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HOSPITAL-ACQUIRED PNEUMONIA IN INTENSIVE CARE PATIENTS

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Nothing great was ever achieved without enthusiasm
Ralph Waldo Emerson
ABSTRACT

The present thesis describes the incidence and risk factors for pneumonia and especially ventilator-associated pneumonia (VAP) among Intensive Care Unit (ICU) patients. Bacteria in samples from the lower respiratory tract of patients receiving mechanical ventilation are reported, including the duration of treatment prior to the first occurrence of different pathogens. The frequency of VAP using Swedish criteria (Swedish Intensive Registry, SIR) was compared with the VAP rate measured with international criteria (US Centre for Disease Control, CDC).

Data were extracted from a local infection surveillance database (paper I-IV) and a trauma registry (paper II). In Paper I the incidence and risk factors for pneumonia and associated death over a two-year period was studied in 221 patients on mechanical ventilation. In paper II pre-hospital and hospital parameters associated with pneumonia within 10 days of ICU admission were evaluated in 322 ICU-treated trauma patients. Paper III focus on 443 bacterial isolates from the lower respiratory tract of 346 mechanically ventilated ICU patients. The occurrence of different pathogens was correlated with duration of hospital stay and time on mechanical ventilation at the time of sampling. In paper IV patients with (n=112) and without (n=224) a new lung infiltrate after ≥48 hours of mechanical ventilation were studied to evaluate the proportion of patients meeting different criteria used to define VAP according to CDC and SIR, respectively. Paper I shows that 15% of patients developed VAP, corresponding to a rate of 29 VAP/1000 ventilator days. Risk factors were aspiration, recent surgery and trauma. The 28-day mortality in patients with VAP was 33% as compared to 16% in those without ICU-acquired pneumonia. In Paper II risk factors for pneumonia were intubation at the site of injury, shock, an initial Glasgow Coma Scale (GCS) of ≤8, major surgery within 24 h of admission to hospital, massive transfusion of blood and ISS > 24. Enterobacteriaca and Staphylococcus aureus were the most common pathogens. Paper III shows that duration of hospital care and mechanical ventilation prior to sampling was ≤2 days for Streptococcus pneumoniae, beta-streptococci and Haemophilus influenzae. With the exception of Stenotrophomonas maltophilia and Pseudomonas aeruginosa, the median duration of time on mechanical ventilation was short and similar for most bacteria. In samples taken on the first day of mechanical ventilation, the rate of pathogens expected to be resistant to ceftoxime was 23%. In Paper IV the SIR and CDC criteria for VAP was met in 84% and 93%, respectively, in 112 situations with a new infiltrate when applying a ± 48 hours time frame for the other criteria in relation to the occurrence of the lung infiltrate.

It is concluded that VAP is a common complication in the ICU, especially among trauma patients. The most important risk factor for VAP in a general ICU patient is aspiration and for a trauma patient an initial GCS of <8. Staphylococcus aureus and Enterobacteriaca are the most common bacteria in samples from the lower respiratory tract in both general ICU patients and in a trauma population. Occurrence of pathogens resistant to common antibiotics increases with the duration of hospital care and mechanical ventilation. The diagnosis of VAP should rely on presence of lung infiltrate and microbiological samples from the lower respiratory tract; clinical criteria add little value.
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<td>BAL</td>
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<td>Community acquired pneumonia</td>
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<td>CDC</td>
<td>Centre for Disease Control and Prevention</td>
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<td>CIVA</td>
<td>Central Intensive Care Unit</td>
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<td>ECDC</td>
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<td>ESBL</td>
<td>Extended-spectrum β-lactamase</td>
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<td>HAI</td>
<td>Healthcare-associated infections</td>
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<td>HAP</td>
<td>Hospital acquired pneumonia</td>
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<td>HELICS</td>
<td>Hospital in Europe Link for Control through Surveillance</td>
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<td>Kiss</td>
<td>Krankenhaus-Infections-Surveillance-System</td>
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<td>Intensive care unit</td>
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<td>Injury Severity Score</td>
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<td>Interquartile range</td>
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<td>MRB</td>
<td>Multiresistant bacteria</td>
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<td>MRSA</td>
<td>Methicillin-resistant Staphylococcus aureus</td>
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<td>NAP</td>
<td>Non-ventilator-associated pneumonia</td>
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<td>NNIS</td>
<td>National Nosocomial Infection Survey</td>
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<td>PNU1</td>
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<td>PSB</td>
<td>Protected brush specimen</td>
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<td>SIR</td>
<td>Swedish Intensive Care Registry</td>
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<td>Quantitative endotracheal aspiration</td>
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<td>VRE</td>
<td>Vancomycin-resistant Enterococcus</td>
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<td>WBS</td>
<td>White blood cells</td>
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1 INTRODUCTION

1.1 HEALTHCARE-ASSOCIATED INFECTIONS

According to the Swedish health authorities, healthcare-associated infections (HAI) are defined as infections that affect patients following hospitalization or treatment on an outpatient basis, regardless of whether the microorganisms causing the infection originate from the patient or is transmitted to the patient during the process of care (107). HAI is therefore considered as an infection that arises as a consequence of the patient being subject to healthcare.

1.1.1 Healthcare-associated infections in general

HAI’s are often associated with the devices used in medical procedures, such as catheters or endotracheal tubes. HAI include central line-associated bloodstream infections, catheter-associated urinary tract infections and ventilator-associated pneumonia (VAP). HAI may also occur as surgical site infections. Depending on continent, hospital and type of medical ward, both the rate and etiology of HAI varies (32, 99, 122). For example, in the EPIC II study (122) the rate of infections caused by *Acinetobacter* differed greatly between different regions, ranging from 3.7% in North America to 19.2% in Asia. The European Centre for Disease Prevention and Control (ECDC) recently conducted a prevalence study including 19.888 hospitalized patients in 23 European countries. On the single day of the study, 7.1% patients had at least one HAI, ranging from 0.2% in psychiatric patients to 28.1% in intensive care patients (127). The reported prevalence was 5.8% of the patients in primary hospitals, 6.3% in secondary hospitals, 7.4% in tertiary hospitals and 7.8% of patients treated in more specialized hospitals (127). This probably reflects the increased severity of the more severely ill patients being treated in specialized hospitals. High age, malnutrition, underlying disease, immunosuppressant therapy and antibiotic treatment that disrupt the normal bacterial flora affects the patients defense against infection and therefore makes the patient more susceptible for HAI (2, 32, 90, 102). HAI is an important aspect of patient safety. Besides the increased costs and hospital length of stay, HAI contributes significantly to patients discomfort, morbidity and mortality (53, 127).

1.1.2 Healthcare-associated infections in the ICU patient

Patients treated in the intensive care unit (ICU) are to a large extent more prone to develop HAI since they are more critically ill and often subject to invasive procedures. One of the most common reasons for patient admittance to the ICU is the need for ventilatory support. This can be provided either by non-invasive and invasive mechanical ventilation. Invasive mechanical ventilation means that an endotracheal tube or cannula is inserted in the natural airway to ensure airway
patency and to enable positive pressure ventilation. This maneuver increases the risk of microorganisms entering the lower respiratory tract resulting in ventilator-associated pneumonia (VAP). The term VAP solely refers to pneumonia in patients receiving invasive mechanical ventilation, (hereafter just mechanical ventilation).

VAP is therefore defined as hospital-acquired pneumonia (HAP) in patients treated with mechanical ventilation for at least 48 hours (Figure 1) (71). Patients presenting with pneumonia at hospital admission or within the first 48 hours of hospital care are defined as community acquired pneumonia (CAP) (29). One of the reasons why this distinction is important is that CAP and HAP to a large extent is cause by different pathogens. The 48 hour period is intended to exclude patients with a community-acquired infection that was in fact incubating at the start of hospital care (3).

**Figure 1.** Diagnosing pneumonia depending on duration of prior hospital and ICU care. Pneumonia presenting within the first 48 h from hospital admission is defined as CAP. Pneumonia occurring after ≥48 h of Hospital care is defined as HAP. For non-intubated patients treated in the ICU ≥48 h pneumonia is a form of HAP and for patients intubated ≥48 h VAP. VAP is formally a subgroup of HAP.

### 1.2 Multiresistant Bacteria

Antibiotic resistance has emerged as one of the greatest global health challenges in the 21st century (14). It is a form of drug resistance where bacteria are able to survive exposure to one or more antibiotics. Resistance may be due to a number of different mechanisms and provide resistant bacteria with a survival advantage which enable them to proliferate and spread in the presence of antibiotics (74, 127). The more a particular antibiotic is used, the more quickly bacteria resistant to that antibiotic will be selected and increase in numbers (112).
Methicillin-resistant *Staphylococcus aureus* (MRSA) was first identified in the United Kingdom in 1961, only two years after the introduction of methicillin (6). In the United States and some European countries, including the United Kingdom, MRSA rates are actually falling but many Asian countries still have increasing rates (81, 109). Vancomycin has been used since the 1950s, but the emergence of resistance in *Enterococcus species* was not reported until 1986, in the United Kingdom and France (18). Over the next decade, vancomycin-resistant *Enterococcus* (VRE) spread throughout Europe and North America but during the last decade the incidence of VRE infections has remained unchanged or even declined (18).

The third generation cephalosporins were introduced in the early 1980s, Gram-negative bacteria resistant producing extended-spectrum β-lactamases (ESBL) was reported already 1985 (66). In tropical regions nosocomial *Acinetobacter baumannii* infections are more frequent than in Europe and the United States (38).

The Scandinavian countries have in general fewer problems with drug-resistant bacteria than most other countries. In Sweden MRSA was the first MRB to be reported in year 2000 and the number of reported cases has increased each year (Figure 2). The incidence of VRE was low in the beginning of the 21st century but during 2008 there was an increase in number of VRE cases reported due to a number of health-care related outbreaks. Lately ESBL has become the most common multiresistant bacteria (MRB) (110). During 2012, the first 23 cases of ESBLcarba were reported in Sweden, this is a form av ESBL that makes the bacteria resistant to an even larger group of antibiotics. One of the major reasons why HAI is so important is that they contribute to the extensive use of broad-spectrum antibiotics, which leads to development of MRB.

![Figure 2. MRB in Sweden reported as reported by Smittskyddsinstitutet (SMI).](image)

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Earlier, the pharmaceutical industry made new antibiotics available, which could replace increasingly ineffective ones. Now a day, drug development pipeline for new antibiotics has been drying out (14, 108). We face an immediate risk of entering a post-antibiotic era which threatens many of the advances made by modern medicine. Coping with HAI in the future will therefore be a tough challenge, particularly in the ICU since outbreaks of infections caused by MRB are not uncommon in this setting (127).

1.3 VENTILATOR-ASSOCIATED PNEUMONIA

Pneumonia is the most important HAI within intensive care. VAP is the most common HAI in ICU-patients and will therefore be the main focus of this thesis.

1.3.1 Definition and diagnosis of VAP

The criteria used to diagnose pneumonia vary and the diagnosis of VAP has been a subject of controversy for a long time (78). The main goals of diagnostic approaches in patients with suspected VAP are 1. to identify which patients have a pulmonary infection, 2. to ensure collection of appropriate cultures and 3. to promote the use of early and effective antibiotic therapy (3).

For those responsible for infection surveillance there is a different situation. When registering VAP frequency for infection surveillance and quality management reasons, it is important that the assessment is based on a definition that is objective and easy to apply. In this situation, there should be no room for subjective criteria (56). Although the interpretation whether a lung infiltrate is infectious or not can never be fully objective. Therefore cultures from lower respiratory tract are valuable diagnostic tools.

In a clinical situation it is important to decide whether antibiotic therapy should be initiated or if there is a need for a change therapy. In that situation a trend of elevated infectious biomarkers and worsening in the status of the patient might be more important than individual clinical findings and laboratory results. Decisions to start antibiotic treatment should also be based on consideration of alternative causes of all findings, including non-infectious causes of lung infiltrates. The clinical evaluation of an individual patient is therefore complex, subjective and not easily captured in a definition or algorithm. It is also important to understand that, regardless of whether a patient is evaluated clinically or using an infection surveillance definition, the result is merely an estimation of the probability that the patient suffer from VAP.

For the clinician there are two strategies when diagnosing VAP, a clinical strategy and a bacteriologic strategy (3). The most common criteria used is the National Nosocomial Infection Survey (NNIS), which are clinically oriented (88).

1.3.1.1 Clinical strategy

The clinical approach involves using clinical data to define the presence of pneumonia and then to initiate empiric therapy in a timely fashion, based on therapy guidelines, modified by local microbiologic data. This strategy is not very specific because many patients with clinical findings of VAP may have noninfectious
etiologies for their findings of a new lung infiltrate in combination with fever, purulent sputum and leukocytosis (17). The difficulty with this strategy is that some patients will be treated with antibiotics when they are not needed alternatively be treated with antibiotics with an unnecessary broad-spectrum. There may also be other causes for the patient to have infiltrates in combination with clinical criteria that allows other infections to remain undiagnosed (3, 87). In an ICU patient, it can be difficult to determine whether fever is due to VAP since 50% of patients not diagnosed with VAP have an elevated body temperature for other reasons (19, 70, 75, 89). Commonly used infection biomarkers i.e. elevated C-reactive protein (CRP) and white blood cells (WBC) counts are frequently present in critically ill patients (56). Therefore clinical criteria for the diagnosis of VAP have limited diagnostic accuracy (35). The clinical strategy emphasizes prompt empiric therapy for all patients suspected of having VAP. The driving force behind this strategy is the consistent findings that delay in the initiation of appropriate antibiotic therapy for patient with VAP is associated with increased mortality.

1.3.1.2 Bacteriologic strategy

The bacteriologic approach is based on, often invasive, quantitative samples of lower-airway secretions. This can be performed by bronchoscope protected brush (PSB), bronchoalveolar lavage (BAL) or quantitative endotracheal aspirate (QEA) (118). The benefit of this, provided that the sample obtained is positive, is that the initially empiric treatment can change to a later directed antibiotic therapy. Antibiotic therapy that is selected on the basis of quantitative culture results is more likely to be adequate than empiric treatment (3, 17, 82, 87). The advantage of that is also to avoid excessive antibiotic use since the antibiotic therapy becomes targeted. Unfortunately, quantitative cultures also have limitations. The bronchoscopist can miss the area of active infection (17, 87). Cultures may be false negative or below the diagnostic threshold, in patients receiving antibiotics therapy at the time of sampling (73). The American Thoracic Society and the European guidelines recommend that QEA should be obtained whenever possible before antibacterial therapy is started, but studies have shown that the specificity of QEA is poor compared to BAL, resulting in an over diagnosis rate of 30 to 40% (3, 52, 55, 82, 115, 125). According to The American Thoracic Society a reliable tracheal aspirate with Gram stain can be used to direct initial empiric therapy. On the other hand, a negative tracheal aspirate in patients without a recent change in antibiotics has a strong negative predictive value for VAP (3, 33, 37, 40).

1.3.2 Pathogenesis of VAP

VAP may develop when a potentially pathogenic microorganism enters the lower respiratory tract in a patient receiving mechanical ventilation. The intubation procedure in itself might cause bacteria to enter the lungs but there are several other manners in which potentially pathogenic microorganisms gain access to the lower respiratory tract (2, 29, 102). Colonization of the lungs occurs endogenously or exogenously. Endogenous colonization of the lower respiratory tract often derives from bacteria carried by the patient in the oropharyngeal cavity or gastrointestinal
tract. In this case, the microbiological flora differs between normal subjects and patients with underlying illness or prior antibiotic therapy, which might result in overgrowth with microorganisms with a greater potential to cause infection (28, 90, 102, 103). The most common endogenous way for bacteria to colonize the lower respiratory tract of a patient is microaspiration (53, 61, 128). This is often a result of aspiration of bacteria containing secretions from the oropharynx (23, 28, 101, 128). In addition, the endotracheal tube may cause accumulation of potentially contaminated secretions above the cuff, i.e., in the subglottic space (2, 11, 29, 118). In situations when care-givers manipulate the endotracheal tube or the cuff is insufficiently inflated, contaminated subglottic secretions might leak past the cuff, resulting in pathogenic bacteria reaching the lower respiratory tract. The endotracheal tube also represents an ideal surface for the formation of bacterial biofilm, which can be easily dislodged by suction catheter use, leading to inoculation of the lower respiratory tract (29, 84, 102). Exogenous colonization involves microorganisms colonizing patients either through direct or indirect contact transmission (28, 40). Direct contact transmission takes place when physical contact without intermediates occurs between the source of microorganism, an infected patient or contaminated healthcare workers, and the susceptible individual (28, 90, 102). Indirect contact transmission involves contamination of the health care surroundings from which the microorganism is transmitted to the patient (Figure 3). This is done with contaminated hands, clothes or objects (equipment, bedside tables, doorknobs, etc.) (28, 102).

Figure 3. Exogenous routes of colonization/infection in mechanically ventilated patient.
1.3.3 Epidemiology

To consider the diagnosis of VAP, patients must have been treated with mechanical ventilation for more than 48 hours (2, 16, 27, 71). The incidence of VAP might be reported as the proportion of patients developing VAP among the total population at risk. More commonly the incidence is quantified as the number of VAP for a number of days of mechanical ventilation (e.g. VAP/1000) which is sometimes referred to as the density rate. Depending on what criteria are used to define VAP, the incidence has been reported to occur between 0-21 VAP per 1000 ventilator days (63, 85, 98, 106, 124). Time of onset is an important epidemiological variable and therefore VAP usually classifies as early-onset or late-onset VAP (2, 3, 29). Early-onset VAP is defined as occurring within the first 4 days of mechanical ventilation and late-onset VAP after more than 4 days (2, 50, 60, 117). It is however important to realize that patients hospitalized for more than four days prior to intubation might already be colonized by pathogens typically associated with late-onset VAP (115). Awareness of the potential microbial cause of VAP and confirmation of the specific etiology in an individual patient is essential to guide optimal antibiotic therapy (90).

The risk of developing VAP at a certain day of mechanical ventilation varies during the course of ventilator treatment. The risk is estimated to be approximately 3% per day during the first week of mechanical ventilation, 2% per day in the second week, and thereafter 1% per day (26, 43, 60). Several studies have demonstrated that patients with VAP require a longer period of mechanical ventilation than patients without VAP. When averaged across several studies, patients with VAP received mechanical ventilation for 14-22 days compared to 5-10 days for patients without VAP (21, 62, 96). Moreover, ICU stay and hospital stay was 12-20 and 26-33 days longer respectively for patients with VAP (21, 51, 62, 96, 122).

1.3.4 Etiology

The microbiological etiology of VAP is influenced by various factors, including the duration of mechanical ventilation, lengths of ICU and hospital stays prior to the development of VAP, presence of co-morbidities and prior use of antibiotics (16, 60, 90, 116, 123). It may also vary between different hospitals, type of ICU and patient population (16, 32, 90, 115, 123). In addition, the local infection pattern can change over time. Earlier hospital care may also affect the patient's general condition so that susceptibility to infections increases. Underlying diseases may predispose patients to infection with specific organisms (90). The incidence of infections caused by multiresistant pathogens is closely linked to local factors and varies widely from one institution to another (16).

Different pathogens cause early and late-onset VAP. Early-onset VAP tend to be caused by microorganisms that also cause community-acquired infections, such as methicillin-sensitive *Staphylococcus aureus*, *Streptococcus pneumoniae* and *Haemophilus influenzae*. In contrast, late-onset VAP is more likely to be caused by less antibiotic sensitive bacteria, including MRSA, *Pseudomonas aeruginosa* and *Acinetobacter baumannii* (3, 10, 16, 60, 63, 90, 114, 119, 122). Overall, the most
common microorganisms in early and late-onset VAP are Gram-negative enteric bacilli, Staphylococcus aureus and Pseudomonas aeruginosa (13, 16, 39, 42, 54, 61, 71, 90, 97, 117, 123).

Different pathogens has also been found depending on whether the patients were on prior antibiotic treatment when diagnosing VAP and whether they were treated with narrow spectrum antibiotics or broad spectrum antibiotics (1). Patients with prior use of broad-spectrum antibiotic and patients hospitalized within the previous 90 days are at greater risk for colonization and infection with MRB pathogens (3). According to several studies, earlier or ongoing antibiotic treatment is a stronger risk factor for Pseudomonas aeruginosa than prior duration of the ventilator support (50, 94). The situation is more favorable in Scandinavia with fewer MRB and lower frequency of infections caused by both Acinetobacter baumannii and Pseudomonas species (1, 20, 45, 46, 49, 86).

1.3.5 Risk factors and preventive measures

Multiple risk factors have been identified for the development of VAP, e.g. high age, unconsciousness, head injury or trauma. Many risk factors are thus not amenable to modification. Since mechanical ventilation is a prerequisite for the development of VAP, it should be avoided when possible (2, 9, 102). Intubation in itself is a risk since bacteria from the oral cavity might be transferred into the lower respiratory tract. For the same reason, reintubation should preferably be avoided (12, 23).

There are, however, also risk factors that should be kept in mind in order to prevent VAP. Orotracheal intubation is preferred over nasotracheal intubation to prevent nosocomial sinusitis and to reduce the risk of VAP (9, 23). Increased duration of intubation is also a risk factor for VAP, the incidence of VAP could therefore be decreased by efforts to minimize the duration of mechanical ventilation, e.g. so called daily wake-up calls (2, 23).

It is of great importance that manipulation of the ventilator circuits is done carefully (102). Contaminated condensate accumulates in ventilator circuits and should be carefully emptied to prevent it from entering the endotracheal tube and reach the lower respiratory tract. Suction of subglottic secretion that accumulates above the cuff should be done regularly to prevent leakage around the endotracheal tube cuff (95). The endotracheal tube cuff pressure should be maintained at a level greater than 20 cm H₂O to prevent leakage of subglottic secretion (95). Transporting patients between units, hospitals and to different clinical examinations within the hospital often results in patient lying in a flat supine position which increases the risk of leakage of subglottic secretion above the endotracheal tube cuff. Supine position is in itself a risk factor for aspiration, especially when receiving enteral feeding. Patients should therefore be kept in the semirecumbent position (30–45°) (2, 9). Enteral feeding in combination with decreased intestinal motility could be a risk factor if it leads to gastric overdistension but is preferred to reduce the risk of villous atrophy of the intestinal mucosa that may increase the risk of bacterial translocation (83).
1.3.6 Economic consequences of VAP

Studies have shown that in comparison with matched controls, patients with VAP have a longer stay in the ICU of 4.3-15 days (21, 48). For an individual patient VAP means a prolonged period of mechanical ventilation, often requiring sedation, additional tests and procedures such as chest x-ray (CXR)/computed tomography (CT) and arterial blood gas samples (21, 62).

There are wide variations in the estimates of the economic burden of VAP, one reason might be differences in study methodology (79). The increase in cost in a patient with VAP compared to a patient without VAP has been estimated to be in the order of $40,000-60,000 (21, 62, 124). These estimates include the total increase in hospital care attributed to VAP.

During a quality improvement project 2005, we calculated the extra healthcare cost related to a patient developing VAP in our clinical context. Assuming that in average VAP causes the need for an additional six days of mechanical ventilation this cost was estimated at 250,000 SEK. In conclusion, VAP is associated with a substantial economic burden.

1.3.7 Outcome

Whether VAP is associated with an increased risk of death has been the subject of many studies. The crude mortality rate in patients with VAP has been reported to be as high as 46% (51). However, many of these critically ill patients die of their underlying disease rather than from VAP (16, 50, 51, 67, 104, 113). Comorbidities, like presence of chronic obstructive pulmonary disease, compromised immune system, chronic heart failure, chronic hepatopathy, or chronic renal failure, have been reported to increase the mortality among patients with VAP (104, 113). Studies have also shown that greater morbidity due to the acute disease, e.g. presence of acute respiratory failure, shock and sepsis, on admission is associated with higher mortality (68, 104, 111). Taken together, these studies show that, in average, patients with VAP are more ill than patients without VAP and this is one important reason for the high mortality associated with VAP. Several studies have suggested that the prognosis for patients with VAP is better for trauma patients, than medical and surgical patients (24, 27, 47, 69, 76, 104).

Increased mortality has also been associated with delayed or absent adequate antibiotic treatment (59, 72, 104, 113).

Mortality among VAP patients also varies with microbiological etiology. In comparison with VAP caused by other pathogens, non-fermenting Gram-negative bacteria have been associated with worse clinical outcome (16, 60, 104). In contrast, Kollef et al. found that Staphylococcus aureus was the only pathogen associated with significantly increased mortality despite only a minority of the cases was caused by MRSA (61).

Late-onset VAP have been reported to be associated with higher mortality rates than early-onset VAP (3, 16, 64, 80, 119). A likely explanation is the greater prominence of multi-resistant microorganisms among late-onset cases (3, 119). However, increased mortality may be due to either the underlying disease or VAP and in these cases it is difficult to know which factor contributes the most.
1.4 INFECTION SURVEILLANCE IN THE ICU

1.4.1 Infection surveillance history

The modern history of infection surveillance begins in the US in the 1960’s. Centers for Disease Control and Prevention (CDC) recommended surveillance of HAI rates to obtain evidence for control measures. During the 1970’s, CDC training courses for infection control personnel stressed conducting surveillance of infections, writing and applying policies for preventive patient-care practices. The National Nosocomial Infections Surveillance System (NNIS) was established in 1970 when selected hospitals in the United States routinely began reporting their nosocomial infection surveillance data for aggregation into a national database. NNIS purpose was to describe the epidemiology of nosocomial infections in U.S. hospitals, to promote epidemiologically surveillance methodology and to establish comparative rates that can be used for local quality improvement efforts. The methods used were standard definitions of infections and standard protocols for data collection. By 1975 more than half of U.S. hospitals had infection control programs. The SENIC study that CDC performed showed that over a 5-year period HAI rates decreased on an average by 32% (44). Four key elements for successful prevention were: presence of an epidemiologist, specialized trained nurse, and existence of a planned surveillance system and restitution of HAI rates (44).

New improvement strategies were introduced between 2002 and 2004 where teams of clinicians from 61 health care organizations participated. The campaign was called “100,000 lives campaign” and the aim was to use a “bundle” of ventilator care processes (peptic ulcer disease prophylaxis, deep vein thrombosis prophylaxis, elevation of the head of the bed, and a sedation vacation) to reduce VAP rates. ICU team members posted data monthly on a Web-based extranet and submitted narrative descriptions describing the changes tested and the strategies implemented (98). Today CDC use The National Healthcare Safety Network, which is a secure, internet-based surveillance system that integrates all surveillance systems previously managed separately in the Division of Healthcare Quality Promotion at CDC. Hospitals reported data electronically to CDC monthly using CDC-provided software, National Surveillance System for Healthcare Workers and CDC published reports of aggregated data.

In Germany, HAI have been recorded since 1997 by an increasing number of ICU’s through voluntary participation in Krankenhaus-Infections-Surveillance-System (KISS), a hospital infection surveillance system run by the National Reference Center for the Surveillance of Nosocomial Infections. HAIs are mainly registered by infection control practitioners but also by intensive care specialists, surgeons and other medical personnel. Data from all ICUs are summarized and made available as reference data for comparison. Gastmeier et al. report a 29% reduction in the number of VAP, a 20% reduction in central line-associated bloodstream infections and a 28% reduction in surgery site infections when comparing the third year of surveillance among ICUs participating in KISS with the first year (41).
There is also an international network aiming at the collection, analysis and dissemination of valid data on the risks of HAIs in European hospitals called Hospital in Europé Link for Control through Surveillance (HELICS). The HELICS Database Management System software enables input, analysis and export of the HELICS data set in hospitals, processes the HELICS data set at the European/national/regional level and allows the transmission of data to the HELICS Coordination Centre. The Swedish Intensive Care registry (SIR) is a national quality registry committed to support the improvement of care in Swedish ICU’s, e.g. through VAP surveillance. An important task for SIR has been to provide a definition of VAP that is now used by all units in our country. The registry enables Swedish ICU to follow their VAP rates over time and to compare these results with those from other units.

1.4.2 Infection surveillance at CIVA

According to the Swedish Social Board's regulations (SOSFS 2005:12), all health care units should have a system that ensures the quality of care. This means that HAI’s are among the adverse patient events that always should be monitored. The purposes of the infection surveillance database at our ICU, CIVA, are 1. to keep track of VAP incidence, 2. to obtain aggregated data on the microbiologic cause of HAI in our unit, 3. to detect infection spreads, 4. to relate the incidence of VAP and other forms of HAI to preventive measures and 5. to provide the staff with feedback in this regard. The development of the infection surveillance program at the Central Intensive Care Unit (CIVA) started in the mid 1990’s. The persons involved were the head over the department, the infection consultant and staff from the infection control department. The program was in full operation in January 2002. In the beginning the database was managed manually using paper and pen. Since then, the introduction of a Patient Data Management System in our unit (2007) has simplified this work substantially.

1.4.3 Infection surveillance and quality improvements

Results of recent quality improvement initiatives suggest that many cases of VAP may be prevented by carefully paying attention to the process of care. After implementation of 14 evidence-based recommendations for VAP prevention Sinuff et al. report a decline in VAP rate from 14% to 9% (105). Resar et al. report results from the “100.000 lives campaign”, among 21 units with >95% compliance to VAP “bundles”, VAP rates decreased from 6.6 to 2.7/1000 ventilator days, a 59% reduction (98). In total the study included 35 units, in average the VAP rate decreased by 44%. Cocanour et al. have described similar results but an important conclusion was that implementation of a ventilator ”bundle” alone did not result in a decreased VAP rate. The rate of VAP decreased only when compliance with the “bundle” was audited and feedback given to the staff on both a daily and weekly basis (22). Murray and Goodyear-Bruch reported a prevention program that resulted in a rate of VAP zero (!) (85). Klompas has described that VAP rates of zero appear to attest more to the growing divide between surveillance and clinical VAP rates than to the feasibility of
eliminating VAP (57). The increasing mismatch between surveillance rates and clinical diagnoses limits the utility of official VAP rates to estimate disease burden and guide quality improvement. Klompas advocates the measurement of objective parameters such as average duration of mechanical ventilation, length of stay, mortality, and antibiotic prescribing as alternatives to measurement of VAP rates (57).
2 AIMS OF THE THESIS

2.1 GENERAL AIMS

The overall aim was to use a local infection surveillance database to gain further knowledge and understanding about pneumonia in patients treated in the ICU.

2.2 SPECIFIC AIMS

- To identify risk factors and to determine the incidence and prognosis of HAP (Paper I).

- To report the overall incidence of pneumonia in ICU-treated trauma patients and to identify potential risk factors for development post-injury pneumonia following severe trauma. In addition, we report pathogens identified in patients that developed pneumonia (Paper II).

- To find out the range of pathogens causing lower respiratory tract infection in mechanically ventilated patients and to analyze whether the first occurrence of specific pathogens varied with prior duration of mechanical ventilation, ICU care and hospital care (Paper III).

- To evaluate the use of CRP, WBC, fever and clinical signs of infection in VAP definitions used for infection surveillance and to compare VAP frequency using the Swedish Intensive Register (SIR) and US Centre for Disease Control (CDC) VAP definitions (Paper IV).
3 MATERIAL AND METHODS

3.1 INFECTION SURVEILLANCE DATABASE

The local ethic committee for research approved study II, III and IV. The first Study I was performed as an examination task within a Master program, ethical approval was not required and the local ethic committee for research has confirmed that.

Since 2002, all patients treated ≥24 hours in the ICU have been registered in an infection surveillance database. Entered data include (Acute Physiology and Chronic Health Evaluation II) APACHE II score, which is used for grading the severity of illness at ICU admission, admission diagnosis, for each day highest and lowest body temperatures, CRP, WBC, results from CXR and CT of the chest, the total duration of mechanical ventilation and ICU care, any episode of aspiration of stomach content, results from blood cultures and quantitative cultures from PSB and/or BAL obtained via bronchoscope and/or QEA. Patients with new or progressive infiltrate on CXR or CT have been analyzed using the SIR definition of pneumonia for diagnosing VAP. In this thesis the same criteria have also been used to define CAP, HAP, non-ventilator-associated pneumonia (NAP). Data is collected until ICU discharge or death. All papers are based on information from this database.

3.2 DEFINITION OF PNEUMONIA

3.2.1 SIR definition

In accordance with the SIR definition, VAP is defined as a new or progressive lung infiltrate on either plain CXR or CT, together with either:

1) body temperature of ≥38.5 and C-reactive protein ≥100 mg/L
   (clinical VAP, C-VAP)

or

2) significant growth of a potential airway pathogen from PSB ≥10^5 cfu/mL, BAL ≥10^4 cfu/mL or QEA ≥ 10^5 cfu/mL
   (verified VAP, V-VAP) (Figure 4).

Importantly, only findings obtained after ≥48 hours of mechanical ventilation can be used to diagnose VAP. Positive cultures from PSB/BAL with *Candida species*, *Enterococcus species*, *Neisseria species* or *coagulase-negative staphylococci*, were excluded since these microorganisms are not considered to cause lower respiratory tract infections. In the following, the term criteria refers to a specific parameter and threshold, e.g. CRP ≥ 100 mg/L while the term definition is used when referring to combinations of several criteria. CAP, HAP and NAP are diagnosed using the same clinical and laboratory criteria as VAP.
<table>
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<th>-48 h</th>
<th>-24 h</th>
<th>New or progressive infiltrate</th>
<th>+24 h</th>
<th>+48 h</th>
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<td>C-VAP</td>
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<td></td>
<td>Body temperature ≥ 38.5°C and CRP ≥ 100 mg/L</td>
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<tr>
<td>V-VAP</td>
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<td>Significant growth from BAL, PSB or QEA (≥ 10⁷, ≥ 10⁶ and ≥10⁵ CFU/ml respectively)</td>
<td></td>
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**Figure 4. Criteria for diagnosing VAP according to SIR.**

Both the C-VAP and V-VAP definitions require a CXR or CT showing a new or progressive lung infiltrate after more than 48 h of mechanical ventilation within a ± 48 h timeframe centered at the time of the CXR/CT showing a new or progressive infiltrate.

### 3.2.2 CDC definition

In Paper IV the SIR definitions described above was compared with definitions used by CDC, see below.

**Radiology signs**

Two or more serial chest radiographs with at least 1 of the following:*  
- New or progressive and persistent infiltrate  
- Consolidation  
- Cavitation

**Clinical signs (PNU1 and PNU2)**

At least 1 of the following:  
- Fever (temperature >38°C [100.4°F] with no other recognized cause)  
- Leukopenia (<4000 white blood cells/µL) or leukocytosis (>12 000 white blood cells/µL)  
- For adults 70 years or older, altered mental status with no other recognized cause

Plus at least 2 of the following:  
- New onset of purulent sputum, or change in character of sputum, or increased respiratory secretions, or increased suctioning requirements  
- New-onset or worsening cough, or dyspnea, or tachypnea  
- Rales or bronchial breath sounds  
- Worsening gas exchange (e.g., O2 desaturations [e.g., PaO2/FiO2 240], increased oxygen requirements, or increased ventilation demand)

**Microbiological criteria (PNU2)**

- At least 1 of the following:  
  - Positive growth in blood culture not related to another source of infection  
  - Positive growth in culture of pleural fluid Positive quantitative culture from BAL (10⁴ cfu/mL) or PSB (10⁵ cfu/mL)  
  - Five percent or more of cells with intracellular bacteria on direct microscopic examination of Gram-stained bronchoalveolar lavage fluid  
  - Histopathological evidence of pneumonia

*In patients without underlying pulmonary or cardiac disease (e.g., respiratory distress syndrome, bronchopulmonary dysplasia, pulmonary edema, or chronic obstructive pulmonary disease), one definitive chest radiograph is acceptable.
3.3 TRAUMA REGISTRY

The Karolinska University Hospital, Solna is the only referral centre for severe trauma cases for the entire county of Stockholm. All trauma patients, ≥15 years, admitted to the unit following initial resuscitation and interventional surgery when indicated, are prospectively registered in the Karolinska Trauma Registry. Pre-hospital and baseline patient data are collected from patient records. During the ICU stay all relevant data needed to assess patients in different scoring systems were entered once daily into a database by a research nurse. Data is collected until ICU discharge or death. Trauma severity is assessed using the Injury Severity Score (ISS), an anatomical description of injury designed to quantify the total load of injury across body regions and probability of survival (5). ISS data is obtained from the Trauma Registry, which uses the Abbreviated Injury Scale (AIS) version 2005. Shock is defined as an admission systolic blood pressure < 90 mmHg. Admission Glasgow Coma Scale (GCS) is assessed on admission to the trauma unit. For patients sedated and intubated in the field the GCS assessed prior to this procedure was used. More than 10 units of blood during the first 24 hours after injury are regarded as massive transfusion. Rescue time is defined as the time from alert to arrival at the trauma unit. Major surgery is defined as surgical procedures involving laparotomy or thoracotomy.

3.4 PAPER I

Data for patients staying more than 48 hours in the ICU from January 2002 to December 2003 were used for this study. The patients were categorized as trauma patients, surgical patients or medical patients. Patients with evidence of pneumonia on admission to the ICU were not included in the study.

In this study two exceptions were made from the above described SIR VAP definitions: we used different criteria for maximal body temperature, ≥39°C and VAP could be diagnosed up to 48 hours after extubation. The reason for using a different definition in this study was that the study was started before SIR had published a definition for VAP.

Twenty-eight and six-month mortality after discharge from the ICU was assessed by controlling the death register on all patients treated in the ICU ≥48 hours. Cultures from PSB and BAL were performed as clinically indicated. QEA were not done at the time. When the same bacteria were isolated in multiple samples from the same patient only the first isolate was included in the analysis. One sample could include more than one pathogen.

3.5 PAPER II

The study cohort consisted of trauma patients admitted to the ICU between February 2007 and July 2011 with an ICU stay of more than 24 hours. Patients admitted from other units than the Karolinska trauma unit were excluded. No other exclusion criteria were applied.

Pre-hospital and baseline patient data were retrieved from the Trauma Registry and patient records. Data necessary to identify pneumonia cases were retrieved from the
infection surveillance database. Data were collected until ICU discharge or death. Mortality for patients discharged alive was assessed at 30 days post injury. Pneumonia was defined in accordance with criteria used by SIR. The primary outcome of the present study was development of pneumonia within the first 10 days after trauma.

3.6 PAPER III

This study focuses on a collection of bacterial isolates obtained from patients included in the infection surveillance database during the years 2002-2010. The collection includes all samples of significant bacterial growth obtained with either PSB or BAL during mechanical ventilation. Besides the pathogens excluded in the VAP definition we also excluded *Alfa haemolytic and milleri group Streptococci* and *Micrococcus*. Further exclusion criteria were isolates obtained without the use of a flexible bronchoscope and isolates obtained from patients that received hospital care outside Sweden before admission to the ICU. When the same bacteria were isolated in multiple samples from the same patient only the first isolate was included in the analysis. For each isolate, the study database included the duration of hospital care, ICU care and mechanical ventilation at the time when the sample was obtained. In addition, for each isolate the study database also included the patient’s admission diagnosis as surgical, medical or trauma, APACHE II, gender and age. Antibiotic treatment on-going at ICU admission was registered in all patients except one.

In all, the positive cultures included 19 different pathogens. To enable the statistical analysis we reduced this number. Pathogens isolated only a few times were grouped together as either *Miscellaneous Enterobacteriaceae* (*Citrobacter* species, *Morganella morganii*, *Pantoea agglomerans*, *Serratia marcescens*, *Proteus mirabilis*, *Enterobacter specis*, *Hafnia alvei*) or other Gram-positive or Gram-negative bacteria (*Moraxella catarrhalis*, *Lactobacillus species* and *Aeromonas species*). The former group was included in the statistical analysis while the heterogeneous group of other Gram-positive or Gram-negative bacteria was excluded. In addition, all pathogens were classified as being susceptible or not to cefotaxime. This classification was not the result of testing of individual isolates but dependent on whether the local susceptibility exceeds 90% of the isolates or not. Thus, *beta-streptococci*, *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Haemophilus influenzae*, *Klebsiella species*, *Citrobacter*, *Escherichia coli*, *Hafnia alvei*, *Moraxella catarrhalis*, *Proteus mirabilis*, *Serratia marcescens*, *Morganella morganii* and *Pantoea agglomerans* were all considered as cefotaxime susceptible.

3.7 PAPER IV

In this study we retrospectively extracted two cohorts of patients from the infection surveillance database. The first cohort consists of patients with at least one CXR or CT demonstrating a new or progressive lung infiltrate after ≥48 hours of mechanical ventilation. We restricted our analysis to infiltrates during the first 7 days at risk of VAP, i.e. day 3-9 with mechanical ventilation. This cohort corresponds to patients that would be evaluated for the presence of VAP for both clinical and infection surveillance reasons. Both SIR and CDC definition (see page above) of VAP were applied to each
situation with a new or progressive infiltrate. Complementary data on airway secretions, respiratory symptoms and findings and gas exchange were obtained from the patient records.

The second cohort consists of patients that were treated with mechanical ventilation for ≥48 hours and were examined by CXR at least once but without any demonstration of a lung infiltrate. This cohort was used to obtain the rate of patients meeting the fever, WBC and CRP VAP criteria without having VAP. The analysis was restricted to the first 7 days at risk of VAP corresponding to day 3-9 of mechanical ventilation.

Lung infiltrates that the radiologist clearly stated was due to pulmonary congestion was disregarded. VAP was defined in parallel according to the CDC and the SIR criteria’s (SIR, CDC). For both V-VAP and C-VAP the additional findings are required to be present within ±48 hours from the CXR or CT showing a new or progressive infiltrate. To allow comparison with the SIR definitions we applied the same time frame to the CDC definitions.

For patients with lung infiltrate, each CXR or CT with a new or progressing lung infiltrate was viewed as a separate situation for evaluation of the presence of VAP. For each situation we identified whether the patients fulfilled the different VAP definitions and also the separate criteria included in each definition. To evaluate the influence of different time frames we applied a time window of either ±48 hours or ±24 hours.

The cohort of patients without lung infiltrate suggesting pneumonia was used to evaluate to what extent patients who are at risk of VAP, i.e. treated with mechanical ventilation for more than 48 hours, but without CXR findings suggesting pneumonia, fulfill the biomarker and fever criteria used to define clinical VAP (PNU1 and C-VAP). We also combined the different findings and the two time frames to evaluate whether the clinical VAP definitions would have been fulfilled if a lung infiltrate had been demonstrated that day.
4 STATISTICS

4.1 PAPER I

All patient data were entered in the StatView software, and further analyses were performed in Stata (version 8). The Kruskal-Wallis test was used to assess whether NAP or VAP affected the length of ICU stay. A Cox regression model was used to assess associations between potential risk factors and outcome, a multivariate logistic regression model was used to assess mortality risk factors. Hazard rate is defined as the probability per time unit that the cases that enter the respective time interval at risk to develop VAP (in this case intubated without VAP) to develop VAP in that time interval.

4.2 PAPER II

Differences between groups for categorical variables were evaluated with the Pearson Chi-square test. Data are presented as medians with interquartile ranges (IQR). Risk factors for pneumonia were evaluated using univariate and multivariable logistic regression models. Multivariable logistic regression included a priori selected variables age and gender, together with variables that were significant at p < .05 in the univariate model. Results are presented as odds ratio together with 95% confidence intervals. The statistical analyses were performed using SPSS 20 (SPSS Statistics IBM, Armonk, New York). Significance was defined as p < 0.05.

4.3 PAPER III

In order to obtain a graphical overview of the data we constructed Kaplan-Meier curves describing the percentage of isolates found after certain duration of treatment for each pathogen. All curves were compared pair-wise using the Mantel-Haenszel test in order to test whether the sampling behavior over time differed significantly between two pathogens. Bonferroni corrections were used to correct for multiple comparisons.

4.4 PAPER IV

This study only includes descriptive results reported as median and interquartile range.
5 SUMMARY OF RESULTS

5.1 PAPER I

5.1.1 Study population

Of altogether 1,964 patients cared for at the ICU during the 2-year study period, 329 patients (17%) fulfilled inclusion criteria. Of the 329 study patients who fulfilled the inclusion criteria, 221 (67%) were at some time on mechanical ventilation (median duration 118 hours; range 48–903 hours) (Figure 5). Thirty-three patients (15% of mechanically ventilated patients) were subsequently diagnosed with VAP corresponding to 29 VAP/1,000 ventilator days. In addition, 8 patients developed pneumonia in the ICU not associated with mechanical ventilation (NAP) during the observation period.

![Figure 5](image.png)

**Figure 5.** Among 221 patients treated with mechanical ventilation, the figure depict the accumulated number of patients with or without an episode of ventilator-associated pneumonia (VAP) in relation to number of days receiving mechanical ventilation.
5.1.2 ICU-acquired pneumonia

Five of the 8 patients with NAP had previously been mechanically ventilated, but >48 hours had passed after the extubation before pneumonia was diagnosed, and another 2 patients required mechanical ventilation after the NAP diagnosis. The patients who did not develop pneumonia had a significantly shorter duration of stay at the ICU (median 3 days; range 2–27 days) than patients with NAP (median 10 days; range 7–35 days) and VAP (median 12 days; range 2–38 days) (p<0.001). The median time from intubation to VAP diagnosis was 4 (range 3–12) days.

5.1.3 Risk factors

No single risk factor was significantly associated with NAP. Significant risk factors for VAP in the Cox regression model were aspiration before or during the time on ventilator, recent surgery and trauma. In patients with no aspiration, the accumulated risk for VAP increased for each day on mechanical ventilation with a relatively constant hazard rate over time. No patient was on mechanical ventilation for more than 10 days without developing VAP.

5.1.4 Mortality

Death within 28 days from admission to the ICU occurred in 59 (18%) patients. Fifty of these patients had been on mechanical ventilation during the time at the ICU. In a logistic regression model (including age, sex, type of patient, APACHE II score, type of pneumonia, and days on ventilator) 28-day mortality increased with age. APACHE II score ≥ 20 on admission was also strong predictor for death within 4 weeks. Eleven VAP patients (33%) died within 28 days, with an Odds Ratio of 1.07 for each day of mechanical ventilation. With regard to late mortality (between 29 days to 6 months after admission) APACHE II ≥ 20 was the only significant risk factor.

5.1.5 Microbiology

Of the 33 patients diagnosed with VAP, 23 patients (70%) were investigated with PSB and/or BAL. In 11 of these patients, a positive culture result was defining the diagnosis. Of the 8 patients diagnosed with NAP, 5 patients (62%) were investigated with PSB and/or BAL, defining the diagnosis in 3 patients. Only one of the VAP patients had growth of the same bacteria in blood and PSB. Three of four patients diagnosed with Stenotrophomonas maltophilia died, as did both patients diagnosed with Staphylococcus aureus. Among the 33 VAP patients, blood cultures were drawn from 29 and were positive in 9 patients (17 positive of 139 cultures).
5.2 PAPER II

5.2.1 Study population

During the study period 322 patients admitted to the ICU were included in the study. A majority of the patients were male (78%) and the median age was 41 years. The median rescue time was 46 minutes and 20% of the patients were intubated in the field. On admission to the trauma unit 52 (16%) patients were in shock with a systolic blood pressure < 90 mmHg. The median GCS was 14. The overall degree of injury was high with a median ISS of 24, and more than half of the patients presented with major chest trauma (AIS ≥ 3). Median ICU and hospital length of stay were three and 16 days respectively, whereas 30-day post injury mortality was 9%.

5.2.2 ICU-acquired pneumonia

Eighty-five (26%) patients developed pneumonia in the ICU within 10 days of injury (Figure 6). VAP occurred in 45 (14%) of the patients. In comparison with the non-pneumonia group, patients with pneumonia were more frequently intubated in the field, more severely injured, had a lower admission GCS and more often in shock on admission. Pneumonia patients also received more blood transfusions and underwent major surgery to a larger extent. In contrast, no differences were noted for age, comorbidity, gender, presence of pulmonary contusion, penetrating injury or chest trauma.

The clinical course was markedly different between patients with and without pneumonia. For patients with pneumonia, ICU and hospital length of stay were nearly four and two times longer, respectively. Pneumonia was typically diagnosed on day 4 after admission (median time to diagnosis 81 hours).
5.2.3 Risk factors

Univariate logistic regression revealed that intubation in the field, shock, GCS 3-8, major surgery within 24 hour after admission, massive transfusion and ISS >24 were all risk factors for subsequent development of pneumonia during ICU treatment. In the multivariable model, only GCS 3-8 was identified as an independent risk factor.

5.2.4 Microbiological findings

In 42 of the 85 cases of pneumonia the diagnosis was defined by significant growth of at least one pathogen in a sample from the lower respiratory tract. Enterobacteriaceae and Staphylococcus aureus were the most common pathogens for both early and late pneumonia. In contrast, three out of four isolates of Streptococcus pneumoniae were obtained within the first 48 hours after admission, whereas all isolates of Pseudomonas species and Acinetobacter species were obtained >48 hours after of admission.
5.3 PAPER III

5.3.1 Study population

443 (35%) isolates from 346 patients fulfilled the study inclusion criteria. All samples were obtained within 70 days after intubation. The most common gram-positive bacteria were *Staphylococcus aureus*, (n=95) and *Streptococcus pneumoniae* (n=41). Among Gram-negatives, most isolates belonged to the *Enterobacteriaceae* family (58 *Escherichia coli*, 49 *Klebsiella* species and 67 other *Enterobacteriaceae*). Of all isolates, 140 were obtained within the first 48 hours of hospital care and 223 within the first 48 hours after intubation. For 329 of the 443 isolates (74%) sampling coincided with a diagnosis of pneumonia, 117 community acquired, 99 hospital acquired pneumonia not VAP and 113 VAP.

5.3.2 Duration of treatment prior to sampling

Duration of hospital care and mechanical ventilation were all short and similar for patients infected with *Streptococcus pneumoniae*, *beta-streptococci* and *Haemophilus influenzae*, causes of CAP. With the exception of *Stenotrophomonas maltophilia* and *Pseudomonas aeruginosa*, the median duration of mechanical ventilation was short and similar for most bacteria. Although only 9 isolates, it is somewhat surprising that the duration of hospital care at the time of sampling was not longer for *Acinetobacter species* than for E. coli. Moreover, 15 of 30 isolates of *Pseudomonas aeruginosa*, 6 of 9 isolates of *Acinetobacter species* and 4 of 15 isolates of *Stenotrophomonas maltophilia* were obtained during the first 4 days of mechanical ventilation.

5.3.3 Prior antibiotic treatment

Of isolates (n= 218) obtained during the first 48 hours in the ICU, 44% came from patients with antibiotic treatment at admission. The median duration of hospital stay at sampling was 3 days for patients with and 2 days for patients without antibiotic treatment. Bacteria associated with CAP dominated among isolates (67%) from patients not treated with antibiotic while Gram-negatives other than *Haemophilus influenza* dominated isolates (59%) from patients with antibiotics.

5.3.4 Duration of treatment and cefotaxime sensitivity

The percentage of isolates presumed to be sensitive to cefotaxime decreased with increased duration of hospital care or mechanical ventilation (Figure 7). However, even for samples obtained the first day of hospital care, 14% of the isolates were pathogens not sensitive to cefotaxime. For the first day of mechanical ventilation the percentage was even higher, 23%. Similarly, among isolates obtained during the first 48 hours of ICU care, isolates from patients with antibiotics at admission were less often susceptible to cefotaxime, 90% than isolates from patients not treated with antibiotics, 95%.
Figure 7. The diagrams demonstrate the percentage of isolates sensitive to cefotaxime as a function of the duration of mechanical ventilation (upper panel) or hospital care (lower panel) at the time of sampling.

5.4 PAPER IV

5.4.1 Patients with lung infiltrate

In 107 patients we identified 112 situations with a new or progressive infiltrate after ≥48 hours of mechanical ventilation. Excluding the first 48 hours, a total of 521 CXR were performed in the same patients during the period of mechanical ventilation. The median duration of mechanical ventilation at the time of the infiltrate was 4.7 days (interquartile range 3.2-8.2 days).

5.4.2 Patients with lung infiltrate, CDS v.s. SIR criteria

When applying the time frame of ±48 hours on the CDC definition, 84% of the situations were consistent with a diagnosis of VAP. For the SIR definitions the corresponding percentage was 93%. For the ±48 hour time frame, 81% of the patients were diagnosed with VAP using both the CDC and SIR criteria, meanwhile 4% fulfilled neither of the definitions, i.e. there was an agreement between the definitions in 85% of the patients. Most of the discrepancy consisted of 12% of the patients meeting the criteria for SIR C-VAP but not the CDC PNU1 criteria. Using the ±48 hour time frame, patients 44% and 41% fulfilled the criteria for microbiologically confirmed VAP with a total agreement between the CDC PNU2 and SIR V-VAP definitions. When applying the criteria for VAP without a positive culture to these patients, 70% and 88% fulfilled the PNU1 and C-VAP criteria respectively. This difference suggests a better sensitivity for the C-VAP than the PNU1 definition.
5.4.3 Patient without lung infiltrate

We identified 224 patients that were treated with mechanical ventilation ≥48 hours and without a lung infiltrate. The median duration of mechanical ventilation was 4.8 days. When averaged across the seven days, each day at risk of VAP 39% of the patients had a WBC <4.0 or ≥12.0 \times 10^9/L, 62% a CRP ≥100 mg/L and 68% and 50% fever of >38.0°C and ≥38.5°C respectively. These percentages were considerably higher when applying the time frames including more than a single day. When averaged across the days at risk of VAP, 95% of the patients fulfilled the CDC temperature and WBC criteria meanwhile 58% fulfilled the SIR temperature and CRP criteria within a timeframe of ±48 hours.
6 DISCUSSION

6.1 INFECTION SURVEILLANCE

Hospital acquired infections are adverse patients events affecting approximately 2 million people each year (15). It has been shown that establishment of rigorous infection surveillance and control programs are strongly associated with a decrease in the incidence of HAI (44). Infection control not only provides information about the frequency of HAI but also knowledge of local resistance patterns. Such knowledge facilitates empirical antibiotic therapy.

Based on this information it is possible to design and implement local preventive strategies to reduce HAI’s. Another important aspect is that the ICU staff gets feedback of infection surveillance results. As mentioned previously, the overall monitoring and meticulous collection of clinical and microbiological data for each patient is time-consuming and not always feasible on a practical basis. A Swedish study from 2004 shows that only approximately 33% of the ICU’s in Sweden had a functioning infection surveillance program in place (45). In recent years, the proportion has increased since it is now mandatory to maintain an infection surveillance system. VAP rate was in 2011 reported by 70% of Swedish ICU’s.

6.2 VENTILATOR-ASSOCIATED PNEUMONIA

HAI are common in the intensive care settings with VAP causing the greatest morbidity. VAP is associated with prolonged mechanical ventilation and ICU. VAP and other HAI also contributes significantly to patients discomfort and morbidity (53, 127). Incidences are highly influenced by the characteristics of the patient population studied and the criteria and techniques applied for diagnosis. Paper I report an rate of 29 cases of VAP per 1,000 ventilator-days which is a quite high incidence. This may be a reflection of the specific patient population treated in our ICU. Karolinska Solna is a level-one trauma centre and trauma patients seems to be more susceptible of getting VAP (16, 25). Paper I report trauma as one of the significant risk factor for VAP. Naturally, there is also an association between underlying diseases on the one hand and need for intensive care and risk for developing VAP on the other.

As in several other studies, our result in Paper I show a significantly longer ICU length of stay for patients developing VAP (9 days) compared to patients who did not develop pneumonia. (21, 62, 96, 122). Increased disease severity is associated with increased risk of VAP (51). Therefore age and severity of underlying diseases may confound the prolonged stay due to VAP. It is therefore difficult to estimate how the true effect of VAP on the duration ICU care due to VAP affect the disease process.
6.3 VAP DEFINITION

In Paper IV our results highlight the limited discriminative value of fever, WBC and CRP to identify infectious lung infiltrate among intensive care patients at risk of VAP. A new or progressive lung infiltrate is obligate for VAP definitions but there are other conditions showing similar results on CXR, atelectasis, pulmonary edema and adult respiratory distress syndrome (126). An infiltrate should therefore raise a suspicion that the patient has pneumonia but additional proofs of infection are needed to make the diagnosis. Knowing the low diagnostic specificity of lung infiltrate for VAP (126), our results suggest that an infiltrate, even when combined with fever, WBC and increased CRP should not be interpreted as definite pneumonia. Rather this situation should lead to microbiological sampling and consideration of empiric antibiotic treatment. Among ICU patients, up to 70% have been reported to have fever at least once and only 50% of these episodes are caused by an infection (65). In our study >95% of patients with a lung infiltrate had fever (>38.0°C) within 48 hours of the CXR. Similarly, for each day of mechanical ventilation, in average 90% of patients without lung infiltrate had a body temperature >38.0°C within a period of ±48 hour. Fever >38.0°C therefore seems to add little discriminative value to the VAP definitions. Fever, CRP and WBC are nonspecific markers of inflammation that can have either infectious or non-infectious causes. Our results suggest that, with 90% of the patients with a new lung infiltrate also having a CRP >100 mg/L, CRP has limited specificity when differentiating patients with VAP from those with other causes of lung infiltrates. Povoa et al. reported that WBC did not differ between patients without infection and patients with VAP. Despite several studies showing that CRP is better at discriminating between ICU patient with and without infection increased WBC is more often included in VAP definitions (91, 92, 93).

Conceptually, all criteria of each VAP definition should be present at the same time. In practice, a definition can be applied in an individual case either by application of a strict time frame or by using observations at other time points to make subjective inferences about the situation at the time of CXR. In the interest of obtaining objective measurements, a strict time frame is preferable in the context of infection surveillance. It is obvious that a wider time frame results in more positive cases but it is unclear what time frame results in the best balance between false positive and false negative cases.

6.4 RISK FACTORS FOR PNEUMONIA

Various risk factors have been reported as being associated with an increased risk of VAP. In Paper I we found that an observed episode of aspiration of stomach content was the strongest risk factor for VAP. As previously mentioned, Paper I report trauma patient to be at an increased risk of developing VAP, especially those in coma (4). Reduced consciousness with a GCS of 3-8 was also reported to be an independent risk factor for developing pneumonia within 10 days of trauma in Paper II. Low GCS has previously been shown to predispose to pneumonia (77). Aspiration, immobilization and atelectasis formation, rather than the decreased consciousness per se may contribute to the development of post-injury pneumonia. Early intubation would
theoretically protect against aspiration, but has also been suggested as a risk factor in
the literature. It is likely that intubation in the field reflects the state of the patient rather
than being a cause of subsequent pneumonia (31, 34, 77). To some extent this is
reflected in Paper II where GCS but not intubation in the field remained a risk factor
after adjustment in the multivariate regression model. The vulnerability of trauma
patients is reflected by the fact that despite being younger and suffering from less
comorbidity than other ICU-patients, they have an increased risk of pneumonia (24).
Age was not a risk factor for the development of VAP in our study, nor in many other
studies (111, 120).

6.5 QUANTITATIVE SAMPLES FROM LOWER RESPIRATORY TRACT

An attempt to establish a microbiological diagnosis is desirable in every patient with
suspicition of VAP, but in many cases such attempts proves unsuccessful. Quantitative
cultures of PSB and BAL have a relatively high sensitivity and specificity even thought
they are not 100% reliable (7, 96). The standard diagnostic threshold might be
inappropriately high if antibiotic therapy has been started or changed shortly before
microbiological sampling. In this situation, quantitative growth below the diagnostic
threshold can still be consistent with infection. In 70% of the 33 VAP patients in paper
I, bronchoscope sampling was obtained but only 42% were positive. In Paper III, we
included all isolates with significant growth in samples obtained using PSB and BAL.
Although some isolates were obtained without a diagnosis of pneumonia, this growth is
considered to be associated with a high likelihood of infection (52).

6.6 BACTERIAL GROWTH IN LOWER RESPIRATORY TRACT

Knowledge of the pathogen causing VAP is important for the selection of optimal
antibiotic therapy and to detect nosocomial spread of problem. Since the range of
pathogens causing VAP varies between different countries and units, it is important to
acquire knowledge about the local situation in a certain unit or hospital but also on a
regional or national level. Different factors, e.g. prior antibiotic treatment (32, 52)
 affect the occurrence of specific pathogens. In Paper III we demonstrated that
pathogens resistant to cefotaxime were more commonly isolated from patients treated
with antibiotics at ICU admission. However, these patients also had a longer hospital
stay prior to sampling.

In Paper I only 19 isolates are reported. Still, no patients with pneumonia were
diagnosed with *Pseudomonas aeruginosa*, and other bacteria likely to be multi-
resistant such as *Acinetobacter species* and *Serratia species* were found only in a few
cultures.

In Paper II, studying only trauma patients, the most common pathogens were
*Staphylococcus aureus* and *Enterobacteriaceae*. Similarly, *Staphylococcus aureus*
and Enterobacteriaceae were the most frequently found pathogens in Paper III which
agrees with previous studies finding that these are the most common causes of VAP
The absence of pneumonia caused by methicillin-resistant Staphylococcus aureus might be surprising to an international reader but this is an uncommon cause of pneumonia in Scandinavia (1, 20, 45).

In Paper III we explored the effect of duration of hospital care, ICU care and mechanical ventilation on the isolation of different pathogens. Staphylococcus aureus was the most common pathogen and were found at all stages and for all types of pneumonia. Similar results have been reported previously (54, 122). Streptococcus pneumoniae, beta-hemolytic streptococci and Haemophilus influenzae were mostly found early reflecting that these are pathogens causing CAP (30, 54, 60). The relatively small number of Stenotrophomonas maltophilia means that this pathogen fortunately is not a common cause of lower respiratory tract infections in our setting. Surprisingly, half (n=15) of all Pseudomonas aeruginosa were obtained within less than 4 days of mechanical ventilation and 9 within less than 4 days of hospital care.

6.7 MORTALITY AND VAP

Several studies have shown that VAP is associated with crude increased mortality but the question is how comorbidities and other factors the crude mortality (36, 50, 51, 67, 104, 113). There is still uncertainty as to how much VAP contributes to mortality. One problem is that the main risk factor for developing VAP, i.e. need for prolonged mechanical ventilation, varies with e.g. disease severity, underlying pulmonary disease and other comorbidities which are also major risk factors for poor outcome.

In Paper I, the 28-day mortality in patients with VAP was 33%, which is within the range usually reported in literature (8, 16, 48, 111). In patients without VAP, the mortality was about half of this but the two groups were not matched for severity of disease or comorbidities. A further confounder is that any delay in adequate antibiotic treatment might contribute to increased mortality among VAP patients (113). In contrast, good standard of care including liberal bronchoscope cultures and proper use of antibiotics might be associated with less effect of VAP on mortality (16, 58, 72, 100, 121).

In Paper II, restricted to trauma patients, we found no difference in 30 day mortality between patients with and without pneumonia. Trauma patient are usually previously healthy and the median age is generally lower than among other patient groups, e.g. in Paper I the median age was 43 and 60 years for trauma and non-trauma patients respectively. The lower age might thus contribute to a more favourable outcome for these patients. In general, mortality among patients that develop VAP varies with case-mix. Several studies have shown that VAP is associated with greater mortality among other patient groups than trauma patients. Similarly, medical patients with VAP have been reported to have greater risk to die than surgical patients with VAP (47, 48, 113).
6.8 CLINICAL IMPLICATIONS

The infection surveillance database has enabled us to monitor our VAP frequency and follow changes over time. These data has e.g. been used in several projects aiming at improved prevention of VAP and reduced VAP incidence. Although we have identified risk factors for pneumonia in trauma patients, they are related to the patient injuries and can therefore not be subject to interventions. The results in Paper III were somewhat surprising considering that they suggest that cefotaxim might be inadequate empiric therapy even for patients with pneumonia after a very short time in the ICU. These results highlight that also prior time in the hospital should be taken into account when choosing antibiotic therapy and that cultures should be obtained before start of therapy. Our results in Paper IV suggest that CPR, WBC and fever criteria have limited value when discriminating between patients with and without VAP. Although definitions including these criteria might still be needed for VAP surveillance these results also advocate the use of quantitative cultures from the lower respiratory to diagnose VAP. Our results also question the use of VAP rate as a measure of quality of care or at least the emphasis that has been put on this rate during recent years.

6.9 FUTURE PROSPECTIVES

We have shown that it is possible to create an infection surveillance database in an ICU by manually extracting data from patient records. It is a time-consuming method and therefore in the future it is preferable that data are generated automatically, although it must be realized that those responsible for the database must have a thorough knowledge within the field. One experience from the work with this thesis has been that new knowledge can be obtained from merging different local registers (Paper II). Increased local knowledge among researchers of each others work might thus reveal opportunities to new studies. A further area where many questions remain to be answered is the health economic consequences of HAI.
7 CONCLUSIONS

The major findings of this thesis are:

• In intubated ICU patient the most important risk factor for VAP was aspiration before or during ventilator treatment, recent surgery and trauma (Paper I).

• Pneumonia including VAP is a common complication among ICU treated trauma patients (Paper I and II).

• Reduced consciousness with GCS of 3-8 is an independent risk factor for development of pneumonia after severe injury (Paper II).

• In an ICU treated trauma population with pneumonia, the most common pathogens isolated in the lower respiratory tract were *Staphylococcus aureus* and *Enterobacteriaceae* (Paper II).

• Occurrence of antibiotic resistant pathogens in the lower respiratory tract increases with increased duration of hospital care and mechanical ventilation. Even after a very short duration of hospital care "difficult to treat" pathogens were more common than expected (Paper III).

• Fever and increased CRP, as used in the SIR and CDC VAP definitions of clinical VAP (C-VAP and PNU1 respectively), are very common among ICU patients. These results question the specificity of these definitions and the usefulness of VAP definitions not including microbiological findings (Paper IV).
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