulmonary obstructive disease, alcoholism and chronic steroid use are major risk factors for pulmonary infections with *Pseudomonas aeruginosa* and other gram-negative bacteria (*Escherichia coli, Klebsiella pneumoniae, Serratia*

spp., Proteus spp.) (Arancibia *et al.* 2002, Mandell *et al.* 2007). The mortality rates related especially to *Pseudomonas aeruginosa* infection have been reported to be high, up to 80% (Ruiz *et al.* 1999, Marik 2000, Khawaja *et al.* 2013). Alcoholism has been found to relate strongly to SCAP caused by *Klebsiella pneumoniae* (Feldman *et al.* 1991, Paganin *et al.* 2004).

Table 4. The number of identified microbes and positive microbiological findings with different microbiological tests in SCAP studies.

Study	Study nature/ country	Number of patients	Microbes indetified (%)	Blood culture positive (%)	Respiratory specimen (%)	U-StpnAg positive (%)
Khawaja 2013	R/ Pakistan	189	25	11.1	-	-
Choi 2012[1]	P/ Korea	189	54	29.6	71.8	28.2
Cillóniz 2011	P/ Spain	362	54	18	49/70[2]	-
Martin-Loeches 2010	P/ Spain	257	46.8	9.2	-	-
Restrepo 2008	R/ United States	145	39	-	-	-
Rodriguez 2007	P/ Spain	529	51.7	16.8	-	-
Marrie 2007	P/ Canada	474	64.4	46.2[3]	16.3/21.1[3,4]	-
Laterre 2005	P/ multicent	602	60	26.7	-	-
Wilson 2005	R/ Australia	96	46	20	20	-
Yoshimoto 2005	R/ Japan	72	44.4	-	-	-
Paganin 2004	P/ France	112	78.6	33	65[5]	-
Rello 2003	P/ Spain	204	57.3	19.6	44.4	-
Angus 2002	R/ US	170	44.7	-	-	-
Gowardman 2000	P/ New-Zealand	32	40	-	-	-
Marik 2000	P/ multicenter	148	52	12.8	-	-
Georges 1999	R+P/ France	505	61.2	27.1[3]	17[3]	-
Ruiz 1999	P/ Spain	89	53	14.6	-	-
Rello 1996[6]	P/ Spain	95	38.9	17.9	-	-

U-StpnAg, urine streptococcus pneumoniae antigen, R, retrospective, P, prospective, -, not reported/ studied

[1] Findings of SCAP (n=64) and healthcare-associated pneumonia (n=134) patients

[2] Positive findings without and with lower respiratory tract samples

[3] Only Streptococcus pneumoniae findings

[4] sputum and endotracheal culture positive

[5] Reported only positive BAL findings

[6] Patients ≥65 years

Table 5. Microbial etiology of SCAP.

Study	S.pneu (%)	S.aur (%)	H.infl (%)	L.pneu (%)	P.aer (%)	M.cath (%)	Gram neg (%)	M.pneum (%)	Viruses (%)
Khawaja 2013	7.8	8.4	-	-	4.8	0.5	3.2	-	-
Wiemken[2] 2013	-	-	-	-	-	-	-	-	23
Mongardon[1] 2012	68	-	-	-	-	-	-	-	-
Choi 2012	18.8	1.6	1.6	0	-	-	10.9	1.6	40.6
Cillóniz 2011	33.7	5.8	2.2	3	3.9	-	2.8	1.7	8.6
Martin-Loches 2010	32.3	23.5	11.7	2.9	1.6	-	12.7	1	-
Restrepo 2008	38.6	21.1	5.3	-	14.0	-	7	-	-
Rodriguez 2007	52.2	8	8.0	8.4	7.3	0.3	7.7	0.3	-
Marrie[3] 2007	46.2/16.3	19.2/9.8	3.8/8.7	-	2.2	1	4	-	-
Laterre 2005	26	14	6	-	4	-	10	-	-
Wilson 2005	13.5	4.2	5.2	1	2.1	1	3	1	10.4[4]
Yoshimoto 2005	13.9	2.8	2.8	2.8	8.3	-	12.5	-	-
Paganin 2004	42.9	1.8	0.9	1.8	1.8	-	27.7	-	-
Rello 2003	20.1	3.0	5.3	11.2	1.0	0.9	3.8	0.9	0.5[5]
Angus 2002	14.7	4.1	4.7	-	-	-		-	-
Gowardman 2000	46	23	-	-	-	-	29	-	-
Marik 2000	19	18	14	3	7	-	10.8	-	-
Georges 1999	27.1	10.7	7.3	-	-	2	1.2	-	-
Ruiz 1999	23.6	2.2	5.6	2.2	4.5	3.3	5.6	3.3	5.6
Mean %	29.3[6]	9.5[6]	5.8[6]	3,6	4.8	1.3	9.5	1.4	14.8

S.pneu, *Streptococcus pneumoniae*, S.aur, *Staphylococcus aureus*, H.infl, *Hemophilus influenzae*, L.pneum, *Legionella pneumophila*,.P.aer, *Pseudomonas aeruginosa*, M.Cath, *Moraxella catharralis*, Gram neg, Gram negative bacteria, M.pneum, *Mycoplasma pneumoniae, - , not reported nor studied*

[1] Only Streptococcus pneumoniae findings were reported

[2] Only viruses were reported

[3] Blood/ sputum

[4] The number of Influenza and respiratory syncytial virus reported only

[5] Ebstein-Barr virus

[6] Calculated without Marrie study

2.8.2 The atypical bacterial etiology of severe community-acquired pneumonia

Mycoplasma pneumoniae, *Chlamydia Pneumoniae* and *Legionella* species are called atypical organisms, because they cannot be detected by Gram stain or cultured by standard bacteriologic methods (Mandell *et al.* 2007). The discovery of these bacteria depends mainly on the methods used (i.e., serological tests, PCR and urine antigen testing). *Legionella pneumophila* is more common among CAP inpatients than among SCAP patients (Table 5). *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* are generally detected among younger adults with CAP, the reported rates varying between 20% and 30% (Arnold *et al.* 2007), while in SCAP the rates are clearly lower (Table 5).

2.8.3 The viral etiology of severe community-acquired pneumonia

Viruses are detected as causative pathogens for CAP in 15–32%. The types of discovered viruses vary worldwide, and viral discovery is also affected by seasonal variation (Luchsinger *et al.* 2013). The most prevalent viruses reported have been rhinovirus (5–17.1%), influenza virus (2.5–8%), parainfluenza virus (2.5–9.6%), respiratory syncytial virus (0.2–7.1%) and adenovirus (0.2–4%) (Templeton *et al.* 2005, Angeles- Marcos *et al.* 2006, Diaz *et al.* 2007, Charles *et al.* 2008, Jennings *et al.* 2008, Johnstone *et al.* 2008, Johansson *et al.* 2010, Lieberman *et al.* 2010, Cillóniz *et al.* 2012, Luschinger *et al.* 2013, Takahashi *et al.* 2013). Two studies have reported a high rate of coronaviruses, up to 13% (Templeton *et al.* 2005, Lieberman *et al.* 2010).

In recent years high rates of influenza A virus H1N1 subtype have been reported. In the US during September 2013–February 2014, 19% of all tested respiratory specimen were positive for influenza virus. Eleven per cent were Influenza A (H1N1) pandemic 2009 viruses, which is known to cause severe respiratory failure and critical illness also in younger patients compared to common influenza A virus infections (Arriola *et al.* 2014, Napolitano *et al.* 2014).

Only two investigations have been published concerning the viral etiology of SCAP. In a Korean study with 64 ICU-admitted SCAP patients, viruses were detected from 26 patients (40.6%). Virus detection was mainly based on nasopharyngeal swabs and partly on bronchoalveolar lavage fluid (Choi *et al.* 2012). The most common viruses were respiratory syncytial virus (10.9%), influenza A virus (9.4%), human metapneumovirus (7.8%) and rhinovirus (6.4%)

(Choi *et al.* 2012). In a US study with 393 adult SCAP patients viruses were identified in 92 (23%) patients by nasopharyngeal swabs. The most common findings were influenza virus (9.6%), rhinovirus (8.4%) and human metapneumovirus (3.3 %) (Wiemken *et al.* 2013).

2.8.4 Polymicrobial severe community-acquired pneumonia

The reported incidence of polymicrobial CAP (i.e. pneumonia due to more than one pathogen) is 6–14% (Gutierrez *et al.* 2005, de Roux *et al.* 2006, Cillóniz *et al.* 2011). The rates of polymicrobial SCAP are, however, not well established. Earlier studies have reported the rates of 3–18% (Ruiz *et al.* 1999, Marik *et al.* 2000, Wilson *et al.* 2005, Restrepo *et al.* 2008). The major reasons for the variation in incidence have been the different case mixes, the rates of prior antimicrobial treatment and the microbial methods used for pathogen detection. One limitation of the studies has been that microbiological tests have not been applied systematically to all pneumonia patients (Cillóniz *et al.* 2011). In a recent Spanish study consisting of 362 ICU-admitted adult SCAP patients, microbial etiology was defined in 54% with the use of a wide scale of diagnostic methods. Eleven per cent of these cases were polymicrobial. *Streptococcus pneumoniae* was the most frequently identified pathogen in polymicrobial infections (72%) followed by respiratory viruses (39%) and *Pseudomonas aeruginosa* (21%). Patients with polymicrobial infection had more often chronic respiratory disease and acute respiratory distress syndrome (Cillóniz *et al.* 2011).

2.8.5 Antimicrobial resistance

The knowledge of bacterial resistance and antimicrobial susceptibility situation will help to choose optimal empiric antimicrobial therapy and improve treatment success. Resistance patterns vary widely in different geographical areas and the local antibiotic prescribing policy has a great impact on antimicrobial resistance (Woodhead *et al.* 2011).

The isolates of drug-resistant *Streptococcus pneumoniae* are increasing worldwide. The resistance to penicillin has been decreasing worldwide, while the resistance to the other β-lactams, especially cephalosporins, and macrolides continues to increase (Song 2013). Several risk factors for β-lactam resistance have been established, such as age <2 years or >65 years, alcoholism, medical

comorbidities, immunosuppressive illness or therapy and exposure to children, for example, in day care center, and preceding treatment with β-lactam (Mandell *et al.* 2007). In Finland, the penicillin resistance of *Streptococcus pneumoniae* cultured from blood has been 0.5–1.5% during the last five years; being 0.5% in the year 2012. The percentage of intermediate resistance strains, however, was 17.7% in 2012. Similar figures were reported for the Northern Ostrobothnia district in 2012. Macrolide resistance is still high; in 2012 18.4% of the strains were macrolide-resistant, compared to 21.2% in 2011.The figures and trends are the same in our area. The numbers of methicillin-resistant *Staphylococcus aureus* cultured from blood and pus have been relatively low, 2–3% during the last five years (Finland, Finres 2012, National Institute for Health and Welfare, Finland, Antimicrobial resistance in Northern Ostrobothnia district 2012, Nordlab, Oulu, Finland).

Pneumococcal conjugate vaccines are shown to decrease both the incidence of invasive pneumococcal diseases and the antimicrobial resistance of pneumococci (Song 2013, Torné *et al.* 2014).

2.9 Treatment of severe community-acquired pneumonia

2.9.1 Indications for intensive care unit admission

The optimal level of care (i.e., outpatient vs. inpatient) is one of the most important factors for the adequate treatment of pneumonia patients. The main indications for ICU treatment are included in severity assessment scores (Table 2, Appendices Tables 18–21) (Fine *et al.* 1997, Lim *et al.* 2003, España *et al.* 2006, Mandell *et al.* 2007, Charles *et al.* 2008). Uniform ICU admission criteria are not available for clinical practice and clinical judgment is still one of the most important factors (Rodriguez *et al.* 2009). The ICU admission decision depends also on the local settings and facilities (Woodhead *et al.* 2011). According to a large US register study the most prevalent indications for ICU treatment were: severe oxygenation disorder requiring mechanical ventilation (57%), hemodynamic monitoring (32%) and septic shock (16%) (Angus *et al.* 2002). A Spanish study concluded that 45% of the patients first admitted to wards were transferred to the ICU during the next 24–72 hours. The main indications for late ICU admission were the progression of respiratory failure or septic shock (Ewig *et al.* 2004). Decompensation of an underlying diseases (i.e., diabetes, renal,

hepatic, cardiac or pulmonary disease) or development of complications (e.g. myocardial infarction) have been identified as reasons for late ICU admissions (Ramirez *et al.* 2008, Renaud *et al.* 2009, Ewig *et al.* 2011).

Delayed transfer to ICU has been shown to increase mortality. In a British register study comprising over 17,000 ICU-admitted CAP cases, hospital mortality rate increased 46.3%, 50.4% and 57.6% depending on whether patients were admitted to ICU <2 days, between 2 and 7 days and >7 days, respectively (Woodhead *et al.* 2006). In other studies delayed ICU admission has shown to prolong hospital stay and increase hospital mortality as well as 28- and 30-day mortality (Renaud *et al.* 2009, Phua *et al.* 2010, Restrepo *et al.* 2010). Moreover, patients seem to obtain suboptimal treatment on the wards (Phua *et al.* 2010).

2.10 Intensive care unit treatment

2.10.1 General aspects

The treatment in the ICU is focused on managing and preventing the development of organ dysfunctions. The main treatment strategies are based on the Surviving Sepsis Guidelines (Dellinger *et al.* 2013). A recent study showed decreased mortality between two treatment periods, 43.6% in 1995–2000 vs. 30.9% in 2005–2010 after administration of the Surviving Sepsis Guidelines for SCAP patients (Georges *et al.* 2013). The practice guidelines recommend blood culture sampling, antibiotic therapy within 4 hours and oxygenation assessment (arterial oxygen saturation or blood gas analysis) within 24 hours after hospital admission as quality indicators for the management of CAP and SCAP (Mandell *et al.* 2007, Waterer *et al.* 2011).

2.10.2 Respiratory support

Oxygenation assessment with pulse oximetry is essential to all hospital admitted CAP patients for the detection of hypoxia and evaluation of disease severity (Blot *et al.* 2007, Lim *et al.* 2009). The patients with arterial oxygen saturation (SaO_2) <94% should have blood gas analysis (Lim *et al.* 2009). The markers of disease severity are: oxygen saturation <90 % (patients >50 years; <93%), arterial oxygen <8 kPa and PF ratio <33 kPa (Lim *et al.* 2009). SCAP patients with severe hypoxemia and respiratory failure not requiring immediate intubation may benefit

from a trial of non-invasive ventilation (NIV) (Mandell *et al.* 2007, Carrillo *et al.* 2012). COPD patients with SCAP are most likely to benefit from a NIV trial (Confalonieri *et al.* 1999). One study has shown that NIV-treated SCAP patients had shorter ICU stay as well as lower ICU and hospital mortality (Carron *et al.* 2010). A recently published study showed that successful NIV was associated with lower mortality, while NIV failure and delayed intubation were associated with decreased hospital survival (Carrillo *et al.* 2012). Worsening radiologic infiltrate in 24 hours after admission, maximum SOFA score, higher heart rate and lower PF ratio as well as bicarbonate level after 1 hour trial of NIV predicted NIV failure (Carrillo *et al.* 2012). A British Society CAP guideline recommends NIV treatment only in the intensive care setting (Lim *et al.* 2009).

A low tidal volume, 6 ml/kg (ideal body weight), has shown to be beneficial among mechanically ventilated patients with acute lung injury and adult respiratory distress syndrome. One study showed an 11 per cent absolute risk reduction for mortality in the pneumonia cohort; the number needed to treat was 9 (Brower *et al.* 2000). The restriction of plateau pressure ≤30 cmH2O and adequate level of positive end-expiratory pressure to prevent alveolar collapse are recommended to prevent alveolar injury (Kilicaya & Gajic 2013, Santa Cruz *et al.* 2013). Patients with respiratory failure, without septic shock, benefited from restricted fluid therapy (Wiedemann *et al.* 2006). There is evidence that interruption of continuous or intermittent sedation reduces the duration of mechanical ventilation and ICU stay (Hughes *et al.* 2012). In severe respiratory failure neuromuscular blocking agents can be useful as a short-course therapy (Papazian *et al.* 2010). Also other strategies (e.g. prone positioning, extracorporeal membrane oxygenation) have been introduced for severe respiratory failure, but studies of their effect on mortality have yielded inconsistent results (Dushianthan *et al.* 2011, Napolitano *et al.* 2014)

2.10.3 Hemodynamic support

SCAP patients with severe sepsis, septic shock and unstable hemodynamics should be resuscitated with fluid therapy. Guidelines recommend the use of crystalloids targeting a mean arterial pressure at 65 mmHg. When adequate fluid challenge fails to correct hemodynamics (i.e., mean arterial pressure, urine output >0.5 mL/kg/h, acidosis, lactate level) vasopressor therapy (norepinephrine, epinephrine, dobutamine) should be administered to stabilize hemodynamics (Dellinger *et al.* 2013). One randomized controlled trial of sepsis patients, 40% of

whom were pneumonia patients, showed early hemodynamic resuscitation targeting at physiologic goals (i.e., mean arterial pressure, central venous pressure, urine output and superior vena cava saturation) within the first 6 hours of admission to the emergency department to be beneficial (Rivers *et al.* 2001).

2.10.4 Corticosteroid treatment

Recent studies have found that the levels of proinflammatory cytokines, such as IL-6, IL-8, IL-10 and TNF-α, to be significantly increased in SCAP and to correlate with the severity of disease and outcome (Endeman *et al.* 2011). Corticosteroids are known to inhibit proinflammatory cytokines (Endeman *et al.* 2011). One study has also reported the findings of relative adrenal insufficiency occurring in a high proportion of SCAP patients (Salluh *et al.* 2006). However, studies on the effectiveness of corticosteroid treatment for SCAP patients without septic shock have revealed conflicting results. The case mix and treatment strategies have varied in the studies. One multicenter study with 46 SCAP patients (74% mechanically ventilated) found a hydrocortisone infusion for seven days to result in an improved PF ratio and chest radiograph opacities, reduction in C-reactive protein levels as well as reduction in delayed septic shock. The length of hospital stay was reduced and hospital mortality was lower among those treated with a hydrocortisone infusion (Confalonieri *et al.* 2005). Another study showed decreased mortality among the SCAP patients treated with antibiotics and methylprednisolone (Garcia-Vidal *et al.* 2007). A prospective Dutch study could not demonstrate an improvement in outcome among hospitalized CAP patients with prednisolone treatment (Snijders *et al.* 2010). Recently published meta-analyses have not been able to confirm the effectiveness of steroid treatment in SCAP (Nie *et al.* 2012, Cheng *et al.* 2014).

Pneumonia is a major risk factor for adult respiratory distress syndrome (ARDS) (Brun-Buisson *et al.* 2004, Linko *et al.* 2009). The largest published randomized controlled study so far did not support the routine use of methylprednisolone for persistent ARDS (Steinberg *et al.* 2006) whereas the recent meta-analyses of pooled studies concluded that low-dose corticosteroids within 14 days of disease onset may reduce mortality in ARDS (Diaz *et al.* 2010, Lamontagne *et al.* 2010).

2.10.5 Acute kidney injury

Acute kidney injury (AKI) is common among ICU-admitted critically ill patients; up to 40% of patients have AKI (Bagshaw *et al.* 2008, Rodriguez *et al.* 2009, Nisula *et al.* 2013). Patients with SCAP are at risk of developing AKI (assessed by RIFLE criteria, i.e., Risk Injury Failure Loss and End-stage renal disease) and the reported rates have reached up to 57.5% (Murugan *et al.* 2010). The patients with AKI had significantly higher hospital, 90-day and 1-year mortality compared to non-AKI patients (Murugan *et al.* 2010). In a French study focusing on ICU-admitted severe pneumococcal pneumonia patients 39.2% of the patients had AKI on admission and 31.5% of them needed renal replacement therapy. In multivariate analysis the need for renal replacement therapy was found as a risk factor for mortality (Mongardon *et al.* 2012). These studies underline the need for careful evaluation, follow-up and support (hemodynamic and respiratory support, fluid therapy) of acute kidney injury among pneumonia patients and emphasize the importance of early admission to ICU.

2.11 Antimicrobial therapy

2.11.1 General aspects

In conjunction with the treatment of organ dysfunctions, one of the most important factors reducing mortality in SCAP is the timing and choice of antimicrobial regimen. The selection of antimicrobial treatment is empirical until the results of diagnostic tests are available (Mandell *et al.* 2007). Because *Streptococcus pneumoniae* is by far the most common pathogen in SCAP, the empiric therapy should always cover pneumococcus (Rodriguez *et al.* 2009). Mortality is increased among SCAP patients receiving antimicrobial treatment not covering the infecting pathogens (Lujan *et al.* 2004, Garcia-Vidal *et al.* 2008). One study showed that the risk of death was ten fold among those pneumococcal bacteremia patients who did not receive β-lactam antimicrobial therapy (Lujan *et al.* 2004).

Early administration of antimicrobial therapy to patients with severe sepsis is essential for improving outcomes. In a retrospective study with all-cause septic patients the administration of antimicrobial treatment within the first hour after documented hypotension was associated with increased hospital survival, while each hour in delay was associated with a 7.6 per cent decrease in survival (Kumar

et al. 2006). In a large population-based study consisting of elderly patients without prior antimicrobial treatment, the initial administration of antimicrobial therapy within 4 hours of arrival at the hospital was associated with a 15 per cent reduction in hospital mortality as well as 30-day mortality (Houck *et al.* 2004). In a Spanish multicenter study delayed (>1 hour after hospital admission) assessment of oxygenation was associated with a significantly longer delay of the first antibiotic dose (6 hours vs. 3 hours). A delay of more than 6 hours in the initiation of antimicrobial therapy was associated with increased mortality (Blot *et al.* 2007).

Studies have shown the IDSA/ATS guideline-concordant antimicrobial therapy to be associated with better outcomes among SCAP patients (Bodi *et al.* 2005, Frei *et al.* 2010). It has also been shown that non-adherence to antibiotic guidelines was associated with a longer duration (3 days) of mechanical ventilation (Shorr *et al.* 2006). A recently published study evaluating the processes of care among septic SCAP patients confirmed further that antibiotic guideline adherence was the strongest indicator for survival together with the delivery of the first antibiotic dose within 6 hours (Menéndez *et al.* 2012).

2.11.2 The Infectious Diseases Society of America/ The American Thoracic Society recommendations

Monotherapy has been suggested to be suboptimal for patients with SCAP (Waterer *et al.* 2001b). Waterer and colleagues demonstrated first that the treatment of severe bacteremic pneumococcal pneumonia with monotherapy was associated with a significantly greater risk of death than treatment with a combination therapy (Waterer *et al.* 2001b). The IDSA/ATS guidelines recommend a combination therapy with β-lactam (cefotaxime, ceftriaxone, or ampicillin-sulbactam) combined with either azithromycin (level II evidence) or a respiratory fluoroquinolone (levofloxacin or moxifloxacin) (level I evidence) administered parenterally for ICU-treated SCAP patients (Mandell *et al.* 2007). If microbiological tests identify the causative pathogen, antimicrobial treatment should be pathogen-directed. When *Pseudomonas aeruginosa* is detected, the guidelines recommend treatment with antipseudomonal β-lactam (piperacillin-tazobactam, imipenem, meropenem, or cefepime) combined with either ciprofloxacin or levofloxacin. For methicillin-resistant *Staphylococcus aureus* vancomycin or linezolid should be added (Mandell *et al.* 2007).

The rationale behind the recommendation of combination therapy in SCAP is the better coverage of the most common etiological pathogens: *Streptococcus pneumoniae*, atypical bacteria and the most common gram-negative bacteria. These antimicrobial combinations also act on two different sites in bacteria: β-lactams affect the cell wall, whereas quinolones and macrolides act inside the cell. Quinolones affect on the nucleic acid synthesis, whereas macrolides have an influence on the protein synthesis (Caballero & Rello 2011).

2.11.3 Studies of combination therapy in severe community-acquired pneumonia

More recent studies, published in the previous decade, have shown the superiority of a combination therapy for SCAP patients with pneumococcal bacteremia, SCAP patients in septic shock and patients requiring ventilatory support (Table 6). In a prospective multicenter study consisting of ward- and ICU-treated patients with bacteremic pneumococcal pneumonia, a combination antibiotic therapy was associated with lower 14-day mortality (23.4% vs. 55.3%) among critically ill SCAP patients but not among ward inpatients (Baddour *et al.* 2004).

A prospective observational cohort study consisting of 529 ICU-admitted SCAP patients, 51% of whom were in septic shock, showed that a combination therapy was associated with decreased mortality among patients with septic shock. The SCAP patients with shock who were treated with a combination therapy (either β-lactam-macrolide or β-lactam-fluoroquinolone) had higher 28-day ICU survival (HR, 2.69) than the SCAP patients who received monotherapy or who did not have septic shock (Rodriguez *et al.* 2007).

Studies of the optimal antibiotic combination for SCAP treatment are not conclusive. Prospective randomized trials comparing two antibiotic-combinations have not been published, either. The increasing resistance of *Streptococcus pneumoniae* to cephalosporines and macrolides favors the use of the β-lactam–respiratory quinolone combination (Mandell *et al.* 2007, Song 2013). On the other hand, macrolides have effective anti-inflammatory properties, reducing, for example, the release of IL-8 and TNF-α, and some studies suggest that macrolides have immunomodulatory effects (Amsden 2005). Quinolones have been reported to have similar effects (Dalhoff & Shalit 2003, Zimmermann *et al.* 2009).

In a retrospective study with SCAP patients, 62% of whom were admitted to ICU, empiric antimicrobial therapy with a β-lactam-fluoroquinolone combination was associated with increased short-term mortality compared to other guideline-

concordant antimicrobial regimens (Mortensen *et al.* 2006). In a retrospective US study with ward- and ICU-treated CAP patients macrolide use was associated with decreased mortality in patients with severe sepsis due to pneumonia (Restrepo *et al.* 2009). The effect of macrolides or fluoroquinolones on survival was assessed among intubated SCAP patients in a prospective multicenter study (Martin-Loeches *et al.* 2010). Eighty per cent of the patients had combination therapy, but only 45.9% of empiric therapy was in accordance with the IDSA/ATS guidelines. The ICU mortality was significantly lower among the patients having combination therapy with macrolides compared to combination therapy with quinolones (26.1% vs. 46.3%, $p<0.05$). When fluoroquinolones were excluded, no difference in mortality was discovered. However, among mechanically ventilated patients with sepsis and septic shock a survival benefit was seen with the use of a macrolide-combination therapy (Martin-Loeches *et al.* 2010).

In a US study with 1,989 elderly (age >65 years) SCAP patients no significant difference was found in 30-day mortalities between β-lactam-respiratory-quinolone and β-lactam-macrolide groups. However, the patients in the β-lactam-respiratory fluoroquinolone group tended to have longer hospital stays (Wilson *et al.* 2012). A recently published meta-analysis based mostly on observational or retrospective reports with different case mixes, disease severities (included CAP cases) and antibiotic combinations, found that macrolide use was associated with an 18 per cent relative reduction in mortality compared with non-macrolide therapies (Sligl *et al.* 2014).

2.11.4 The duration of treatment

The optimal duration of antibiotic treatment in SCAP is not known. The BTS guidelines propose 7–10 days of treatment for most SCAP patients (Lim *et al.* 2009). The IDSA/ATS guidelines suggest five to seven days of treatment for those CAP patients being afebrile for 48–72 hours and reaching clinical stability. Patients at risk for complications may need longer treatment (Mandell *et al.* 2007). One study suggested that antibiotics could be safely discontinued after seven days among SCAP patients with a good clinical response (Choudhury *et al.* 2011). Serial procalcitonin measurements have been shown useful in the guidance of discontinuation of the antibiotic treatment in acute respiratory tract infections (Schuetz *et al.* 2012). However, it has been stated that in bacteremic patients PCT values may remain higher for longer period, so an exact PCT value for antibiotic

discontinuation is difficult to define, and longer duration of antibiotic therapy (more than one week) will be necessary (Venkatesh *et al.* 2009). An association between a shorter duration of antibiotic treatment and cost-effectiveness has been shown (Shuetz *et al.* 2012).

Table 6. The studies of combination therapy in SCAP.

Author	Year	Cohort	Site	Study design	Outcome
Wilson *et al.*	2012	≥65 years with SCAP	ICU	multicenter retrospective	no difference in 30-d mortality with βM or βQ
Martin-Loeches *et al.*	2010	Intubated SCAP	ICU	multicenter prospective	lower ICU mortality IDSA/ATS comb. with macrolide
Restrepo *et al.*	2009	Severe sepsis pneumonia	Ward	multicenter retrospective	lower 30-d and 90-d mortality with combination
Rodriguez *et al.*	2007	SCAP	ICU	multicenter retrospective	lower 28-d mortality with combination
Mortensen *et al.*	2006	2/3 SCAP patients	Ward+ICU	multicenter retrospective	lower mortality with β-lactam+other than βQ
Baddour *et al.*	2004	BPP	Ward+ICU	multicenter prospective	lower 14-d mortality with combination

CAP, community-acquired pneumonia, βM, beta-lactam-macrolide, SCAP, severe community-acquired pneumonia, ICU, intensive care unit, βQ, beta-lactam-quinolone, BPP, bacteremic pneumococcal pneumonia

2.12 Clinical failure in severe community-acquired pneumonia

A clinical failure is defined as a lack of treatment response and clinical deterioration during treatment (Aliberti *et al.* 2008). The lack of treatment response, especially during the first 2–3 days of treatment, has been shown to increase the risk of complications, length of hospital stay and mortality (Menendez *et al.* 2004, Hoogewerf *et al.* 2006). The incidence of early clinical failure in CAP has been reported to be 6–15%: in SCAP the rates are higher, up to 31% (Menéndez *et al* 2004, Roson *et al.* 2004, Hoogewerf *et al.* 2006, Aliberti *et al.* 2008).

Severe sepsis or progression of septic shock, progressive pneumonia, acute myocardial infarction and arrhythmias are the most prevalent clinical failures (Angus *et al.* 2002, Roson *et al.* 2004, Marrie & Shariatzadeh 2007, Aliberti *et al.* 2008, Ramirez *et al.* 2008). Especially patients with bacteremic pneumococcal SCAP have been shown to have a substantial risk for acute myocardial infarction, arrhythmias and congestive heart failure (Musher *et al.* 2007). Recent studies have reported empyema or complicated parapulmonic effusions with rates from 5% to 7.2% in CAP patients (Chalmers *et al.* 2009, Falguera *et al.* 2011). Similar rates have also been reported in SCAP (Rello *et al.* 2003, Rodriguez *et al.* 2009).

Several factors have been reported to predict the clinical failure. The most common factors defined have been advanced age, hypotension, acidosis, hypoxemia, hypothermia, thrombocytopenia, altered mental state, pleural effusion, multilobar pneumonia, severity of pneumonia and discordant antibiotic treatment (Menendez *et al.* 2004, Roson *et al.* 2004, Hoogewerf *et al.* 2006, Aliberti *et al.* 2008)

2.13 Intensive care unit and hospital mortality

The ICU and hospital mortality rates among ICU-admitted SCAP patients are high despite advanced treatment techniques. The mortality rate varies according to country and patient populations (Table 7). Most recent studies have included the severity of illness scores, but variation between the scores used makes direct comparisons between patient populations difficult. However, most of the studies have reported the number of patients with septic shock and mechanical ventilation. Only few SCAP studies have reported ICU mortality, which has ranged from 27% to 43% (Table 7). Hospital mortality has been the main outcome in the majority of published studies. Hospital mortality rate has varied from 18%

to 57% (Table 7). Thirty-day mortality has ranged between 15.3% and 47% (Table 7).

Many risk factors have been reported to be associated with short-term adverse outcome. The main risk factors for mortality are septic shock, need of mechanical ventilation, advanced age, severity of disease on hospital or ICU admission, acute kidney injury, bacteremia, pneumococcal SCAP, rapid progression of pulmonary infiltrates, bilateral pulmonary infection, immunosuppression, leukopenia, alcoholism and ICU-related complications (ARDS, multiorgan failure) (Moine *et al.* 1994, Leroy *et al.* 1995, Rello *et al.* 1996, Georges *et al.* 1999, Gowardman *et al.* 2000, Marik 2000, Paganin *et al.* 2004, Rodriguez *et al.* 2007, Wilson *et al.* 2005, Yoshimoto *et al.* 2005, Mongardon *et al.* 2012, Khawaja *et al.* 2013).

2.14 Long-term outcome

In CAP, 90-day mortality rates of 7.6% to 12.8% and 1-year mortality rates of 17.1% to 33.6% have been reported (Johnstone *et al.* 2008, Yende *et al.* 2008, Bruns *et al.* 2011). Few studies have reported longer follow-up times (Waterer *et al.* 2004, Johnstone *et al.* 2008, Bruns *et al.* 2011).

The long-term outcome in SCAP is not well established as most published studies concern CAP. According to studies with a general ICU population it is well known that in-hospital mortality underestimates the true mortality of ICU patients. Moreover, the mortality in the first months after hospital discharge is substantial (Brinkman *et al.* 2013a). The mortality after hospital discharge also differs between ICU subgroups (Brinkman *et al.* 2013b).

Among SCAP cases 90-day mortality rates have been 25–28% (Angus *et al.* 2002, Restrepo *et al.* 2008). In a Canadian study of SCAP patients with a mean age of 61 years and with 16% of the patients from nursing homes, 30-day mortality was 11% and 1-year mortality 27%. The mortality rates increased to up to 39% and 49% for patients who were functionally dependent (Sligl *et al.* 2011). CAP studies as well as a few studies on SCAP have found that mortality after hospital discharge is strongly influenced by the severity of pneumonia at hospital admission, co-morbidities, especially cardiovascular and cerebrovascular diseases, preexisting or new malignancy and patient's age and male sex (Kaplan *et al.* 2002, Waterer *et al.* 2004, Johnstone *et al.* 2008, Sligl *et al.* 2011, Brinkman *et al.* 2013, Restrepo *et al.* 2013). Ongoing inflammation after hospital discharge has been suggested as one factor influencing long-term outcome. One investigation reported that circulating IL-6 concentrations at hospital discharge

were higher among those CAP patients who died of cardiovascular disease, kidney injury, infection and cancer during the 1-year follow-up (Yende *et al.* 2008).

Table 7. ICU, hospital and short-term mortality in SCAP.

Study	Year/location	Design P/R	Severity score	No. of patients	Cohort specificities M/F (n/n), age (y; SD or pct)	MV/shock (%)	ICU mortality (%)	Hospital mortality (%)
Rello	1996/ Spain	P	APACHEII mean 22 (≥65y)	156 <65y 95 ≥65y	62/33, 72 (658–3)	82/41.8	-	40.0 ≥65y 32.5 <65y
Ewig	1998/ Chile	P	NA	64	47/17, 63±±16	37/38	-	30.0
Ruiz	1999/ Spain	P	NA	89	58/31, 65±±14	57/36	-	29.0
Georges	1999/ France	R/P	SAPS mean 12.5	505	335/170, 63.4±17.7	57/16.2	-	28.5
Gowardman	2000/ New Zealand	R	APACHEII mean 20.4	32	-/-, 58.5	-	31.0	-
Marik	2000/US	P	APACHEII mean 30	148	93/55, 58	-	-	28-d: 47.0
Rello	2003/ Spain	P	NA	204	164/40, 61.1±17.9	51.9/15.2	-	23.5[1]
Angus	2002/ US, Canada	R	PSI V: 23.8%	170	-/-, 62.3	57/47.6	-	18.2/ 30-d: 15.3 90-d: 24.7
Paganin	2004/ France	P	SAPS 46.4±21.6	112	94/18, 54.7±17.1	41/48	-	43
Yoshimoto	2005/ Japan	R	APACHEII >23, 36%	72	54/18, 72.9	76.4/39	42.9	57.1
Wilson	2005/ Australia	R	PSI V: 30.2%	96	54/42, 59.5±16.6	73/63	-	32
Laterre[2]	2005/ Multicenter	P	PSI V: 62.4%, CURB65 >3: 70.3%, APACHEII >25: 53.3%	602	-/-, 57.5	65 plc/73 DrAA 64 plc/63DrAA	-	28-d: 31.3 plc/ 23.5 DrAA
Marrie	2007/ Canada	P	PSI V: 35.8%, APACHEII mean 17.5, CURB >3: 30.7%	374	217/157, 61.5±17.7	81/19	-	17.9
Rodriguez	2007/Spain	P	APACHEII mean 21.6 with shock	529	380/149, 59.8	66/51	27.9	41.8 with shock

Study	Year/location	Design P/R	Severity score	No. of patients	Cohort specificities M/F (n/n), age (y; SD or pct)	MV/shock (%)	ICU mortality (%)	Hospital mortality (%)
Restrepo	2008/US	R	PSI V: 35.7%	145	128/17, 60.7±15.5	48/23	-	30-d: 23 90-d: 28
Martin-Loeches	2010/ multicenter	P	SAPSII mean 46.5±16.1	218	149/69, 60.4±16.4	100/75.7	37.6	-
Mongardon [3]	2012/France	R	SAPSII mean 47 (366–4)	222	146/76, 60 (497–5)	84/76.6	26.6	28.2
Khawaja	2013/Pakistan	R	APACHEII mean 19.1/28.2[4]	189	110/79, 60.8±18.8	24.9/43.3	-	51

[1] 44.3% with mechanical ventilation and 61.2% with septic shock

[2] PROWESS study

[3] only ICU-treated pneumococcal pneumonia patients

[4] Survivors/ non-survivors

P, prospective, R, retrospective, No, number, M, male, F, female, y, year, SD ,standard deviation, pct, percentile , MV, mechanical ventilation, NA, not available, plc, placebo, DrAA, drotrecogin alfa, d, day

3 Aims of the present research

The aim of the present study was to obtain more information on the diagnosis, etiology, treatment, characteristics, and outcome of SCAP in a mixed tertiary level academic adult ICU.

In detail, the following questions were addressed:

1. Does thoracic CT on admission add any new information for SCAP treatment compared to chest radiograph? (Study I)
2. What is the frequency and clinical course of viral infections in mechanically ventilated SCAP patients? (Study II)
3. Is the β-lactam-respiratory quinolone combination superior to the β-lactam-macrolide combination for the treatment of SCAP? (Study III)
4. Does the outcome of severe community-acquired pneumonia differ from that of hospital-acquired and ventilator-associated pneumonia? (Study IV)

4 Patients and methods

This single-center study was conducted in a mixed medical-surgical adult ICU in a tertiary-level academic teaching hospital, Oulu University Hospital in Oulu, Finland. Both retrospective (Studies I, III, IV) and prospective (Study II) data were collected. The study protocol of the prospective study was approved by the Ethics Committee of Oulu University and written informed consent was obtained from the patient or a legal surrogate in all cases. In the retrospective studies, exemption from consent was obtained from the Ethics Committee as the data had already been collected for clinical purposes.

4.1 Definition

For the studies, SCAP was defined as an acute lower respiratory tract infection with fever or hypothermia, cough, or dyspnea acquired outside the hospital. The presence of pneumonia was confirmed by a chest radiograph with a new pulmonary infiltrate. The patients fulfilled the criteria for severe sepsis and needed ICU treatment (Levy *et al.* 2003).

4.2 Patients and study settings

The retrospective study I consisted of a cohort of SCAP patients admitted between January 2000 and May 2012 to our mixed medical-surgical ICU and on whom both a chest radiograph and a chest CT scan was performed. The patients were included in the study, if a concomitant chest radiograph and chest CT scan were performed on ICU admission or within the first 48 hours of ICU stay. Exclusion criteria were a time interval longer than 24 hours between the chest radiograph and CT, or a CT scan ordered later than 48 hours after ICU admission. Chest CT was performed according to clinical judgment without a dedicated scanning protocol.

To define the etiology of SCAP, a prospective patient population consisting of a cohort of SCAP patients admitted to ICU between June 2008 and May 2012 was collected for study II. Adult patients (older than 18 years) with SCAP who were expected to require intensive care treatment for more than 48 hours, and who required mechanical ventilation within the first 48 hours following ICU admission, were included in this study. Patients with a life expectancy less than

24 hours due to the severity of their disease or whose hospital stay prior to ICU was more than two days admission were excluded.

Study III was conducted to compare the effectiveness of two guideline-concordant antibiotic combination therapies for SCAP treatment. The retrospectively collected study population consisted of a cohort of ICU-admitted SCAP patients between January 2000 and December 2010. Antimicrobial treatment was analyzed to identify patients in whom β-lactam-quinolone (βQ) or β-lactam-macrolide (βM) combination therapy had been initiated within 24 hours of hospital admission. According to our guidelines the attending physician had been able to choose either the β-lactam–quinolone or β-lactam–macrolide combination. The patients with aspiration pneumonia and the patients with PCR-verified H1N1 influenza were excluded, as were the patients with SCAP who had received other antimicrobials or combinations than βQ or βM (Fig. 5).

Study IV evaluated the hospital and long-term outcomes among ICU-treated SCAP, HAP and VAP patients admitted to the ICU during the period from May 2002 to June 2003. Three fourths of the the study population was originally prospectively collected to report the epidemiology and outcome of ICU patients with and without infections (Ylipalosaari *et al.* 2006a, Ylipalosaari *et al.* 2006b, Ylipalosaari *et al.* 2007). In the previous studies, different infections, such as pneumonias, were not separately analyzed. The occurrence of pneumonia was reanalyzed in the patient cohort retrospectively and the patients were followed up until 12 months after hospital discharge. All patients with pneumonia on admission or who acquired pneumonia during their ICU stay were included in this study. Criteria for exclusion were healthcare-associated pneumonia due to difficulty of classifying them as either SCAP or HAP and transfer from other ICU due to the lack of of essential clinical data.

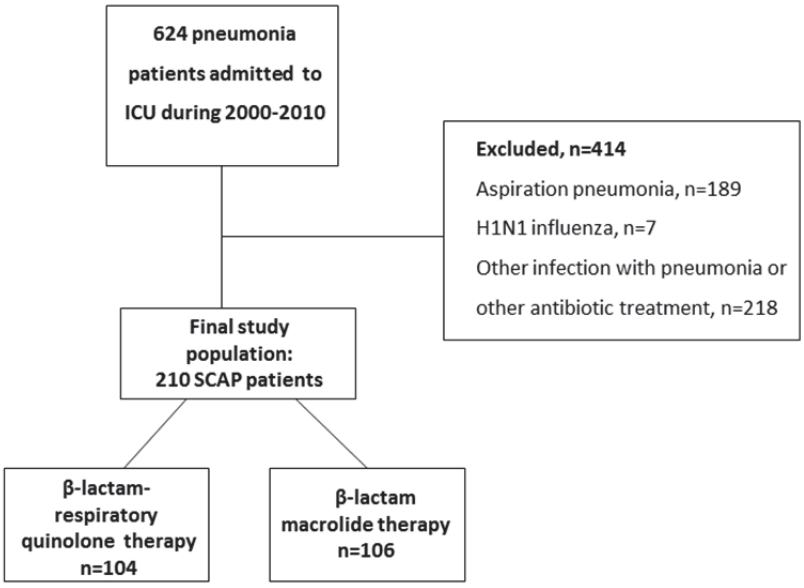

Fig. 5. Flowchart for study III.

4.3 Clinical data

4.3.1 Data collection

In the retrospective analyses (I, III, IV) the ICU records were retrieved from a prospectively collected electronic patient database in the ICU (Centricity Critical Care 7.0 SP3 (7.03.036F), GE Healthcare, IL, USA). The demographic and treatment data outside the ICU were retrieved from the hospital's electronic patient data record system (ESKO, Oulu University Hospital). In the retrospective series the proportion of missing data was fairly low, less than 5%.

Radiographs and CT images were retrieved from the digital image archive of our hospital. The images were reviewed using a neaPACS workstation (neaView Radiology 2.30, Neagen, Oulu, Finland).

4.3.2 Clinical characteristics

For all studies patient characteristics including age, sex, body mass index, pre-existing co-morbidities, alcoholism, and smoking were recorded.

The results of the following laboratory parameters were collected of all study patients from the laboratory's database: daily white cell count, platelet count, CRP, blood gas analyses, electrolytes and serum creatinine and urea level, if available. In the study II serum procalcitonin level was also measured daily.

The need and duration of mechanical ventilation, presence of septic shock on admission or during the ICU stay and the duration of vasoactive drug use as well as the need for corticosteroid treatment (III, IV) during the ICU stay were assessed. The occurrence of acute kidney injury (defined by renal SOFA score 3 or 4, Table 24) and need for renal replacement therapy were recorded (II, III, IV).

The antimicrobial treatment before sampling and ICU admission and during the ICU stay was also registered for all study patients.

4.3.3 Intensive care unit and pneumonia severity scores

The data required to calculate the severity of illness scores were retrieved from the ICU database. The severity of illness on ICU admission was assessed using the Acute Physiology and Chronic Health Evaluation (APACHE) II score (Appendices, Table 23) (Knaus *et al.* 1985). The severity of organ dysfunctions during the ICU stay was assessed daily by using the Sequential Organ Failure Assessment (SOFA) score (Appendices, Table 24) (Vincent *et al.* 1996).

To assess the severity of pneumonia, the IDSA/ATS major and minor criteria were calculated on ICU admission for study II and retrospectively for study III (Table 2) (Mandell *et al.* 2007). The severity of SCAP was further assessed by calculating the Pneumonia Severity Index (PSI) (Appendices, Table 18) (Fine *et al.* 1997) and CURB-65 (Appendices, Table 19) (Lim *et al.* 2003) in the study II. In a study III the severity of pneumonia was also evaluated by using the PIRO (Predisposition Injury Response Organ dysfunction) score (Rello *et al.* 2009) (Appendices, Table 22).

4.4 Imaging methods

Chest radiograph (II, III)

Radiological data were retrieved from the hospital's electronic patient data record. The type of pneumonia and the number of infected lobes were collected from the radiological reports.

Chest CT scan (I)

The chest CT scans had been requested by the treating physicians and performed according to clinical judgment without a dedicated scanning protocol. The main indications for scanning were recorded for study I. Chest CT was performed with a one-row (HiSpeed, General Electric Medical Systems, Milwaukee, WI, USA), a four-row (Toshiba Aquilion, Toshiba Medical Systems, Tokyo, Japan), 16-row (LightSpeed, General Electric Medical Systems), or 64-row scanner (Siemens Sensation 64, Erlangen, Germany). High-resolution CT was performed with 1 mm collimation, 10 mm increment, and a bone reconstruction algorithm. Spiral CT was obtained using 1–5 mm collimation and a soft tissue reconstruction algorithm.

Comparison of chest radiograph and chest CT scan (I)

In study I, each image pair (the chest radiograph and chest CT scan) was retrieved from the hospital's digital image archive, reassessed and interpreted (first the chest radiograph and then the chest CT) independently by two experienced senior thoracic radiologists (L.A. and E.R.). The radiologists were blinded to the clinical information as well as to the earlier radiological reports. The presence, appearance and distribution of parenchymal, pleural and mediastinal abnormalities was analyzed. The type and localization of pneumonia as well as the number of affected lung lobes were evaluated. If the two radiologist's views differed as to the type or extent of pneumonia, a consensus decision was made in each case. The radiographic patterns of pneumonia were divided into three main categories: airspace or alveolar pneumonia, bronchopneumonia, and interstitial pneumonia (Hansell *et al.* 2010a, Hansell *et al.* 2010b). When at least two different patterns of opacities were observed in separate lung lobes, the pneumonia was classified as mixed pneumonia.

4.5 Microbiological data

4.5.1 Bacterial diagnostics

Blood cultures (I–IV)

For studies I, III and IV, the blood culture results were retrieved from the laboratory database. In study II at least two blood samples were obtained from each patient during the first 24 h after hospital or ICU admission for blood culture using the automatic blood culture monitoring system (BactAlert™). A microorganism was considered the definite cause of SCAP if it was cultured from blood (Marston *et al.* 1997).

Respiratory specimens (I–IV)

In study II, lower respiratory tract specimens were obtained with fiberoptic bronchoscopy BAL specimen sampling, or bronchial aspirates were suctioned through the intubation tube. Tracheal aspirates were Gram-stained. When purulent samples had a high leukocyte/epithelial cell ratio (>5) and yielded one or two different bacteria, they were considered as good-quality specimens and the findings as significant. The respiratory tract specimens were cultured quantitatively for bacterial pathogens and fungi. In addition, the BAL samples were subjected to Papanicolau and May-Grunwald Giemsa staining to obtain cellular differential counts, as well as to Gomori methenamine silver staining for *Pneumocystis jirovecii*. Mycobacterium was detected by staining, culturing, or PCR. A microbe was considered the etiology of SCAP only if it grew from good-quality bronchial aspirates (cutoff $\geq 10^5$ cfu) or BAL (cutoff $\geq 10^4$ cfu). For studies III and IV, the microbiological results of the respiratory tract specimens were retrieved from the laboratory's electronic database.

Urine antigen testing (I, II, III)

BinaxNOW® *Streptococcus pneumoniae* urine antigen (BinaxNOW® Alere Scarborough, Inc., USA) testing has been available for routine use in our hospital since 2005. The results of the pneumococcal antigen detection test were recorded for studies I and III when available. In study II, urine pneumococcal antigen and

Legionella pneumophila antigen testing (BinaxNOW® Alere Scarborough, Inc., USA) were performed for all study patients. If urine antigen testing for *Streptococcus pneumoniae* or *Legionella pneumoniae* was positive, they indicated probable etiology of SCAP (Marston *et al.* 1997).

Pleural fluid culture (I–III)

The microbiological results of pleural fluid cultures were recorded when available. A positive culture of pleural fluid provided a definitive SCAP etiology.

Serological tests (II)

Paired serum samples for serological detection of *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* were obtained upon ICU admission and before hospital discharge for study II. The presence of IgM antibodies and/or a significant increase (at least a two-fold rise) in IgG antibody levels between paired serum samples was considered an acute *Mycoplasma pneumoniae* or *Chlamydia pneumoniae* infection.

4.5.2 Viral diagnostics (II)

Three sets of nasopharyngeal swabs (NP) were collected for the detection of respiratory viruses. The NP swabs were obtained using a Copan brush, and each swab was stored in a sterile sample tube and deep-frozen at -75°C until analysis. During the first two ICU days, bronchoalveolar lavage (BAL) was performed for respiratory viral diagnostics whenever possible. Two 3-mL samples of BAL fluid were stored at -75°C until PCR analysis. When a BAL study was not possible due to a patient's severe condition, normal bronchoscopy was performed, or alternatively, a bronchial suction aspirate sample was collected via intubation tube for virus detection. The NP swabs and two samples of BAL fluid or bronchial suction aspirates were sent for analysis of respiratory viruses to the Virus Diagnostics Laboratory, University of Turku.

All nasopharyngeal swabs, bronchial aspirates, and BAL samples were analyzed by PCR. A multiplex PCR test kit (Anyplex RV16, Seegene, South Korea) was used to detect the following: adenovirus; influenza A and B viruses; parainfluenza virus types 1–4; rhinovirus; respiratory syncytial viruses A and B; bocavirus; coronaviruses 229E, NL63, and OC43; metapneumovirus; and

enteroviruses. In addition, an in-house PCR test was used to detect enteroviruses and rhinoviruses (Peltola *et al.* 2008). In the present study viruses were considered a probable cause of SCAP when they were detected in the NP swabs by PCR. When a lower respiratory tract specimen PCR was positive it was considered the definitive cause of SCAP.

4.6 Outcome assessment (I–IV)

The main outcome variables were mortality (ICU, hospital and 28-day) and the length of ICU and hospital stay. In study III 30- and 60-day mortalities were recorded. In study IV one-year mortality was analyzed. Data concerning mortality and length of stay were obtained from the ICU and hospital databases. The data on sixty-day and one-year mortalities were obtained from the official national database (Statistics Finland, Helsinki Finland).

4.7 Statistical methods

The statistical analyses were performed using SPSS software versions 16.0 and 19.0 (SPSS, Chicago, Ill, USA) for studies IV and III and SPSS version 20.0 (IBM SPSS Statistics for Windows. Armonk, NY: IBM Corp.) for studies I and II. Summary measurements were expressed as means with standard deviation (SD) where appropriate, or as medians with 25th–75th percentile for continuous variables, and as counts (%) for categorical variables, unless otherwise stated. Student's t-test (normal distribution) (I–III) or Mann-Whitney U-test (non-normaldistribution) (II, III) was used for between-group analyses with continuous variables and χ^2 or Fisher's exact test with categorical variables. In study IV comparisons between the independent groups were performed with the non-parametric Kruskal-Wallis test. The comparisons between the chest radiograph and chest CT findings (categorical variables) were performed using the McNemar's test or McNemar-Bowker test, with the latter test used for more than two classes (I). Spearman's correlation coefficient (ρ) was calculated for continuous variables (I). In study III the simple pneumonia severity score was calculated by summing the values of the IDSA/ATS minor and major criteria. This pneumonia severity score and APACHE II score-adjusted logistic regression model was created to compare the two combination therapy groups. The results of the logistic regression model were reported as odds ratios with 95% confidence

intervals (95% CI). Kaplan-Meier survival curve and the log rank test result were calculated for 1-year survival in study IV. Two-tailed p-values were reported.

5 Results

5.1 Patients

After the exclusions presented in the Methods section, altogether 441 SCAP patients were included in the four studies. In addition, study IV consisted of 66 hospital-acquired pneumonia and 25 ventilator-associated pneumonia cases, and their data are presented in more detail in Table 16. There were 93 (21.1%) overlapping cases in the four studies (Table 8).

Table 8. Number of overlapping cases in the four studies.

Study	I (n)	II (n)	III (n)	IV (n)
I	65	27	31	2
II	-	49	21	0
III	-	-	210	25
IV	-	-	-	208

The demographic data of the SCAP patients included in the four studies are presented in Table 9. The majority of ICU-admitted SCAP patients were men, except in study II in which more than half of the cases were women. The median age of admitted patients did not change remarkably during the twelve-year period, and the majority of the patients had at least one co-morbid illness.

The patients' median APACHE II score was 21, except in study II (Table 9). Organ dysfunctions, determined by the admission day SOFA score, the presence of septic shock and the need of mechanical ventilation were common at ICU admission. More than 10% of the cases developed AKI during the ICU stay (Table 9).

Compared to the patients in studies III and IV, the patients in studies I and II had the longest ICU and hospital stay, as shown in Table 9. The longer length of stay can be explained by the number of cases with septic shock and the need of mechanical ventilation among those patients. The ICU mortality was low during the whole study period. The hospital mortality among SCAP patients during the prospective study period was lower than earlier.

Table 9. Baseline characteristics of all SCAP patients included in the four studies, number, n (%), median (25th, 75th percentiles).

Variable	Study I	Study II	Study III	Study IV[1]
Study design	Retrospective	Prospective	Retrospective	Retrospective
Study period, years	2000–2012	2008–2012	2000–2010	2002–2003
n	65	49	210	117
Male/Female	53.8/46.2	42.9/57.1	64.8/35.2	62/38
Age	56 (44–68)	54 (47–68)	54 (44–67)	56 (44–67)
Comorbidities	64.6	73.5	69.5	71
APACHEII	21 (15–26)	18 (13–24)	21 (15–27)	21 (17–27)
SOFA[2]	8 (5–11)	7 (5–11)	7 (4–9)	7 (4–9)
Septic shock	40 (61.5)	21 (42.9)	99 (47.1)	27 (22)
Need of MV	49 (75.4)	47 (95.9)	110 (52.4)	99 (85)
AKI	8 (12.3)	10 (20.4)	32 (15.2)	15 (12.8)
ICU LOS, days	6.0 (3.0–9.0)	7.0 (4.0–10.0)	4.0 (2.0–7.0)	2.9 (1.6–5.6)
Hospital LOS, days	14.0 (10.0–24.0)	16.0 (11.0–22.0)	11.0 (7.0–18.0)	10 (6.0–17.0)
ICU mortality	7 (10.8)	3 (6.1)	23 (11)	7 (6.0)
Hospital mortality	13 (20)	6 (12.2)	43 (20.5)	28 (23.9)
28-day mortality	13 (20)	5 (10.2)	43 (20.5)	27 (23.1)

[1] Data presented only of SCAP patients

[2] SOFA first 24 h, MV, mechanical ventilation, AKI, acute kidney injury, ICU, intensive care unit, LOS length of stay

5.1.1 Early chest CT in the treatment of severe community-acquired pneumonia (I)

A total of 155 chest CT scans of 479 SCAP patients were acquired during the first ICU treatment week. Patients were excluded as follows: 75 with scans performed later than 48 hours after ICU admission and 15 who lacked a simultaneous chest radiograph for comparison. The final study population consisted of 65 SCAP patients with a concurrent chest CT and plain chest radiograph. The chest CT was performed on admission in 35 cases (53.8%), within 24 hours of admission in 26 cases (40%), and 24–48 hours after admission in four cases (6.2%).

The median count of infected lobes was four on the chest radiograph and five on CT. The number of infected lobes identified via chest CT correlated positively with the levels of C-reactive protein (ρ 0.299, P=0.016) and negatively with the lowest PF ratio on the scanning day (ρ -0.326, P=0.008). Similar correlations of infected lobes identified via chest radiograph were not observed. Significant

association was not found between the number of affected lobes and hospital mortality or length of hospital stay among the surviving SCAP patients.

In 38 cases (58.5%) the CT revealed new findings not detected by the chest radiograph, pleural fluid being the most common finding (36.9%). Pleural fluid and atelectasis were observed more often with CT scan than with the chest radiograph (Table 10).

The CT results motivated procedures and therapeutic interventions in 28 SCAP patients (43%). Bronchoscopy was the most common procedure accounting for 12 out of 22 (54.5%) procedures, while extending or initiating new antimicrobial therapy was the most common therapeutic intervention in 11 out of 22 cases (50%). Although pleural fluid was a common finding, the number of pleural puncture was low (Table 11).

Table 10. Main findings in the 65 pairs of chest radiographs and chest CT scans, median (25^{th}, 75^{th} percentiles), number (%).

Variable	Chest radiograph	Chest CT scan	P-value
Number of infected lobes	4 (4–5)	5 (3–5)	0.67
Number of infected lobes in case of positive a blood cultures (n=20)	4 (3–5)	5 (4–5)	0.025
Type of pneumonia			
Alveolar	47 (72.3)	49 (75.4)	NA
Bronchopneumonia	5 (7.7)	4 (6.2)	NA
Pleural fluid	17 (26.2)	41 (63.1)	<0.001
Bilateral	5 (7.7)	21 (32.3)	0.13
Atelectasis	10 (15.4)	22 (33.8)	0.002

Table 11. Procedures and therapeutic interventions based on CT results, number (%). Percentages calculated per 65 SCAP patients.

Intervention	n (%)
Procedures	22 (33.8)
Bronchoscopy and bronchoalveolar lavage to open atelectasis	12 (18.4)
Pleural ultrasound to guide drainage	7 (10.8)
Pleural puncture	3 (4.6)
Therapeutic interventions	22 (33.8)
Extension of the spectrum of antimicrobials[1]	11 (16.9)
Start of diuretics	5 (7.7)
Thoracoscopy/ thoracotomy	2 (3.1)
Laparotomy[2]	2 (3.1)
Start of anticoagulant therapy[3]	1 (1.5)
Whitdrawal of treatment[4]	1 (1.5)
Total	44 (67.7)

[1] Induced by wider pneumonic opacities revealed by CT than chest radiograph

[2] SCAP with unexpected bowel perforation

[3] SCAP and pulmonary embolism

[4] SCAP with inoperable lung cancer

5.1.2 Etiology of severe community-acquired pneumonia (II)

A total of 67 SCAP patients with mechanical ventilation were applicable for the study. Eighteen of them were excluded for the following reasons: life expectancy less than 24 h due to severity of disease (4), long hospital stay before transfer to ICU (3), or no-study personnel available (11). Among the 49 mechanically ventilated patients the etiology of SCAP was identified in 92% (45/49) of the cases. Pure bacterial etiology of SCAP was diagnosed in 43% (21/49), while viruses were found in 49% (24/49) of the patients when PCR methods were applied. Ten per cent (5/49) of the patients probably had pure viral pneumonia while 39% (19/49) had mixed bacterial-viral pneumonia (Table 12). Out of 26 viruses, 21 (81%) were detected from bronchial specimens and five (19%) from nasopharyngeal swabs. Rhinovirus and adenovirus were the most common viral findings. *Streptococcus pneumoniae* was the most common bacteria identified, presenting as the sole pathogen in 15 cases (Table 12).

Table 12. Microbial etiology detected in the 45 SCAP patients by the different diagnostic tests.

Microbe	Total no. of microbes	Blood culture (n)	Nasopharyngeal swabs (n)	Tracheal specimens (n)	U-Stpnag (n)	Serology (n)
S. pneumoniae	28	16	-	16	25	-
H. influenzae	2	1	-	1	-	-
S.aureus	2	-	-	2	-	-
M. catarrhalis	1	-	-	1	-	-
P. aeruginosa	1	1	-	1	-	-
K. pneumoniae	1	-	-	1	-	-
E. coli	1	1	-	1	-	-
M. pneumoniae	8	-	-	-	-	8
Rhinovirus	15	-	4	11	-	-
Adenovirus	4	-	-	4	-	-
Coronavirus	2	-	-	2	-	-
Enterovirus	2	-	1	2	-	-
Parainfluenzavirus	1	-	-	1	-	-
Respiratory syncytial	1	-	1	1	-	-
Influenza virus	1	-	1	-	-	-

no, number, U-Stpnag, urine pneumococcal antigen, *S.pneumoniae, Streptococcus pneumoniae, H.influenzae, Haemophilus influenzae, S.aureus, Staphylococcus aureus, M.Catharralis, Moraxella catharralis, P.aeruginosa, Pseudomonas aeruginosa, K.pneumoniae, Klebsiella pneumoniae, E.coli, Escherichia coli, M.pneumoniae, Mycoplasma pneumoniae*

The clinical characteristics were similar among the patients with pure bacterial and mixed bacterial-viral infections. There were no statistically significant differences in the severity of illness or the pneumonia severity scores between these patients, except that the patients with a pure bacterial infection had highest APACHE II scores on admission. The patients with a mixed bacterial-viral etiology had the highest peak CRP levels while the patients with a probable viral etiology had the lowest peak PCT levels. Patients with a pure bacterial pneumonia had longer hospital stay when compared to patienst with a bacterial-viral infection (Table 13).

Table 13. Comparisons of the severity of illness, admission laboratory values and outcome between the SCAP patients with different types of etiology, number (%), median (25^{th}, 75^{th} percentiles).

Variable	Bacterial group n=21	Bacterial- viral group n=19	Probably pure viral group n=5	No etiology group n=4	p-value1
Age	53 (49–58)	55 (44–65)	48 (44–57)	62 (46–72)	>0.9
Male sex	10 (48)	8 (42)	2 (40)	1 (25)	0.76
Smoking	9 (45)	9 (47)	3 (60)	1 (25)	>0.9
Alcoholism	3 (14)	5 (26)	0 (0)	0 (0)	0.44
Days with symptoms before pneumonia dg	2 (0–4)	3 (1–4)	2 (0–2)	4 (1–5)	0.81
APACHE II	22 (18–25)	16 (12–21)	13 (11–20)	17 (15–19)	0.05
SOFA (24 h)	9 (7–11)	7 (5–11)	7 (5–8)	6 (5–9)	0.61
Septic shock	8 (38)	10 (53)	2 (40)	2 (50)	0.53
Time on noradrenaline[2]	45 (30–96)	85 (56–118)	74 (73–151)	39 (25–51)	0.48
CRP, mg/L, peak	299 (213–350)	356 (294–416)	152 (120–192)	234 (149–314)	0.05
PCT, µg/L, peak	14.3 (3.1–63.5)	24.3 (6.2–40.4)	1.7 (1.6–1.7)	11.0 (1.1–37.0)	0.68
ICU LOS, days	8 (511)	7 (5–9)	10 (8–14)	4 (4–5)	0.26
Hospital LOS, days	17 (12–25)	14 (11–17)	21 (20–39)	11 (10–13)	0.02
ICU mortality	0 (0)	3 (15.8)	0 (0)	0 (0)	0.1
Hospital mortality	2 (10)	4 (21)	0 (0)	0 (0)	0.4

[1] Comparisons between bacterial and bacterial-viral groups [2] hours

dg, diagnosis, CRP, C-reactive protein, PCT, procalcitonin, ICU, Intensive care unit, LOS, length of stray

5.1.3 Combination antibiotic therapy in severe community-acquired pneumonia (III)

Treatment with a combination of antibiotics was started within 24 hours of hospital admission and is shown in Table 14.

Table 14. Distribution of the antibiotics used in the patients receiving a combination therapy with either a β-lactam-respiratory quinolone or a β-lactam-macrolide.

Antibiotic	βQ-combination (%)	βM-combination (%)
moxifloxacin	88.5	
levofloxacin	11.5	-
azithromycin	-	76.4
erythromycin	-	23.6
cefuroxime	80.8	88.7
ceftriaxone	1.0	-
piperacillin- tazobactam	18.3	11.3

The patients receiving the βQ combination had higher admission lactate than the patients receiving the βM combination. The prevalence of blood culture positivity did not differ significantly between the groups, but septic shock as well as the need of mechanical ventilation was more frequent among patients receiving the βQ combination (Table 15). When the severity of disease was compared, admission median APACHE II score was lower in the patients receiving the βQ combination, while no difference was found in the SOFA 24 hour or SOFA max scores. The patients with the βQ combination fulfilled IDSA/ATS criteria for SCAP more often, whereas no difference was found in the IDSA/ATS minor criteria (Table 15).

Table 15. Severity of SCAP, length of stay and outcome in the patients receiving combination antibiotic therapy with either β-lactam-respiratory quinolone or β-lactam-macrolide, number [n (%)], median (25^{th}-75^{th} percentiles), mean (SD).

Variable	β-lactam-respiratory quinolone combination n= 104	β-lactam-macrolide combination n= 106	P- value
Age	54 (446–7)	55 (436–7)	0.67
Male sex	67 (64.4)	69 (65.1)	>0.9
Chronic underlying disease	69 (66.3)	77 (72.6)	0.37
Blood lactate (mmol/L)	2.14 (1.51–3.57)	1.57 (1.06–2.29)	0.002
CRP (mg/L) max	267 (162–336)	277 (177–355)	0.41
Bacteremia	29 (27.9)	32 (30.2)	0.76
Septic shock	50 (48.1)	41 (38.7)	0.21
Need of mechanical ventilation	65 (63.1)	45 (42.5)	0.004
APACHE II	18 (17–27)	22 (13–26)	0.003
SOFA 24h	7 (4–10)	7 (3–9)	0.40
SOFA max	8 (5–11)	7 (4–10)	0.15
IDSA/ATS SCAP criteria fulfilled	87 (83.7)	73 (68.9)	0.015
IDSA/ATS minor criteria fulfilled	49 (47.1)	44 (41.5)	0.49
ICU LOS, days	5.3 (4.3)	5.3 (5.2)	>0.9
Hospital LOS, days	16.1 (18.3)	13.4 (10.3)	0.2
ICU mortality with septic shock	10 (17.9)	9 (28.7)	0.80
30-day mortality	17 (16.3)	26 (24.5)	0.17
with bacteremia on admission	6 (20.7)	10 (31.2)	0.40
with septic shock	11 (19.6)	14 (32.6)	0.16
60-day mortality	21 (20.2)	30 (28.3)	0.20

SOFA 24h, during the first 24h after admission, SOFA max, maximal SOFA score during ICU treatment period, LOS, length of stay

Neither ICU LOS nor ICU, hospital, 30-day or 60-day mortality differed significantly between the two groups (Table 15). In case of bacteremia or septic shock, no difference in mortality was observed between patients receiving the βQ and βM combination therapies (Table 15). In APACHE II and IDSA/ATS SCAP score-adjusted multivariate logistic regression analysis, the odds ratio (OR) for 30-day mortality did not differ statistically between the groups (OR 1.4; 95% CI, 0.62–3.0; P =0.44).

5.1.4 The outcome of pneumonia (IV)

Among the ICU-admitted pneumonia patients, the HAP and VAP patients had more malignant underlying diseases, and the HAP patients were older than the SCAP and VAP cases. While the admission APACHE II scores did not differ between the groups, the VAP patients developed more organ dysfunctions during their ICU stay defined by the SOFA score. Septic shock was most common among the SCAP patients (Table 16).

The length of ICU stay was longest in the VAP group, while the total hospital stay was longest among the HAP patients. No statistically significant difference was found in the ICU, hospital or 28-day mortality across the pneumonia groups (Table 16).

Mortality was highest during the first 60 days after hospital admission in all the pneumonia categories (Fig. 6). All the deaths in the VAP group occurred during the first 90 days, while the survival rate decreased in the HAP group during the whole follow-up period. The 1-year mortality of hospital survivors was higher in the VAP (41.2%) and HAP (35.3%) groups compared with the SCAP (18.0%) group (Table 16).

Table 17 shows the risk factors of hospital mortality in univariate analysis. In a multivariate logistic regression model, when the need of RRT, septic shock, APACHE II >25 and CRP max >100 mg/L were used as adjusting variables, the OR for hospital mortality of HAP and VAP was 0.84 (95% CI 0.35–2.0, P = 0.7) and 1.8 (95% CI 0.63–5.2, P = 0.27), respectively, compared to that of SCAP.

Table 16. Baseline characteristics, ICU scores, length of stay and outcome among the ICU-treated SCAP, HAP and VAP patients, number [n (%)], mean (SD) or median (25^{th}-75^{th} percentiles).

Variable	SCAP n=117	HAP n=66	VAP n=25	P-value
Age	55 (17)	62 (14)	54 (17)	0.023
Chronic underlying disease	82 (71)	54 (83)	14 (56)	0.028
Malignancy	8 (7)	20 (30)	6 (24)	<0.001
APACHE II	22 (8)	21 (8)	22 (6)	>0.9
SOFA (24h)	7 (4)	6 (3)	9 (3)	0.003
SOFA max	7 (4)	6 (3)	10 (4)	<0.001
ICU mortality	7 (6.0)	5 (7.6)	4 (16.0)	0.25
ICU LOS, days	2.9 (1.6–5.6)	3.1 (1.6–6.0)	7.8 (6.3–17.3)	<0.001
Hospital mortality	28 (23.9)	15 (22.7)	8 (32)	0.66
Hospital LOS, days	10 (6–17)	19 (10–34)	16 (13–31)	<0.001
One-year mortality for hospital survivors	16/89 (18.0)	18/51 (35.3)	7/17 (41.2)	0.032

SOFA max, maximal SOFA during ICU treatment period, LOS, length of sray

Table 17. The risk factors of hospital mortality; univariate analysis, odds ratio (OR), confidence interval (CI).

Characteristic	OR (95% CI)	P- value
Need for RRT	6.1 (2.1–17.9)	0.001
AKI	5.1 (2.0–12.9)	0.001
Septic shock	5.0 (2.3–10.7)	<0.001
SOFA max >8	4.0 (2.1–7.8)	<0.001
APACHE II >25	2.8 (1.4–5.4)	0.002
Chronic underlying disease	2.8 (1.2–6.8)	0.018
Mechanical ventilation >2 days	2.5 (1.3–5.1)	0.008
CRP max >100 mg/L	2.8 (1.1–7.7)	0.039

RRT, renal replacement therapy, AKI, acute kidney injury

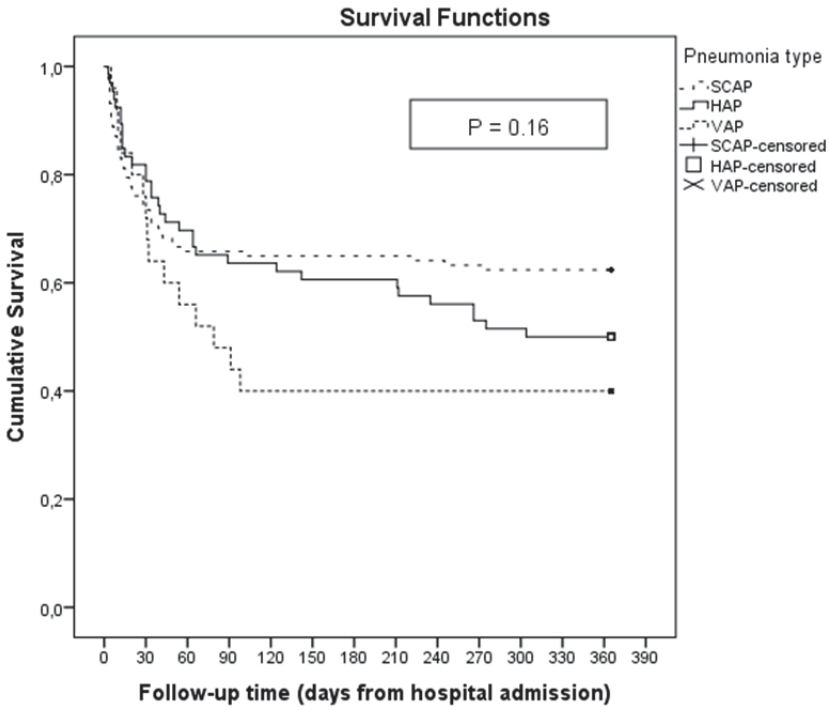

Fig. 6. Kaplan-Meier survival curves for the different types of pneumonia. Out of the 208 admitted SCAP, HAP and VAP patients 92 (44.2%) died during the one-year follow-up. P-values according to log-rank test.

6 Discussion

6.1 The strengths and limitations of the study

6.1.1 Generalization of the results

This was a single-center study in a mixed academic medical-surgical ICU, which limits the generalizability of the findings for other types of ICU populations. Although our study population for the retrospective study IV was gathered almost a decade ago and the recruitment periods in the retrospective studies I and III were ten and twelve years, the results are considered rather relevant for the following reasons: firstly, the basic clinical characteristics of the patients, i.e., mean age, number of comorbidities, APACHE II and SOFA scores have not changed significantly over the years. Secondly, the admission and discharge policies have not changed remarkably, and thirdly, the current treatment guidelines such as lung protective ventilation (year 2000), glucose control (year 2001) and hydrocortisone for vasopressor-dependent septic shock (year 2002) have been followed since they were introduced (Brower *et al.* 2000, van den Berghe *et al.* 2001, Annane *et al.* 2002). However, within the past ten years many other practices have changed, for example, changes in on call practices, the critical care outreach service on the wards, the implementation of medical emergency team, setting up the step-down unit as well as improvements in cardiac arrest action, which may have influenced the results. These changes in practices may be reflected especially in the lower hospital mortality rates in the prospective study II during the years 2008–2012 compared to other studies.

Despite the above-mentioned limitations the findings in the current study are generalizable concerning the use of early chest CT for all SCAP patients, viral findings for intubated SCAP patients and the results of combination antimicrobial therapy for SCAP populations with low prevalence of multidrug-resistant microbes.

6.1.2 Methodological considerations

Three out of the four studies in this thesis were of retrospective nature. This requires some consideration. Missing data is a confounding factor in retrospective analyses and can a have significant effect on the conclusions. However, in our

retrospective series the number of missing data was fairly low. Missing data might therefore not have a substantial influence on the results. Other known disadvantages in retrospective studies are the lack of a strict study protocol, no control over exposure or outcome assessment, difficulty to achieve compatibility between the exposed and non-exposed, and the fact that temporal relationships are often difficult to determine (Altman 1991).

The sample size in both the retrospective and prospective studies was relatively small and underpowered for robust statistical conclusions. One main reason for the limited number of cases in the prospective study II was the high cost of viral PCR analyses. The small sample size affects the choice of statistical analysis; for example, multivariate logistic regression analyses could not be performed. However, despite the limited number of study patients, this examination of viral findings in SCAP patients, including bronchoscopic PCR sampling, is thus far the largest series in mechanically ventilated SCAP patients. While study III is one of the largest studies comparing respiratory quinolone (n=104) and macrolide (n=106) combination therapies, a *post hoc* sample size calculation showed that 298 patients would have been needed for both the βM and βQ combination groups to show a difference with statistical significance.

In study IV the small number of VAP cases was reflected in the wide confidence intervals for the comparison of ORs between VAP and the other pneumonia types. Thus it cannot be definitively ruled out that in a larger study, for example with a multicenter approach giving a larger population of VAP cases, the differences in hospital mortality between VAP and SCAP and HAP might be significant.

In our retrospective series the total number of positive microbiological findings was somewhat lower than reported earlier, for example 38% in the study III. However, the number of positive blood cultures was fairly high compared to earlier reports. The blood culture positivity in our prospective series without previous antibiotic treatment was 50%. This suggests that in etiological evaluations the information concerning previous antibiotic treatment is essential and should be clearly reported.

6.1.3 Ethical considerations

In the retrospective studies, in accordance with the principles of the local ethics committee, exemption from consent was obtained as the data retrieved from the databases had already been recorded for patient treatment purposes. The study

protocol of the prospective study was approved by the Ethics Committee of Oulu University before the onset of the data collection. Written informed consent was obtained from the patient or a legal surrogate in all cases. In study IV the data were collected prospectively by Dr. Ylipalosaari after approval from the Ethics Committee and written informed consent was obtained as discussed above. The data were analyzed retrospectively for the current study.

In the prospective study II all patients were treated according to our standard clinical practice. Patients with a severe oxygenation disorder or critical condition were excluded from the BAL study.

The study data have been handled anonymously and stored as stipulated by the relevant national data registration requirements.

6.2 The usefulness of early CT in treatment of severe community-acquired pneumonia (I)

Our study evaluated for the first time the utility of chest CT among SCAP patients and the results of the study were rather promising. Chest CT yielded new imaging findings for more than half of our SCAP patients. Better characterization of pneumonia and extent of opacities demonstrated by CT led to procedures or treatment changes in nearly half of the SCAP patients during their first 48 hours of ICU stay.

In the present study pleural fluid was detected 2.4 and atelectasis 2.2 times more often with the CT scan than with the plain chest radiograph radiograph in the patients with SCAP. These findings are in line with earlier studies on CAP, which have also shown the superiority of CT for pleural fluid detection compared to plain chest radiograph (Tan Kendrick *et al.* 2002, Kitazono *et al.* 2010, Brixey *et al.* 2011). A previous large CAP study has shown that the presence of pleural fluid was independently associated with hospital mortality (Fine *et al.* 1997). The number of cases in the present study was fairly low for comprehensive statistical conclusions.

One interesting observation in the present study was that in 17% of patients the chest radiograph depicted more infected lobes than the same-day CT scan. The majority of these cases proved to be either pleural effusions or atelectasis in the chest CT, suggesting that the additional opacities in the chest radiograph interpreted as infected lobes may actually reflect non-pneumonic changes. With a better tissue contrast and three-dimensional visualization of anatomic structures CT allows better identification of infiltrates compatible with pneumonia and more

accurate characterization of the pneumonia type and extent as has also been shown earlier (Romano *et al.* 2008, Hansell *et al.* 2010b).

There is, so far, only one study supporting our results of the utility of the chest CT scan for treatment decisions in pneumonia (Banker *et al.* 2007). This retrospective study with emergency room CAP patients showed that chest CT directed treatment procedures in one fourth of the patients, leading to antibiotic changes in one in every ten patients (Banker *et al.* 2007). These figures were lower than those in our study with more severely ill SCAP patients in the ICU setting.

In the present study the number of infected lobes in the chest CT correlated positively with the serum levels of C-reactive protein and bacteremia, but no correlation was found with the number of infected lobes in the chest radiograph. Similarly, the severity of hypoxia correlated with the extent of lung involvement only on CT.

The results of the current study suggest that in hypoxemic SCAP patients an admission or early chest CT reveals information that might be useful for guiding treatment decisions, especially, when there is a differential diagnostic problem or if infectious complications are suspected, or when the selected treatment strategy seems to fail or the patient's condition deteriorates. However, larger prospective studies are needed to find out whether this approach would lead to a shorter hospital stay, less use of antimicrobials and a better outcome. Ultra-low-dose CT has radiation doses comparable to those in the conventional chest radiograph with acceptable diagnostic quality. These new imaging techniques may lower the threshold for using chest CT also in critically ill pneumonia patients (Börjesson *et al.* 2011, Neroladaki *et al.* 2013). In the future, lung ultrasound could also be a useful alternative for the diagnosis of pneumonia (Chavez *et al.* 2014).

6.3 Viral etiology of severe community-acquired pneumonia (II)

According to the results of the current study the etiology of SCAP was defined in 92% of the patients with the large-scale diagnostic testing and the PCR techniques. Corresponding figures in earlier studies have been varied from 40% to 75% depending on the diagnostic tests used. Thirty-seven per cent of our patients were already on antibiotics before the sampling and bacterial PCR test was not available during the study period, which could decrease the number of positive findings.

Viral etiology was common among our ICU-admitted SCAP patients. Viruses were defined in 49% of the patients when PCR techniques were applied to the respiratory samples, and majority of the viruses were found in the lower respiratory tract samples. Only two studies have reported the rates of viruses among ICU-treated SCAP cases. A Korean single-center study found viruses in 41% of the SCAP cases, while in a US multicenter study the corresponding rate was 11–23%, the count alternating seasonally (Choi *et al.* 2012, Wiemken *et al.* 2013).

The importance of viruses in the etiology of SCAP has been challenged, because most earlier etiological studies have relied on nasopharyngeal swab sampling. Viral findings in nasopharyngeal specimens might represent only coincidental upper airway infection (Johansson *et al.* 2010). The importance of lower respiratory tract samples in viral detection was seen during Influenza A (H1N1) pandemic 2009 (de la Tabla *et al.* 2010, Lopez Roa *et al.* 2012). In the current study with intubated SCAP patients, all patients had lower respiratory specimens sampled via bronchoscopy (BAL) or endotracheal aspiration. The recovery of viral PCR was 1.8-fold higher from the lower respiratory tract specimens than from the nasopharyngeal swabs emphasizing the significance of viruses in SCAP etiology. In our study the duration of respiratory symptoms did not differ significantly between different etiological groups and this finding supports the the role of viruses in SCAP etiology.

In the present series rhinovirus was the most common virus detected. A similar finding has also been reported in previous SCAP studies (Choi *et al.* 2012, Wiemken *et al.* 2013). In our material rhinovirus was discovered in 31% of the cases, and 73% of the rhinovirus findings came from the lower respiratory tract samples. The significance of rhinovirus has been debated; however, the findings of rhinovirus in BAL and endotracheal specimens support their etiological significance (Minosse *et al.* 2008). Moreover, an association between rhinovirus and severe pneumonia has been shown in a pediatric study (Imakita *et al.* 2000).

In the present study a higher yield of viral diagnoses in the SCAP patients was achieved with highly qualified and quite expensive multiplex PCR methods and invasive sampling. For respiratory viruses antiviral agents are currently available for the influenza and adenoviruses, so wider use of this approach, at least outside the academic-level ICUs, should be carefully considered.

6.4 Combination therapy in severe community-acquired pneumonia (III)

In the present study no significant difference in outcome was obsereved in the SCAP patients treated with either a βQ combination or a βM combination. No outcome differences in mortality were observed even in the patients with septic shock. Previous small, mainly retrospectively performed analyses with different case mixes and study settings have shown a better outcome in the SCAP cases treated with a macrolide combination therapy (Table 6). So far, only two prospective studies have been conducted without any clear mortality advantage for the βM combination over the βQ (Rodriguez *et al.* 2007, Martin-Loeches *et al.* 2010). These results are in line with the current investigation. The patients receiving a βQ combination had alonger hospital stay. A similar finding was also shown in a US study comparing two antibiotic combinations (Wilson *et al.* 2012). One possible explanation for the finding in the present study and the US study might be the greater propotion of patients with septic shock and the more frequent need for mechanical ventilation on admission among the patients receiving βQ or better inflammation control with macrolides as stated by Wilson (Wilson *et al.* 2012). However, quinolones have also been shown to have similar anti-inflammatory properties as the macrolides (Dalhoff & Shalit 2003, Amsden 2005, Zimmermann *et al.* 2009). The time spent on mechanical ventilation did not differ statistically between the two goups, either (data not shown).

Adherence to antibiotic guidelines has shown to decrease mortality in SCAP (Bodi *et al.* 2005). During our study, the attending physician was able to choose either a βQ or a βM combination in accordance with the IDSA/ATS guidelines, but without a strict protocol. In the last five years a respiratory quinolone was used more often. The change was most likely due to the cumulative experience obtained in our unit, and took place in spite of papers published at that time suggesting the superiority of macrolides. One main reason for the change in the practice was concern for increasing pneumococcal resistance to penicillins or cephalosporines and macrolides. However, the propotion of resistant pneumococci is still low in our hospital as well as in Finland as a whole. In the present study a macrolide resistant *Streptococcus pneumoniae* strain was detected from blood culture in four patients in the βM group, but all these strains were betalactam-susceptible.

The IDSA/ATS concordant antibiotic policy in our unit is also in accordance with other Finnish ICUs, where the β-lactam-respiratory-quinolone combination

is the most commonly used combination in SCAP patients. A query on the choice of the first-line antimicrobial therapy in SCAP was sent by e-mail to all Finnish mixed-medical adult ICUs or high-dependency units (n=29) in January 2014. Twenty units (69%) responded to the query as follows: the first-line antibiotic choice was moxiflocacin plus cefuroxime (n=8), levofloxacin plus cefuroxime (n=7), moxiflocacin plus ceftriaxone (n=3) and ceftriaxone plus roxithromycin (n=1) and plain amoxicillin (n=1).

The timing of antimicrobial treatment has been shown to be crucial in severe infections, being an independent risk factor for mortality (Houck *et al.* 2004, Houck *et al.* 2005, Kumar *et al.* 2006). In our study the exact timing of the initiation of antibiotic treatment was not available in all cases. However, in the present series all patients received the combination therapy within 24 hours of hospitalization and the first antibiotic dosage was given between six to eight hours after hospital admission, in accordance with earlier investigations.

6.5 Long-term outcome (IV)

Previous literature comparing the different ICU-treated pneumonia types (SCAP, HAP and VAP) is sparse. Our results suggested that hospital mortality was not dependent on the type of ICU pneumonia. However, among hospital survivors, SCAP patients had a better one-year outcome than the HAP and VAP patients. In all pneumonia categories, mortality was highest during the first 60 days after hospital admission. This was especially true for SCAP patients, but all deaths in the VAP group also occurred during the first 90 days, while the survival rate in the HAP group decreased during the whole follow-up period. The patients' underlying diseases might be a more important prognostic factor in HAP than in SCAP or VAP. Similar comparisons of long-term mortalities are lacking concerning HAP and VAP patients.

Previous studies have mainly concentrated on CAP patients and similarly reported higher mortality rates during the first three months after hospital discharge (Murugan *et al.* 2010). In a large US register study a decreased 90-day survival was reported among SCAP patients (Angus *et al.* 2002). A Canadian study with ICU-treated SCAP patients confirms the findings of the present investigation (Sligl *et al.* 2011). They reported 30-day and 1-year mortality rates of 11% and 27%, respectively, compared to 25% and 37% in the present study. Our patients were more severely ill based on the APACHE II score as the criterion of severity of disease (Sligl *et al.* 2011). A Dutch study investigating the long-

term mortality of up to three years in different types of ICU-discharged patients also showed that the highest risk of death after hospital discharge was within the first three months. It was observed both in unadjusted and adjusted models that the 1-year mortality risk among subgroups with SCAP, acute kidney injury and cancer, was significantly higher than in the general ICU population (Brinkman *et al.* 2013).

We did not study the factors affecting long-term outcomes. Earlier studies focusing on pneumonia patients and the general ICU population have shown that age, co-morbidities, peak number of organ dysfunctions, high APACHE II score and new malignancy are the main determinants of long-term survival (Williams *et al.* 2008, Sligl *et al.* 2011, Brinkman *et al.* 2013a, Brinkman *et al.* 2013b, Restrepo *et al.* 2013). The present study emphasizes that further studies are needed to better understand the long-term outcome and the factors affecting the outcome among different types of pneumonia patients treated in the ICU.

7 Clinical implications and future perspectives

The optimal level of care is a crucial factor to determine SCAP outcomes. Many studies have shown delayed ICU transfer to increase mortality in SCAP. While septic shock and development of organ failure are important factors defining outcomes, the inflammatory pathway and the immunological differences between patients have been studied insufficiently, and further investigations are needed. It has been shown that on admission IL-6 concentrations were higher in those who subsequently developed severe sepsis compared to those who did not (Kellum *et al.* 2007). It is important to develope further prognostication markers for severe pneumonia; this will help to identify patients who might benefit from early supportive measures, monitoring or adjuvant therapies. One interesting and intensively studied prognostic marker at the moment is the soluble urokinase-type plasminogen activator receptor (suPAR) (Mölkänen *et al.* 2011, Donatello *et al.* 2012, Jalkanen *et al.* 2013). Flow cytometric expression of leukocytes' surface antigens might also be a useful prognostic marker in septic patients (Venet *et al.* 2011, Jämsä *et al.* 2011). Further prospective studies are also needed for the evaluation of chest CT in the treatment of SCAP patients.

The etiology of SCAP has not been completely defined. The proportion and importance of viruses needs further evaluation, also in terms of optimizing the treatment. On the other hand, the incidence of viral infections among SCAP patients was notable in the current study, which raises questions about viral transmission and infection control in the ICU, as has been highlighted in other studies (Sandrock *et al.* 2008). The guidelines of the US Centers for Disease Control and Prevention recommend prompt viral diagnosis and the use of isolation practices during periods of increased prevalence of symptoms of viral respiratory illness (Tablan *et al.* 2004). Larger studies are needed to demonstrate the prognostic value of possible transmission of respiratory viral infections in the critical care environment. This should be taken into account when planning new ICUs with single rooms (Levin *et al.* 2011).

Combination antimicrobial therapy has shown to be beneficial in decreasing mortality in SCAP patients, especially those with septic shock, but the optimal combination is still an open question. The anti-inflammatory action of macrolides in the treatment of SCAP is well documented, and the results of observational and retrospective studies favor macrolide use in SCAP (Siddiqui 2004). The present study could not demonstrate any superiority of the β-lactam-macrolide combination. It is important to remember that respiratory quinolones have similar

anti-inflammatory properties and coverage of atypical pathogens as have been thought to explain the favorable results of macrolides. Thus far there is a lack of prospective studies comparing antibiotic combinations with quinolone and macrolide. Larger prospective multicenter studies are urgently needed to find optimal antibiotic therapies.

In the present series, hospital mortality was two to three times higher compared to ICU mortality. Our findings strongly emphasize the critical evaluation of SCAP patients' treatment processes and the need to develop further strategies to lower mortality after critical illness, especially on the wards. In our unit, we have been able to reduce the mortality gap between ICU and the ward by setting up a step down-unit and a medical outreach team. These measures may have been reflected in the lower hospital mortality rates during the prospective study period during 2008–2012. Other factors influencing the outcomes might have been the multidisciplinary ICU team and the active rehabilitation practice in our ICU targeting the restoration of muscle strength and respiratory muscle and lung function, which are essential for convalescence from critical illness (Calvo-Ayala *et al.* 2013).

The present study is one of the few published studies showing that ICU-treated pneumonia patients also have considerable long-term mortality at least up to one year. There is also some evidence that SCAP impairs survival for an even longer time interval. Cardiac complications and prolonged inflammatory response, as well as comorbidities at hospital admission are suggested as factors affecting long-term outcomes (Waterer *et al.* 2011, Brinkmann *et al.* 2013b). The quality of life after SCAP and factors influencing the long-term survival are not sufficiently understood and are crucial to investigate. The results will help to organize adequate follow-up and rehabilitation after hospital discharge for patients at risk. One way to improve the patients' follow-up are the ICU follow-up clinics, which were first set up in the early 1990s and have been in practise in our hospital since 2004.

8 Conclusions

Based on this study, the following conclusions can be made:

1. Chest CT yielded new imaging findings for more than half of our SCAP patients and led to procedures or treatment changes in nearly half of the SCAP patients during their first 48 hours of ICU stay. In addition, the severity of the oxygenation disorder and the extent of lung involvement in the early chest CT, but not in the plain chest radiograph, showed good correlation.
2. Viral etiology is common in SCAP. Viral findings were demonstrated in nearly half of the SCAP patients. The frequency of viral detection depends on the availability of PCR techniques and lower respiratory specimens. Clinical characteristics and outcome were similar between patients with pure bacterial infections and bacterial-viral infections.
3. The mortality rate of SCAP patients was not shown to be better whether they had been treated with a βQ or a βM combination. Neither was any difference observed between the two antibiotic combinations among bacteremic patients and patients in septic shock.
4. In the ICU-treated SCAP, HAP and VAP patients the type of pneumonia did not have a significant association with hospital mortality. However, among the hospital survivors, the patients with SCAP had a better long-term outcome than the HAP and VAP patients.

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Appendices

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Table 18. Pneumonia Severity Index (PSI) score.

Age	(1 point/year, -10 if female)
Nursing home resident	10 points
Neoplastic disease	30 points
Liver disease	20 points
Congestive heart failure	10 points
Cerebrovascular disease	10 points
Renal disease	10 points
Altered mental status	20 points
Respiratory rate > 30/min	20 points
Systolic blood pressure <90 mmHg	20 points
Temperature <35 or ≥40°C	15 points
Pulse ≥125/min	10 points
Arterial pH <7.35	30 points
Urea ≥11 mmol/L (≥30mg/dL)	20 points
Sodium <130 mmol/L	20 points
Glucose ≥14 mmol/L (≥250 mg/dL)	10 points
Hematocrit <30%	10 points
PaO_2 <60 mmHg or SaO2 <90%	10 points
Pleural effusion	10 points

(Fine *et al.* 1997)

Table 19. Confusion-urea- respiratory rate- blood pressure- age ≥ 65 (CURB-65) score.

Confusion	1 point
Urea >7 mmol/ L	1 point
Respiratory rate ≥30 breaths / minute	1 point
Systolic blood pressure <90 mmHg or diastolic blood pressure ≤60 mmHg	1 point
Age ≥65 years	1 point

(Lim *et al.* 2003)

Table 20. Systolic blood pressure Multilobar lung involvement Albumin Respiratory rate Tachycardia Confusion Oxygenation pH (SMART-COP) score.

Abbreviation	Variable			Points
S	Systolic blood pressure <90 mmHg			2
M	Multilobar chest x-ray involvement			1
A	Albumin <3.5 g/dL			1
R	Respiratory rate (RR)- age adjusted cut-offs			1
	Age	≤50 years	≥50 years	
	RR	≥25 breaths per minute	≥30 breaths per minute	
T	Tachycardia ≥125 beats per minute			1
C	Confusion (new onset)			1
O	Oxygen low-age-adjusted cut-offs			2
	Age	≤50 years	≥50 years	
	PaO_2	<70 mmHg (9 kPa)	<60 mmHg (8 kPa)	
	SaO_2	≤93%	≤90%	
	PaO_2/FiO_2	<333 mmHg (44 kPa)	<250 mmHg (33 kPa)	
P	Arterial pH <7.35			2

0–2 points low risk, 3–4 points moderate risk, 5–6 points high risk, ≥ 7 points very high risk needing intensive respiratory or vasopressor support

(Charles *et al.* 2008)

Table 21. SCAP-score.

Variables	Points	Criteria
pH <7.30	13	Major
Systolic pressure <90 mmHg	11	Major
Respiratory rate <30 breaths/minute	9	Minor
Blood urea nitrogen >30mg/dL (>11 mmol/L)	5	Minor
Altered mental status	5	Minor
PaO_2/FiO_2 <250 mmHg (33 kPa)	6	Minor
Age ≥80 years	5	Minor
Multilobar/bilateral X-ray	5	Minor

(Epaña *et al.* 2006)

Table 22. Predisposition-Insult-Response-Organ dysfunction (PIRO) score.

Score	Variables	Point
Predisposition	Comorbidities (COPD or immunocompromise)	1
	Age >70 years	1
Insult	Bacteremia	1
	Multilobar opacities in chest radiograph	1
Response	Shock	1
	Severe hypoxemia	1
Organ dysfunction	Acute kidney injury	1
	Adult respiratory distress syndrome	1
Score range		0–8

(Rello *et al.* 2009)

Table 23. Acute Physiology and Chronic Health Evaluation (APACHE II) score.

Physiological variables	Temperature	Arterial pH
	Mean arterial pressure	Serum sodium
	Heart rate	Serum potassium
	Respiratory rate	Serum creatinine
	Glasgow Coma Scale	Haematocrit
	Oxygenation	White blood cell count
Age		
Chronic points (p):	Cardiovascular	Liver
Nonoperative/emergency postoperative:	Respiratory	Immunocompromised
5p	Renal	
Elective postoperative: 2p		

Worst values of 12 physiological variables during the first 24 hours following ICU admission along with evaluation of patient's chronic health and admission diagnosis. The score can vary from 0 to 71 points. (Knaus *et al.* 1985)

Table 24. Sequential Organ Failure Assessment (SOFA) Score.

Score	0	1	2	3	4
Respiratory (PaO_2/FiO_2 kPa)	>53.3	≤53.3	≤40.0	≤26.7 and MV	≤13.3 and MV
CNS (GCS)	15	13–14	10–12	6–9	<6
CVS (drug doses µg/kg/min)	MAP ≥70 mmHg	MAP <70 mmHg	Dop ≤5 (Dobutamine any dose)	Dop >5 or E ≤0.1 or NE ≤0.1	Dop >15 or E >0.1 or NE >0.1
Liver (Bil, µmol/L)	<20	20–32	33–101	102–204	>204
Coagulation (Plat, $x10^9$/L)	> 150	≤150	≤100	≤50	≤20
Renal (Crea, µmol/L)	<110	110–170	171–299	300–440 or urine output < 500mL/day	>440 or urine output <200mL/day

MV, mechanical ventilation, CNS, central nervous system, GCS, Glasgow Coma Scale, CVS, circulation vasopressor support, MAP, mean arterial pressure, Dop, dopamine, E, epinephrine, NE, norepinephrine, Bil, bilirubin, Plat, platelet count, Crea, creatinine

(Vincent *et al.* 1996)

Original publications

I Karhu J, Ala-Kokko TI, Ahvenjärvi L, Rauvala E, Ohtonen P & Syrjälä H (2014) Early Chest CT scan compared to plain chest x-ray in acute severe community-acquired pneumonia. Manuscript.

II Karhu J, Ala-Kokko TI, Vuorinen T Ohtonen P & Syrjälä H (2014) Lower respiratory tract virus findings in mechanically ventilated patients with severe community-acquired pneumonia. Clin Infect Dis 59(1): 62–70.

III Karhu J, Ala-Kokko TI, Ohtonen P & Syrjälä H (2013) Severe community-acquired pneumonia treated with β-lactam-respiratory-quinolone vs. β-lactam-macrolide combination. Acta Anaesthesiol Scand 57(5): 587–593.

IV Karhu J, Ala-Kokko TI, Ylipalosaari P, Ohtonen P, Laurila JJ & Syrjälä H (2011) Hospital and long-term outcomes of ICU-treated severe community-acquired, hospital-acquired and ventilator-associated pneumonia patients. Acta Anaesthesiol Scand 55(10): 1254–1260.

Original publications are not included in the electronic version of the dissertation.

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