Epidemiology of Nosocomial Pneumonia in Adults Hospitalized in Canadian Acute Care Facilities

by

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Abstract

Background: Nosocomial pneumonia (NP) is a significant cause of morbidity and mortality in hospitalized patients.

Objective: The objectives of this study were to describe the epidemiology of NP in adult patients hospitalized in Canadian acute care facilities and identify prognostic indicators for death.

Methods: A retrospective cohort study was conducted in 114 patients with NP admitted to hospitals that participated in a 2002 Canadian point prevalence survey.

Results: A high proportion of NP patients had a rapidly or ultimately fatal underlying illness. NP in non-intensive care unit (ICU) patients accounted for the larger proportion of these infections. There was no mortality difference between patients with and without ventilator-associated NP, or with and without ICU-acquired NP. Delayed initiation of appropriate antimicrobial therapy was associated with a poorer outcome.

Discussion: Strategies that result in the timely administration of appropriate antimicrobial therapy should be investigated in an effort to reduce NP-associated mortality.
Acknowledgments

I gratefully acknowledge the support and expertise of my Thesis Committee: Dr. Allison McGeer, Ms. Marianna Ofner-Agostini, Dr. Andrew Simor, and Dr. James Scott. This thesis took years to complete and Marianna (who started as my supervisor), Allison (who finished as my supervisor) and Andy remained encouraging and supportive throughout, making very constructive comments on the several drafts. I learned much from their astute observations on my study findings and interpretation. I would never have finished my thesis without their helpful nudges. James was kind enough to step in at the last minute as a replacement member of my Thesis Committee, without whom I would have been unable to defend my thesis. He too offered comments that strengthened this final report.

I am thankful to the many infection control practitioners who assisted in data collection and the hospital epidemiologists who provided me with the opportunity to include their hospitals in this study.

Finally, I am forever grateful to my family. My parents instilled in me a love of learning and my siblings, their spouses, and my nieces and nephews give me reason to enjoy every day.
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Chapter 1
Introduction

Developing a nosocomial (health care-acquired) infection (NI), one not present or incubating on admission, is a well-recognized adverse outcome of hospitalization. In 1996 the Centers for Disease Control and Prevention (CDC) estimated that more than 2.1 million NIs occur annually in the United States (US), of which more than one third is preventable. These estimates continue to be quoted as the likely incidence of NI in the US each year. A 1994-95 study from England found that 7.8% of inpatients developed at least one NI during hospitalization. Based on their results, the authors estimated that NIs cost the National Health System £930.62 (Can$1814.71) million/year. Adjusted for inflation, this would equal Can$2509.56 million in 2011 (http://www.bankofcanada.ca/en/rates/inflation_calc.html; accessed April 17, 2011). In a national prevalence survey conducted in Scotland over two years (2002 and 2003), 9.5% of patients in acute care hospitals developed a NI. A Canadian multicentre study conducted in February 2002 revealed that patients hospitalized in Canada are similarly affected, with 10.2% of patients developing a NI. A similar study conducted in 2009 in association with a nationwide surveillance program found that 12.3% of patients hospitalized in 49 Canadian hospitals had a NI (personal communication: Denise Gravel, Public Health Agency of Canada). While there is some understanding of the scale of morbidity and mortality related to NIs, a number of other factors are less well explored, such as the financial costs to the health care system, patient and family, and society in general. Thus, the impact of NIs may be even greater than appreciated and is an area where further research is both required and warranted.

There are several types of NIs and they vary in their associated morbidity and crude mortality. Of these, nosocomial pneumonias (NP) and bacteremias have the greatest impact on patient outcome. Given that NP occurs more frequently than bacteremia and is associated with a similarly high crude mortality, it accounts for the largest number of deaths related to NI-related deaths. Identifying effective preventive and management strategies for NP has the potential to significantly improve patient outcomes.

Numerous studies have demonstrated that mortality rates associated with severe NI such as pneumonia are high. It has been difficult to establish whether these infections represent
independent risk factors for death. If the evidence supports an independent association between NP and death, this would further support the need for additional research into preventive strategies. Additionally, it is not clear whether there are factors that, if modified, might reduce mortality rates due to NP. The overall purpose of this thesis is to describe the epidemiology of NP in adults hospitalized in Canadian acute care facilities.
Chapter 2
Objectives

The primary analysis objective of this thesis is:

- To describe the epidemiology of NP in adult patients hospitalized in Canadian acute care facilities; specifically the demographics, coexistent morbidities, selected characteristics of the hospital setting, pneumonia type and treatment factors, as well as patient outcomes.

The secondary analysis objective of this thesis is:

- To identify prognostic indicators for death in adults with NP in Canadian acute care facilities. Expected factors for consideration are age, underlying severity of illness, duration of hospitalization before onset of the NP, and adequacy of treatment for the NP.
Chapter 3
Literature Review

3.1 Nosocomial infection overview – frequency and mortality

Since the 1960s, NIs have been recognized as an important health problem associated with significant morbidity, mortality, and cost\(^5\)\(^-\)\(^8\). The Study of the Efficacy of Nosocomial Infection Control (SENIC) project estimated that there were 2.1 million NIs among 37.7 million hospitalized patients over a one-year period in 1975-76\(^7\), or 5.7 NIs/100 admissions and 7.18 NIs/1000 patient-days. A study of the rate and costs of NI in a general hospital in England between 1994 and 1995 found that 7.8% of patients developed one or more NIs\(^2\). In a national prevalence survey conducted in Scotland over two years (2002 and 2003), 9.5% of patients in acute care hospitals were found to develop a NI\(^3\). More recently, the first year of data regarding number of NIs in Pennsylvania hospitals, following introduction of legislation mandating reporting, reported 7.5 NIs per1000 admitted patients\(^9\). The first nationwide assessment of the impact of NI in Canada was conducted in February 2002. In this point prevalence survey involving 29 hospitals in 9 Canadian provinces, it was determined that 686 of 6745 patients (10.2%) had one or more NIs on the day of the survey\(^4\). A follow-up survey conducted in 2009 involving 49 hospitals in 9 Canadian provinces revealed an increase to 11.8% (personal communication: Denise Gravel, Public Health Agency of Canada).

Nosocomial infection rates are higher among critically ill patients than in the general patient population. A 1992 prevalence survey in intensive care units (ICUs) in 17 Western European countries found that 20.6% of patients developed an ICU-acquired infection\(^10\)\(^-\)\(^13\). A prospective, multicentre incidence survey in five university hospital ICUs in France over 3 months in 1994-95 found that 13.1% of patients had an ICU-acquired infection, reflecting a rate of 20.3 NIs per 1000 patient-days\(^11\). The occurrence of ICU-related infections does not appear to have changed substantially over the years despite improved knowledge about their etiology and the implementation of targeted preventive strategies\(^12\)\(^,\)\(^13\).

Nosocomial infections have been associated with excess hospital mortality. In a systematic review of 1000 postmortem reports of inpatient deaths, NI was found to be the direct cause of death in 7.4% of cases and a contributing factor in another 6.3%\(^14\). In another study, it was noted
that NIs were more common in patients who died during their hospitalization (33%) than in survivors (13%)\textsuperscript{15}. The European ICU prevalence study reported an overall NI-associated mortality rate of 16.8\%\textsuperscript{10}. In a study carried out ten years after the European ICU prevalence study, investigators in Finland found an 8.8\% ICU mortality and 31.3\% hospital mortality for patients with an ICU-acquired infection, which represented an independent risk for death (OR 2.7; 95\% CI: 1.34-5.40, \( p=0.005 \))\textsuperscript{12}. In a cohort study published in 2006, the odds of death in patients with a NI increased in the presence of ventilator-associated pneumonia (VAP) (\( p<0.0001 \))\textsuperscript{9}. Additionally, patients with a NI had longer lengths of stay (13 days vs. 5 days) and higher hospital costs (US\$173, 206 vs. US\$ 44,367) than those without. These data suggest that there are excess mortality, morbidity, and costs that can be attributed to a NI.

The four most common NIs are urinary tract, surgical site, pulmonary, and bloodstream infections\textsuperscript{16}. Their relative frequency has varied somewhat from study to study, in part related to different patient populations studied and changing hospitalization patterns. Overall, NP typically ranks second or third most common in frequency\textsuperscript{4,5,16}. Nosocomial pneumonia accounted for 15\% of infections in the patient population studied by Wenzel in the early 1970s\textsuperscript{8}. During a prevalence survey of NI in 72 German hospitals in 1994, NP accounted for 20.7\% of all such infections\textsuperscript{17}. In the Canadian prevalence survey, NP accounted for 26.6\% of all NIs\textsuperscript{4}. Nosocomial pneumonia represents the first or second most common NI in the ICU setting\textsuperscript{2,10}. In the European Prevalence of Infection in ICU Study, pneumonia was the most common (46.9\%) of the NIs\textsuperscript{10}. This is similar to other ICU studies where NP accounted for 25.2\% – 47.4\% of NIs\textsuperscript{12,13}.

### 3.2 Nosocomial pneumonia – diagnosis

Pneumonia is infection mediated inflammation of the distal lung caused by a variety of different microorganisms. Nosocomial pneumonia may be classified as ventilator-associated (VAP), further sub-classified as early-onset and late-onset VAP, or non-VAP. One of the greater limitations to the study of NP has been the difficulty in achieving consistent and reliable diagnosis, especially in ventilated patients. Historically, and for routine hospital surveillance purposes, a clinical definition based on the presence of certain symptoms and signs (specifically new onset of sputum production or a change in sputum characteristics and crackles or dullness to percussion on chest examination), microbiological culture results, and radiographic findings has been used. The poor specificity of clinical diagnosis has been suggested by various
investigators\textsuperscript{18-20}. Additionally, one study has questioned even the sensitivity of clinical diagnosis\textsuperscript{21}. As a result, the use of invasive diagnostic techniques has been promoted to improve diagnostic specificity, thereby reducing misclassification and enhancing the validity of studies of NP. These techniques have included the collection and culture of transtracheal or transthoracic aspirates and bronchoscopy to collect protected specimen brush (PSB) and bronchoalveolar lavage (PBAL) samples\textsuperscript{19,20,22-24}. Unfortunately, some of these procedures cannot be safely performed in critically ill patients. Furthermore, the sensitivity of PBAL may be as low as 69\%\textsuperscript{24}. When the outcomes of VAPs diagnosed using both clinical (suspected) and microbiological (confirmed) criteria were examined by multivariable analysis in a study investigating the usefulness of PBAL, only suspected VAP remained associated with increased mortality\textsuperscript{24}. One interpretation of this finding is that a clinical diagnosis carries the same significance as a microbiologically confirmed one. Similarly, Timsit et al found that suspected VAP (clinical diagnosis alone) and confirmed VAP (confirmed by PSB and PBAL) had similar mortality\textsuperscript{25}. This finding was confirmed in a study evaluating the benefit of PBAL in managing VAP, which reported a high mortality in patients for whom there was a strong clinical suspicion of VAP regardless of whether the diagnosis was confirmed by PBAL\textsuperscript{26}. In one study of pneumonia (both community- and hospital- acquired) requiring ICU admission, it was estimated that 22 of 152 cases represented false positive diagnoses once the clinical course and diagnostic results became apparent\textsuperscript{27}. Obtaining a specimen to make a microbiological diagnosis can be difficult in non-ICU patients. In their study of general medical and surgical patients, Everts found that only 41\% of patients submitted a suitable respiratory specimen. Of these, only 37\% demonstrated a microbial etiology\textsuperscript{28}.

Currently, there is insufficient evidence to support the superiority of a diagnosis of VAP made using invasive methods over a clinical diagnosis, and good evidence that survival is similar for patients with a strong clinical suspicion of VAP and those with a culture-confirmed diagnosis. At the same time, the potential for misclassification of patients and its impact on research findings, as well as the comparability of different studies, must always be kept in mind. In general, misclassification bias arising from suboptimal diagnostic techniques would contribute to an inability to identify differences between case and control patients. Uncertainty surrounding an accurate diagnosis remains one of the major limiting factors in interpreting the NP literature.
3.3 Nosocomial pneumonia – frequency

The literature reports a range of NP rates, using a variety of metrics, including incidence and prevalence rates, and incidence density rates (Table 1). The SENIC project reported that NP occurred in 0.6% of hospital admissions with an incidence density rate of 0.76 pneumonias/1000 patient-days\(^7\). This is generally similar to rates reported at the University of Virginia over two time periods (1972-1975\(^8\) and 1979-1983\(^29\)); by the National Nosocomial Infection Surveillance (NNIS) program in the US in 1984\(^5\); the Winnipeg Health Sciences Centre between 1987-1988\(^30\); Christchurch Hospital in New Zealand from 1994-1995\(^28\); and a hospital in Nagasaki, Japan from 1996-2000\(^31\). The 2002 Canadian prevalence survey found that 175 of 5750 adult patients (3%) developed a NP\(^4\). In the 2009 Canadian survey, a similar (2.7%) prevalence of NP was identified (personal communication: Denise Gravel, Public Health Agency of Canada). A limitation of these two Canadian studies, by virtue of their being prevalence surveys, is that incidence density rates cannot be determined, either in terms of patient- or ventilator- days at risk. Thus, we are left with only an approximation of the incidence of NP in adults admitted to hospital in Canada.

With the realization that mechanically ventilated patients are at greater risk to develop NP than non-ventilated patients, attention has focused on NP rates in ICUs. In a prevalence study conducted in 72 German hospitals in 1994, NP prevalence was 0.51% and 0.26% on general medicine and surgery wards respectively, but 5.87% in ICU\(^17\). A number of published studies have reported NP rates in ventilated patients in critical care units ranging from 9.6%–26.7%\(^11,13,18,19,32-36\). This variation in rates is likely contributed to by the use of differing case definitions and diagnostic strategies, as well as different patient populations (e.g. trauma patients, post-surgical patients) and unit types (e.g. cardiovascular surgery ICU, medical ICU). It is also possible that regional and national factors, such as antimicrobial use and antimicrobial resistance patterns, contribute to NP rate differences among the various studies. The major risk factor for NP in ventilated patients relates to mechanical ventilation itself. Nosocomial pneumonia rates are therefore more appropriately reported in terms of device exposure, for which rates range from 6.7-37.6 VAP cases per 1000 ventilator- days\(^11-13,19,34-38\).
<table>
<thead>
<tr>
<th>Years</th>
<th>NP Type</th>
<th>% of admits</th>
<th>% of patients</th>
<th>/1000 admits</th>
<th>/1000 discharges</th>
<th>/1000 pt-days</th>
<th>/1000 vent-days</th>
</tr>
</thead>
<tbody>
<tr>
<td>1975-6</td>
<td>All</td>
<td>0.60</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.76</td>
</tr>
<tr>
<td>1972-5</td>
<td>All</td>
<td></td>
<td></td>
<td>9.40</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1979-83</td>
<td>All</td>
<td></td>
<td></td>
<td>8.60</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1984</td>
<td>All</td>
<td></td>
<td></td>
<td>6.00</td>
<td></td>
<td></td>
<td>5.70</td>
</tr>
<tr>
<td>1987-8</td>
<td>All</td>
<td></td>
<td></td>
<td>6.00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1984-5</td>
<td>Non-VAP</td>
<td></td>
<td></td>
<td>6.10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1984-2000</td>
<td>Non-VAP</td>
<td>1.86</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2002</td>
<td>All</td>
<td>3.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1994</td>
<td>Gen Med</td>
<td>0.51</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1994</td>
<td>ICU</td>
<td>5.87</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1994-5</td>
<td>ICU</td>
<td>9.60</td>
<td></td>
<td>9.40</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2002-3</td>
<td>ICU</td>
<td>8.10</td>
<td></td>
<td>18.8</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>2002-5</td>
<td>ICU</td>
<td>18.9</td>
<td></td>
<td>26.50</td>
<td></td>
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</tr>
<tr>
<td>1983-4</td>
<td>VAP</td>
<td>21.00</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>1990-1</td>
<td>ICU</td>
<td>7.80</td>
<td></td>
<td>12.50</td>
<td>20.50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1983-4</td>
<td>VAP</td>
<td></td>
<td></td>
<td>26.60</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1996-7</td>
<td>ICU</td>
<td>15.40</td>
<td></td>
<td>20.00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2002&amp;3</td>
<td>ICU</td>
<td>15.00</td>
<td></td>
<td>29.00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1999-2003</td>
<td>VAP</td>
<td>22.30</td>
<td></td>
<td>37.60</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1992-6</td>
<td>VAP</td>
<td>17.50</td>
<td></td>
<td>14.80</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1992-7</td>
<td>VAP</td>
<td></td>
<td></td>
<td>11.80</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not stated</td>
<td>ICU</td>
<td>18.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>18.30</td>
</tr>
<tr>
<td>1997-2003</td>
<td>ICU</td>
<td>16.90</td>
<td></td>
<td>15.90</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2005-6</td>
<td>Non- ICU</td>
<td></td>
<td></td>
<td>3.30</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1994-2000</td>
<td>VAP</td>
<td></td>
<td></td>
<td>19.90</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
3.4 Nosocomial pneumonia – risk factors for occurrence

A number of studies have examined risk factors (Table 2) for the occurrence of NP. Most have focused on those patients most at risk, i.e. patients in ICU. The results have been discrepant for several reasons including differences in study methodology, population composition, case definitions, sample sizes, and risk factors examined.

Table 2. Independent risk factors for nosocomial pneumonia

<table>
<thead>
<tr>
<th>Country, yr.</th>
<th>Study Design</th>
<th>Patients</th>
<th>Risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>US</td>
<td>Prospective cohort</td>
<td>358 MICU 28 VAP</td>
<td>Low serum albumin, PEEP ≥7.5cm H₂O, no antibiotics, colonization with GNR, pack-yrs smoking, duration of ventilation</td>
</tr>
<tr>
<td>Canada</td>
<td>Prospective cohort</td>
<td>1014 ICU 177 VAP</td>
<td>Burns, trauma, CNS disease, respiratory disease, cardiac disease, ventilated prior 24 hrs, witnessed aspiration, paralytic agents, prior antibiotics protective</td>
</tr>
<tr>
<td>US</td>
<td>Prospective cohort</td>
<td>3668 M/SICU 420 HAP</td>
<td>↑APACHE score, reintubation, H₂ blockers, duration of ventilation, tracheostomy</td>
</tr>
<tr>
<td>US</td>
<td>Prospective cohort</td>
<td>277 ICU 43 NP</td>
<td>Organ system failure score ≥3, age ≥60 yrs, prior antibiotics, patient head positioning</td>
</tr>
<tr>
<td>Spain</td>
<td>Prospective cohort</td>
<td>322 ICU 78 NP</td>
<td>&gt;1 intubation, prior aspiration, ventilation &gt;3 days, COPD, PEEP</td>
</tr>
<tr>
<td>US</td>
<td>Prospective cohort</td>
<td>888M/SICU 132 VAP</td>
<td>Tracheostomy, multiple central line insertions, reintubation, antacids</td>
</tr>
<tr>
<td>Spain</td>
<td>Case control</td>
<td>120 each group, ICU and non-ICU</td>
<td>Intubation, depressed level of consciousness, chronic lung disease, thoracic or upper abdominal surgery, large volume aspiration, age &gt;70yrs</td>
</tr>
<tr>
<td>Country</td>
<td>Year(s)</td>
<td>Study Type</td>
<td>Patients</td>
</tr>
<tr>
<td>---------</td>
<td>---------</td>
<td>------------</td>
<td>----------</td>
</tr>
<tr>
<td>Germany</td>
<td>1994</td>
<td>Prevalence survey</td>
<td>14966 patients 107 LRTI</td>
</tr>
<tr>
<td>Brazil</td>
<td>1996-1997</td>
<td>Prospective cohort</td>
<td>540 ICU 83</td>
</tr>
<tr>
<td>France</td>
<td>1996-2001</td>
<td>Case control</td>
<td>177 each group</td>
</tr>
<tr>
<td>Germany</td>
<td>2000-2001</td>
<td>Prospective cohort</td>
<td>1876 158 NP</td>
</tr>
<tr>
<td>Sweden</td>
<td>2002&amp;2003</td>
<td>Prospective cohort</td>
<td>221 ICU 33 VAP</td>
</tr>
<tr>
<td>Switzerland</td>
<td>1999-2003</td>
<td>Prospective cohort</td>
<td>2470 ICU 262 VAP</td>
</tr>
<tr>
<td>France</td>
<td>1997-2003</td>
<td>Prospective cohort</td>
<td>1856 ICU 319 VAP</td>
</tr>
</tbody>
</table>

Given these discrepancies, it is difficult to draw definitive conclusions regarding which factors are most likely to put patients at risk for developing NP.

### 3.5 Nosocomial pneumonia - outcomes

Although not the most common NI, NP is overall responsible for the greatest NI-attributable mortality in the hospital setting. In a study of postmortem findings, Daschner et al found that the most frequent NI causing or contributing to death was NP\(^{14}\). In a review of 100 consecutive inpatient deaths at two facilities, it was determined that when a NI was causally related or contributory to death, infection of the lower respiratory tract was predominant\(^{50}\). At the University of Virginia between 1979 and 1983, the overall case fatality rate of NP was 30%, with an attributable mortality of 33% (p=0.089) and a 7 day longer hospital stay (p<0.0001) compared
to patients without NP. Louie et al reported a NP mortality rate of 25% in patients at a tertiary care centre in Winnipeg from 1987-1988. This is greater than the 11% case fatality rate noted in New Zealand patients and 6.5% in patients on general wards in Japan. While secular trends in mortality may reflect improvements in diagnosis and treatment over the years, differences in outcome between studies may also be due to differences in study design, case definitions, study populations, and duration of follow-up. Mortality rates for NP (Table 3) have been generally been higher in ICU patients, ranging from 33%-58%.

Table 3. Mortality risk of nosocomial pneumonia in critically ill patients

<table>
<thead>
<tr>
<th>Country, yr.</th>
<th>Design</th>
<th>Patients</th>
<th>Summary results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>US 1997-98</td>
<td>Prospective cohort</td>
<td>3668</td>
<td>Adjusted OR 1.74 (95% CI 1.50-2.03)</td>
<td>Clinical diagnosis; multivariable analysis; 50% ‘high-risk’ bacteria</td>
</tr>
<tr>
<td>US 1994</td>
<td>Prospective cohort</td>
<td>314</td>
<td>‘High-risk’ bacteria adjusted OR 3.40 (95% CI 1.21-10.00)</td>
<td>Clinical diagnosis; multivariable analysis; insufficient power to determine risk due to all bacteria</td>
</tr>
<tr>
<td>France 1996-99</td>
<td>Matched case-cohort group</td>
<td>135</td>
<td>Adjusted OR 2.10 (95% CI 1.20-3.60)</td>
<td>PSB diagnosis; time-dependent, multivariable analysis; 32% with ‘high-risk’ bacteria</td>
</tr>
<tr>
<td>France 1989-94</td>
<td>Prospective cohort</td>
<td>1978</td>
<td>Adjusted OR 2.08 (95% CI 1.55-2.80)</td>
<td>PSB diagnosis; multivariable analysis</td>
</tr>
<tr>
<td>France 1988-90</td>
<td>Matched case-cohort group</td>
<td>48</td>
<td>Risk ratio 2 (95% CI 1.41-3.71)</td>
<td>PSB diagnosis; matching successful for 92.5% variables; higher mortality with ‘high-risk’ bacteria</td>
</tr>
<tr>
<td>US 1992</td>
<td>Prospective cohort</td>
<td>277</td>
<td>Crude OR 6.34</td>
<td>Clinical diagnosis; NP fell out with multivariable analysis</td>
</tr>
<tr>
<td>Spain</td>
<td>Prospective</td>
<td>265</td>
<td>Crude risk ratio 1.10</td>
<td>Many patients had PSB; univariate</td>
</tr>
<tr>
<td>Year</td>
<td>Type</td>
<td>Number</td>
<td>Mortality</td>
<td>Diagnosis</td>
</tr>
<tr>
<td>------</td>
<td>------</td>
<td>--------</td>
<td>-----------</td>
<td>-----------</td>
</tr>
<tr>
<td>1988-89</td>
<td>Prospective cohort</td>
<td>58</td>
<td>Crude risk ratio 1.73</td>
<td>Some patients had PSB; NP not examined in multivariable analysis</td>
</tr>
<tr>
<td>1987-88</td>
<td>Prospective cohort</td>
<td>322</td>
<td>VAP mortality 40%</td>
<td>Patients had PSB; Unable to find matches for 12/97; stratified analysis for nonmatched factors; most surgical patients</td>
</tr>
<tr>
<td>1989-93</td>
<td>Matched Case-cohort</td>
<td>85 each group</td>
<td>NonVAP mortality 39%</td>
<td></td>
</tr>
<tr>
<td>1998-99</td>
<td>Prospective cohort</td>
<td>888</td>
<td>VAP mortality 46%</td>
<td>Clinical diagnosis</td>
</tr>
<tr>
<td>1992-96</td>
<td>Matched Case-cohort</td>
<td>173 each group</td>
<td>Attributable mortality 5.80% (95% CI –2.40-14.00%)</td>
<td>Patients had PSB; stratified analysis; done in context of randomized controlled trial</td>
</tr>
<tr>
<td>2002&amp;2003</td>
<td>Prospective cohort</td>
<td>221</td>
<td>Adjusted OR 2.73 (0.97-7.63)</td>
<td>70% of patients had PSB and/or BAL</td>
</tr>
<tr>
<td>1999-2003</td>
<td>Prospective cohort</td>
<td>2470</td>
<td>VAP mortality 33.50%</td>
<td>Clinical diagnosis. VAP divided into early and late onset</td>
</tr>
<tr>
<td>2000-2001</td>
<td>Prospective cohort</td>
<td>1876</td>
<td>Crude risk ratio 0.87</td>
<td>VAP not a risk in multivariable analysis</td>
</tr>
<tr>
<td>2002-2003</td>
<td>Prospective cohort</td>
<td>101</td>
<td>Attributable mortality 18.50% (95%CI 3.10-34.80)</td>
<td>All confirmed with PSB. Attributable mortality= Expected based on APACHE-observed. Excess mortality in late VAP</td>
</tr>
<tr>
<td>Europe</td>
<td>Prospective cohort</td>
<td>2436</td>
<td>NP mortality 37.70%</td>
<td>Not all had invasive diagnosis. No multivariable analysis for mortality</td>
</tr>
</tbody>
</table>
Not given $^{39}$ & No-NP mortality 31.60% & from NP & |
| France 1996-2007 $^{59}$ | Prospective cohort | 2873 434 VAP | Attributable mortality 8.10% (95%CI 3.10-13.10%) | Clinical diagnosis allowed. Study compared logistic regression and time-dependent models. |
| Various $^{60}$ | Meta-analysis | 52 studies | Overall RR: 1.27 (95%CI 1.15-1.39) | Heterogeneity among studies other than those in trauma and ARDS limits ability to quantify RR |
| & & & Trauma RR: 1.09 (95%CI 0.87-1.37) | |
| & & & ARDS RR 0.86 (95%CI 0.72-1.04) | |

PSB=protected specimen brush  BAL=bronchoalveolar lavage

Several studies identify NP as an independent predictor for death $^{21,22,43,51,52}$, while others do not $^{44-46,55-57}$. Mortality rates are higher in severely ill patients, even in the absence of infection. Nosocomial pneumonia and mortality share several risk factors that confound their relationship. Thus, the question is whether death in a patient with a NP arises primarily as a consequence of infection, if infection merely hastens the conclusion of an underlying disease process, or if the infection is non-contributory to death. Each of the studies looking at outcome has demonstrated the important role that the patient’s associated conditions and premorbid status play. When evaluating the various studies, the balance of evidence tends to favour an independent role for NP as a prognostic factor in critically ill patients. The only study to examine prognostic factors associated with NP in non-critically ill patients has not identified the pneumonia as an independent risk factor for death $^{61}$.

A number of studies have examined risk factors for death in ICU patients (Table 4). Among these are inappropriate initial antibiotic therapy $^{62}$ and infection with ‘high-risk’ microorganisms $^{43,51}$ such as *Pseudomonas aeruginosa* $^{27,51,63}$, *Acinetobacter* species $^{63,64}$, methicillin-resistant *Staphylococcus aureus* $^{65}$ and *Aspergillus* species $^{47}$. Other studies have not been able to attribute risk to these pathogens; discrepant findings again may have arisen from varying diagnostic strategies and sample sizes $^{43,55,56,66}$.
Table 4. Independent risk factors for death in nosocomial pneumonia studies

<table>
<thead>
<tr>
<th>Country, yr.</th>
<th>Design</th>
<th>Patients</th>
<th>Risks</th>
</tr>
</thead>
<tbody>
<tr>
<td>US 1983-84</td>
<td>RCT of ventilator</td>
<td>233</td>
<td>↑creatinine, pneumonia on admission, no bronchodilators, duration of</td>
</tr>
<tr>
<td></td>
<td>circuit changes</td>
<td>49 VAP</td>
<td>ventilation, no abdominal surgery, admission from other ward of</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>hospital, coma on admission</td>
</tr>
<tr>
<td>US 1997-1998</td>
<td>Prospective cohort</td>
<td>3668 M/SICU</td>
<td>Use of vasopressors, multiorgan failure, NP, underlying malignancy,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>420 HAP</td>
<td>use of steroids, APACHE II score, age</td>
</tr>
<tr>
<td>US 1994</td>
<td>Prospective cohort</td>
<td>314 ICU</td>
<td>VAP due to high-risk bacteria. Organ system failure score ≥3,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>87 VAP</td>
<td>nonsurgical diagnosis, premorbid lifestyle score≥2, antacids or H₂</td>
</tr>
<tr>
<td>France 1996-99</td>
<td>Matched case-</td>
<td>135 ICU</td>
<td>Neurologic diagnosis, cardiac diagnosis, chronic alcoholism, surgery</td>
</tr>
<tr>
<td></td>
<td>cohort patients</td>
<td></td>
<td>during ICU stay, NP due to resistant organisms</td>
</tr>
<tr>
<td></td>
<td>each group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>France 1989-94</td>
<td>Prospective cohort</td>
<td>1978 ICU</td>
<td>APACHE II score, # dysfunctional organs, NP, nosocomial bacteremia,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>328 NP</td>
<td>fatal underlying disease, admission from other ICU</td>
</tr>
<tr>
<td>US 1992</td>
<td>Prospective cohort</td>
<td>277 ICU</td>
<td>Organ system failure score ≥3, premorbid lifestyle score ≥2, supine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>43 NP</td>
<td>head positioning</td>
</tr>
<tr>
<td>Spain 1987-88</td>
<td>Prospective cohort</td>
<td>322 ICU</td>
<td>Ultimately or rapidly fatal disease, worsening respiratory failure,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>78 NP</td>
<td>septic shock, inappropriate antibiotic</td>
</tr>
<tr>
<td>US 1998-99</td>
<td>Prospective cohort</td>
<td>888M/SICU</td>
<td>Bacteremia, compromised immune system, higher APACHE II score, older</td>
</tr>
<tr>
<td></td>
<td></td>
<td>132 VAP</td>
<td>age</td>
</tr>
<tr>
<td>Spain 1980s</td>
<td>Case control</td>
<td>120 each group, ICU and non-</td>
<td>High-risk microorganism, bilateral involvement, respiratory failure,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Country</td>
<td>Study Period</td>
<td>Study Type</td>
<td>Cases</td>
</tr>
<tr>
<td>--------------</td>
<td>--------------</td>
<td>------------</td>
<td>-------</td>
</tr>
<tr>
<td>France</td>
<td>1994-1996</td>
<td>Prospective cohort</td>
<td>7226 ICU, 628 NP</td>
</tr>
<tr>
<td>Japan</td>
<td>1997</td>
<td>Prospective cohort</td>
<td>Wards 80 NP</td>
</tr>
<tr>
<td>Canada</td>
<td>1993-1994</td>
<td>Prospective cohort</td>
<td>Wards 92 NP</td>
</tr>
<tr>
<td>Taiwan</td>
<td>1999-2000</td>
<td>Prospective cohort</td>
<td>Wards &amp; ICU 132 NP</td>
</tr>
<tr>
<td>Sweden</td>
<td>2002&amp;2003</td>
<td>Prospective cohort</td>
<td>221 ICU, 33 VAP</td>
</tr>
<tr>
<td>France</td>
<td>1994-2001</td>
<td>Prospective cohort</td>
<td>3797 ICU, 168 HAP</td>
</tr>
<tr>
<td>Spain</td>
<td>1993-2000</td>
<td>Prospective cohort</td>
<td>96 severe HAP</td>
</tr>
<tr>
<td>Argentina</td>
<td>1999-2003</td>
<td>Retrospective cohort</td>
<td>508 ICU 76 NP</td>
</tr>
<tr>
<td>France</td>
<td>1996-2007</td>
<td>Prospective cohort</td>
<td>2873 ICU</td>
</tr>
<tr>
<td>Country</td>
<td>Study Type</td>
<td>Number</td>
<td>Characteristics</td>
</tr>
<tr>
<td>-------------</td>
<td>----------------</td>
<td>--------</td>
<td>---------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Turkey</td>
<td>Prospective cohort</td>
<td>45679</td>
<td>Age, chronic renal failure, aspiration risk, steroid use, multilobar infiltrates</td>
</tr>
<tr>
<td>Various</td>
<td>Meta-analysis</td>
<td>26 studies</td>
<td>Acute respiratory failure, prior CAP, malignancy, inappropriate initial therapy, bacteremia, ARDS/ALI, shock, late VAP, sepsis, infection with <em>Acinetobacter baumanii</em></td>
</tr>
</tbody>
</table>

Regardless of whether VAP increases the risk of death, most studies have demonstrated that it does prolong the length of hospitalization by 7–17 days\cite{21,35,36,43,45,55,56,71}. Kollef et al compared patients hospitalized with community-acquired pneumonia (CAP), hospital-acquired pneumonia (HAP), and VAP in a large, multi-centre database study\cite{72}. They determined that the mean hospital charge for CAP was US$25,218, increasing to US$ 65,292 for HAP, and US$150,841 for VAP\cite{72}. Recognizing the importance of NP in terms of frequency and associated complications (morbidity, mortality and costs), there has been great interest over the years in studying its epidemiology and evaluating preventive measures.

### 3.6 Nosocomial pneumonia – Canadian experience

Despite the large literature on NP, there is very little describing the Canadian experience. One study examined the morbidity and mortality attributable to VAP in critically ill patients who participated in a randomized controlled trial (RCT) of sucralfate versus ranitidine in 15 university affiliated ICUs across Canada. It found that there was a trend towards increased mortality in patients with VAP\cite{57} compared to patients who did not develop VAP. As with most RCT, the study participants may not be representative of patients with NP and results must be interpreted with caution\cite{57}. The other three studies are single centre (two from one centre) and largely descriptive reports that did not assess attributable mortality\cite{30,67,73}. Among those who had NP, predictors for death were older age, a greater number of comorbidities, and residing on a medical ward\cite{67}. A great deal more remains to be learned about NP in Canadian health care facilities.
3.7 Nosocomial pneumonia - summary

The literature speaks to the clinical impact of NP. It is one of the most common of the NIs and associated with a high crude mortality rate. Its role as an independent risk factor for death is not clear, with different results reported in various studies. Given the variation in results from study to study, the epidemiology of NP in Canada is not necessarily predictable. One reason for this may be regional differences in the prevalence of antimicrobial-resistant microorganisms. Several studies show a poorer outcome for patients whose NP is caused by a high-risk microorganism, including antimicrobial-resistant strains\textsuperscript{27,43,51,63-65}. Canadian data have suggested a relatively low prevalence of the important antimicrobial-resistant pathogen, methicillin-resistant \textit{S.aureus} (MRSA). However, the incidence of infection with this bacterium has increased 17-fold (0.36 to 3.43/10,000 patient days) from 1995 to 2007, suggesting that it is likely to emerge as a more common nosocomial pathogen\textsuperscript{74}. It may well be that NP in Canada is associated with mortality rates that differ from those reported in the literature, in part because of a lower prevalence of antimicrobial-resistant bacteria. With the paucity of Canadian data and the discrepant results in the literature, it is crucial that we have a better understanding of the significance of NP as a health issue for Canadians. If the evidence supports a relationship between NP and death then further research into prognostic indicators and preventive strategies is warranted.
Chapter 4
Methods

4.1 Research design

_Study design:_ We conducted a retrospective cohort study to describe the epidemiology of NP in adult patients hospitalized in Canadian acute care facilities and to identify prognostic indicators for death in adults with NP.

_Study population:_ The target population is adult patients admitted to acute-care hospitals in Canada. Patients admitted to adult acute care facilities across Canada that participated in the Canadian Nosocomial Infection Surveillance Program (CNISP) point prevalence survey of hospital-acquired infections, conducted in February 2002, formed the sampling population. Patients potentially eligible to be included in the prevalence survey were identified by the hospital census on a single day. All patient units were surveyed except long term care, rehabilitation, psychiatric, and maternity wards. The study population was adult patients admitted to a unit where surveillance was performed and who were identified as having a NP at the time of this one-day cross-Canada CNISP point prevalence survey.

_Study setting:_ CNISP hospitals are major teaching hospitals, and located in all provinces except Prince Edward Island. At the time of the study, each of the country’s medical schools had a CNISP affiliated hospital. These hospitals have been collaborating on NI surveillance projects since 1995.

_NP detection:_ Experienced infection control practitioners (ICPs) reviewed the charts of all inpatients on the wards where surveillance was conducted on the day of the point prevalence survey. They identified patients who had NP (newly diagnosed that day or previously diagnosed and still on treatment) according to point prevalence study definitions based on accepted surveillance definitions.

_NP definition:_ Nosocomial pneumonia was diagnosed, according to CDC definitions, based on the presence of either i) abnormal findings on physical examination (rales or dullness to percussion) or ii) chest radiograph findings (new or progressive infiltrate, cavitation or pleural effusion) and any one of a) new onset of purulent sputum or change in character of sputum, b)
microorganism isolated from blood culture, c) isolation of pathogen from specimen obtained by transtracheal aspirate, bronchial washing, brushing, or biopsy, d) isolation of virus or detection of viral antigen in respiratory secretions, e) diagnostic single antibody titer (IgM) or fourfold increase in paired serum samples (IgG) for pathogen, or f) histopathologic evidence of pneumonia.

**Inclusion criteria:** Patients were included if they had been admitted for at least 48 hours on the day of the census or had a previous admission within the last 30 days and met the criteria for NP.

**Exclusion criteria:** The following criteria resulted in exclusion from the study: age under 16 years, a prior NP during the admission, and hospitalization for more than 90 days before the onset of the pneumonia.

### 4.2 Data collection

**Data abstraction:** Data were abstracted from the hospital record by an experienced ICP, research nurse, or the site principal investigator at each participating hospital using a standard questionnaire (Appendix I), definitions (Appendix II) and instructions (Appendix III). The data abstraction form was pilot tested for question form, content, readability and usability by an experienced ICP and the primary investigator (PI) on 10 patients with NP who were not part of the cohort. The answers were compared for questionnaire reliability. Data abstractors received in-depth training on study definitions and completion of the questionnaire by the PI who had regular email and, as needed, telephone contact with each participating site to maintain data reliability to the highest degree possible.

**Data collected:** Study patients were identified by the number (known as the survey number) assigned to them by Health Canada at the time of the point prevalence survey. Each participating hospital maintained a log of survey number and hospital identification number. The hospital identification number was not part of the information collected for this study.

A number of independent variables related to host, hospitalization, and NP that represent potential confounding factors were obtained from the inpatient record. Demographic variables included age and sex. Host factors included admission diagnosis and number and type of comorbidities, presence of an ultimately, rapidly or non-fatal underlying condition according to
criteria proposed by McCabe and Jackson\textsuperscript{76}, APACHE III score on admission as defined by Knaus et al\textsuperscript{77}, and smoking history. Hospitalization factors included date of admission and, where applicable, dates of ICU admission and discharge; presence, type and date of other NI; surgical procedures during the hospitalization; type of service at time of pneumonia onset; use of corticosteroid/ immunosuppressant/anticancer drugs; prior use of antimicrobials; presence and duration of endotracheal and tracheostomy tubes and mechanical ventilation (invasive and non-invasive); and reason for ventilation. Infection-related variables included associated bacteremia, diagnosis of VAP or non-VAP, presence and identity of infecting microorganisms, time (in days) to initiation of an appropriate antimicrobial regimen as measured by the interval between the initiation of antimicrobial therapy and the NP diagnosis, duration of treatment, and whether the use of empiric antimicrobials and treatment duration was “correct” as defined by current IDSA guidelines for treating NP\textsuperscript{78}. These guidelines differentiate NP as occurring with and without defined risk factors, and as early (within the first 4 days of hospitalization) or late (after 4 days). Treatment recommendations are specific to these different subsets of case characteristics. In terms of duration, for the purposes of this study a treatment course of 7 days was considered acceptable for all pathogens except \textit{P. aeruginosa}.

\textit{Definitions}: The pneumonia was defined as ventilator-associated if the patient had been intubated and ventilated for \textit{\geq} 48 hours prior to and within 48 hours of the pneumonia. ICU pneumonia was similarly defined: the patient had been in ICU for \textit{\geq} 48 hours prior to and within 48 hours of the pneumonia. To assess whether NP survival might be positively influenced by a preponderance of prevalent cases (survivors) that were systematically different from recently diagnosed cases, patients were compared according to whether they were a prevalent or incident NP. A time frame of 3 days was arbitrarily chosen, anticipating that most patients with NP have at least a three-day survival. Incident pneumonia was defined as a NP case newly diagnosed within 3 days of the survey. A NP present for more than 3 days at the time of the survey was called a prevalent pneumonia. High risk microorganisms were defined as methicillin-resistant \textit{S. aureus}, \textit{P. aeruginosa}, and \textit{Acinetobacter} species. Correct use of antimicrobials was defined as prescribing of empiric therapy and duration of antibiotic use as outlined by the 2005 IDSA guidelines for treating NP\textsuperscript{78}. The prescribed antimicrobial was defined as appropriate when it covered the pathogen isolated or when there was no pathogen isolated. The outcome of interest was mortality at discharge from hospital or four weeks from the NP diagnosis, whichever
occurred first. Four weeks was arbitrarily chosen since it was felt likely that most deaths related to a NI would have occurred by that time.

4.3 Data analysis

Data submission: Completed data collection forms were faxed to the PI at Dalhousie University where they were held in a locked filing cabinet kept by the PI. Computer files were accessible only to the investigators by personal and confidential passwords.

Data entry and analysis: Data were entered into an Access (Microsoft Office 2000) database created specifically for this study and analysis was with SAS version 9.2 (SAS Institute, Cary, NC). Each questionnaire was reviewed by the PI for completeness and consistency. Accuracy of data entry was assessed by manual review of each patient data abstraction form entered into the database and review of summary data for errors and inconsistencies. Data entry, verification, and analysis (Appendix IV) were conducted by the PI.

Primary analysis objective: Categorical values were analyzed using $\chi^2$, with continuity adjustment where there were <5 values in a cell. Where 20% of the cells had < 5 observations, the Fisher’s exact test was used. Continuous variables were analyzed using Student’s t test. All analyses were two-sided at an alpha of 0.05. Results are reported as relative risks with 95% confidence intervals. Correlations were determined using Pearson correlation coefficient.

Secondary analysis objective: Variables judged to be clinically important (i.e. number of days before an effective antibiotic was initiated) or associated with the outcome in univariate analysis were entered stepwise into multivariable models (Model 1 with variables significant at $p \leq 0.10$ and Model 2 with variables significant at $p \leq 0.05$; forward selection) to test the independence of the pneumonia death relationship and identify prognostic factors, taking into consideration potential confounding and modifying factors. The effect of the McCabe classification was examined in four ways: i) the McCabe score (an ordinal variable), ii) McCabe scores 2 and 3 compared to McCabe score 1, iii) McCabe score 3 compared to McCabe scores 1 and 2, iv) McCabe score 2 compared to McCabe score 1, and v) McCabe score 3 compared to McCabe score 1. None of the variables entered into the model was a potential mediator (i.e. a factor that occurs in the causal pathway from an independent to a dependent variable). Interactions between
the time before treatment and age, APACHE score, presence of high-risk microorganism, and whether a specimen was collected were assessed.

*Model 1:* Mortality (Alive) = intercept + age + gender + McCabe + APACHE + surgery + ICU + service + specimen collected + time before treatment ± high-risk bacteria + error

*Model 2:* Mortality (Alive) = intercept + McCabe + surgery + ICU + service + time before treatment ± high-risk bacteria + error

### 4.4 Ethical considerations, potential benefits and harms

Permission to conduct this study was received from the Research Review Board of each participating facility for which this type of study is not considered part of usual quality assurance activity as well as the University of Toronto Research Ethics Committee. Under the TriCouncil agreement, recognizing there were no patient interventions associated with this study, informed patient consent was not required.
Chapter 5
Results

5.1 Epidemiology of nosocomial pneumonia

There were 6747 patients (5750 adult, 997 pediatric) surveyed at the 29 hospitals during the February 2002 prevalence survey\textsuperscript{4,79}. Among the 758 identified NIs (667 adult, 91 pediatric) there were 196 NPs (175 adult, 21 pediatric)\textsuperscript{4,79}. Nosocomial pneumonia accounted for 26% of NIs in adults (47% of NI in critical care) and 3% of adults surveyed during the point prevalence study had NP, making it the second most common NI. Among surgical patients, 39/2112 (1.9%) had a NP and for medical patients this number was 47/2619 (1.8%)\textsuperscript{4}. However, 72/462 critical care patients (15.6%) had NP, making it the most common NI in those units\textsuperscript{4}. The remaining 17 NPs were in trauma/burn (5), transplant (5), and hematology/oncology (7) unit patients.

Figure 1 graphically represents participation on this study. Fifteen of the 25 hospitals in the adult point prevalence survey, all university teaching hospitals, participated in this NP retrospective cohort study. Non-participating hospitals averaged 6 NP case per site (range 1-10). Participating hospitals submitted data abstraction forms on 134 patients identified as having NP during the survey. This represented 76.6% of NP identified in adults during the point prevalence survey. Twenty patients (14 men and 6 women; mean age 65.5 years (range 37-92 years); 18 alive at hospital discharge) were excluded from the retrospective cohort study. Subsequent review by the local ICP deemed that eleven patients did not, in retrospect, meet criteria for NP. Among the additional nine patients excluded, in one the pneumonia occurred $>90$ days after admission, in five it was the second NP, and in three the pneumonia had its onset at a non-CNISP hospital. The study includes 114 patients (78 men and 36 women) with NP. In all but three patients, there was an abnormal chest radiograph supporting the diagnosis of NP. The remaining three patients met accepted clinical criteria for NP.
The characteristics of the study population (114 patients) are presented in Table 5. Men constituted more than two-thirds of the study population. The majority of patients (70.2%) had a condition that was considered ultimately or rapidly fatal. Where that information was available (86 patients), 80.6% of the patients were smokers or ex-smokers. The vast majority of study patients (86.8%) had received an antibiotic in the month prior to their pneumonia. Close to one third had some form of immune suppression, due either to steroids, chemotherapy, or immune suppressant drugs. Another NI preceded or accompanied the NP in 20.2% of patients.
Table 5. Characteristics of the study population

<table>
<thead>
<tr>
<th>Variable (n=114)</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years (mean±SD)</td>
<td>64.0±15.6</td>
</tr>
<tr>
<td>Male (n and (%))</td>
<td>78(68.4)</td>
</tr>
<tr>
<td>Female (n and (%))</td>
<td>36(31.6)</td>
</tr>
<tr>
<td>Discharged alive (n and (%))</td>
<td>80(70.2)</td>
</tr>
<tr>
<td>Alive at 28 days (n and (%))</td>
<td>87(76.3)</td>
</tr>
<tr>
<td>Alive within 15 days of NP (n and (%))</td>
<td>98 (86.0)</td>
</tr>
<tr>
<td>Total length of stay in days (mean±SD)</td>
<td>51.9±54.1</td>
</tr>
<tr>
<td>Number of conditions (mean±SD)</td>
<td>2.9 ±1.6</td>
</tr>
<tr>
<td>McCabe nonfatal (n and (%))</td>
<td>34(29.8)</td>
</tr>
<tr>
<td>McCabe ultimately fatal (n and (%))</td>
<td>57(50.0)</td>
</tr>
<tr>
<td>McCabe rapidly fatal (n and (%))</td>
<td>23(20.2)</td>
</tr>
<tr>
<td>Admission APACHE score (mean±SD)</td>
<td>49.0±20.9</td>
</tr>
<tr>
<td>Non-smoker (n and (%))</td>
<td>14(19.4)</td>
</tr>
<tr>
<td>Smoker (n and (%))</td>
<td>58(80.6)</td>
</tr>
<tr>
<td>Smoking missing data (n and (%))</td>
<td>42(36.8)</td>
</tr>
<tr>
<td>Surgery during admission (n and (%))</td>
<td>64(56.1)</td>
</tr>
<tr>
<td>Ventilated during admission (n and (%))</td>
<td>51(44.7)</td>
</tr>
<tr>
<td>CPAP during admission (n and (%))</td>
<td>15(13.2)</td>
</tr>
<tr>
<td>Ventilator days before pneumonia (mean±SD)</td>
<td>11.4±13.4</td>
</tr>
<tr>
<td>Tracheostomy during admission (n and (%))</td>
<td>11(9.7)</td>
</tr>
<tr>
<td>ICU stay during admission (n and (%))</td>
<td>59(51.8)</td>
</tr>
<tr>
<td>ICU days before pneumonia (mean±SD)</td>
<td>11.2±13.8</td>
</tr>
<tr>
<td>Other NI (n and (%))</td>
<td>23(20.2)</td>
</tr>
<tr>
<td>Steroids (n and (%))</td>
<td>30(26.3)</td>
</tr>
<tr>
<td>Prior antibiotic (n and (%))</td>
<td>99(86.8)</td>
</tr>
<tr>
<td>Variable (n=114)</td>
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</tr>
<tr>
<td>------------------------------------------------------</td>
<td>--------</td>
</tr>
<tr>
<td>Chemotherapy (n and (%))</td>
<td>8(7.0)</td>
</tr>
<tr>
<td>Any immunosuppression (n and (%))</td>
<td>35(30.7)</td>
</tr>
<tr>
<td>Documented HAP criteria (n and (%))</td>
<td>69(60.5)</td>
</tr>
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<td>VAP (n and (%))</td>
<td>40(35.1)</td>
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<td>ICU</td>
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<td>CCU</td>
<td>8(7.0)</td>
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<td>Secondary BSI (n and (%))</td>
<td>2(1.8)</td>
</tr>
<tr>
<td>High-risk bacterium (n and (%))</td>
<td>16(21.6)</td>
</tr>
<tr>
<td>Days before correct treatment (mean±SD)</td>
<td>0.6±1.3</td>
</tr>
<tr>
<td>Correct empiric drugs (n and (%))</td>
<td>26(22.8)</td>
</tr>
<tr>
<td>Correct duration of therapy (n and (%))</td>
<td>94(82.5)</td>
</tr>
<tr>
<td>Microorganism(s) covered: (n and (%))</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>6(5.3)</td>
</tr>
<tr>
<td>Yes</td>
<td>63(55.3)</td>
</tr>
<tr>
<td>N/A</td>
<td>40(35.1)</td>
</tr>
<tr>
<td>U/K</td>
<td>5(4.4)</td>
</tr>
<tr>
<td>Duration of treatment (n and (%)) &lt; 8 days</td>
<td>20(18.4)</td>
</tr>
</tbody>
</table>

n= number   SD = standard deviation   U/K = unknown   N/A = not applicable

Fifty-nine patients (51.8%) had an ICU stay (mean 11.1 days, range 0-77) and 51 patients (44.7%) were mechanically ventilated (mean 11.38 days, range 2-77) prior to their pneumonia; although, the pneumonia was ICU-acquired in only 36.8% and ventilator-associated in only 35.1%. Most (75.4%) of the pneumonias were late, occurring at least 4 days after admission. Bacteremia secondary to the pneumonia was observed in only 2 NP cases (1.8%).
Almost all patients received an antimicrobial to treat their pneumonia. The minority of patients (26/114; 23%) in the cohort received one of the IDSA recommended empirical agent(s). However, the majority (82.5%) of all treated patients received an antibiotic for at least the recommended duration. Those who were treated empirically according to IDSA guidelines received appropriate treatment (i.e., an antibiotic that covered the causative agent) earlier than those not given an antibiotic recommended in the IDSA guideline (0.2 days vs. 0.7 days, p=0.005) and tended to have a higher APACHE score (55.2 vs. 47.2, p=0.09). Patients from whom a specimen was collected were started on treatment later than those who did not have a specimen collected (0.82 days vs. 0.15 days, p=0.001). Patients who were infected with a high risk bacteria also had a delay in receiving appropriate treatment compared to those who did not have such bacteria (1.86 days vs. 0.52 days, p=0.04).

There were no differences between men and women in demographic, hospital, and infection factors apart from a greater recent use of antibiotics (p = 0.05) and number of ventilator days before pneumonia (p=0.03) in men and a tendency for women to have fewer days in ICU before the diagnosis of pneumonia (p=0.14).

The NP was considered an incident pneumonia in 31.6% of patients, diagnosed within 3 days of the prevalence survey. There were no differences between patients with incident and prevalent pneumonia (Table 6) in terms of age and number of hospital, ICU, and ventilator days before the NP.

Table 6. Characteristics of patients with incident and prevalent pneumonia

<table>
<thead>
<tr>
<th>Variable</th>
<th>Incident n=36</th>
<th>Prevalent n=78</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years (mean±SD)</td>
<td>63.1 ± 18.8</td>
<td>64.4 ± 14.1</td>
<td>0.72</td>
</tr>
<tr>
<td>McCabe rapidly fatal, n (%)</td>
<td>5 (13.9)</td>
<td>18 (23.1)</td>
<td>0.51</td>
</tr>
<tr>
<td>McCabe ultimately fatal, n (%)</td>
<td>20 (55.5)</td>
<td>37 (47.4)</td>
<td></td>
</tr>
<tr>
<td>McCabe nonfatal, n (%)</td>
<td>11 (30.6)</td>
<td>23 (29.5)</td>
<td></td>
</tr>
<tr>
<td>APACHE score (mean±SD)</td>
<td>44.7 ± 20.6</td>
<td>51 ± 20.9</td>
<td>0.14</td>
</tr>
</tbody>
</table>
Table 7. Characteristics of patients with and without all pneumonia criteria

<table>
<thead>
<tr>
<th>Variable</th>
<th>All criteria n=69</th>
<th>Not all criteria n=45</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years (mean±SD)</td>
<td>63.7±15.1</td>
<td>64.5±16.6</td>
<td>0.80</td>
</tr>
<tr>
<td># of underlying conditions (mean±SD)</td>
<td>2.9±1.7</td>
<td>3.0±1.4</td>
<td>0.83</td>
</tr>
<tr>
<td>McCabe rapidly fatal, n (%)</td>
<td>15(21.7)</td>
<td>8(17.8)</td>
<td>0.60</td>
</tr>
<tr>
<td>McCabe ultimately fatal, n (%)</td>
<td>32(46.4)</td>
<td>25(55.6)</td>
<td></td>
</tr>
<tr>
<td>McCabe nonfatal, n (%)</td>
<td>22(31.9)</td>
<td>12(26.7)</td>
<td></td>
</tr>
<tr>
<td>APACHE score (mean±SD)</td>
<td>49.4±20.3</td>
<td>48.4±22</td>
<td>0.80</td>
</tr>
</tbody>
</table>
A respiratory specimen was obtained on 64.9% of patients (93% of VAP and 50% of non-VAP patients; p <0.0001), and 67.6% of them were on antibiotics when the specimen was taken. Patients from whom a specimen was taken did not have a greater number of days in hospital or in ICU before the NP. Patients from whom a specimen was obtained tended to have a higher APACHE score (p=0.14) and have a longer period of time before appropriate therapy was started (p=0.0013).

The microorganisms isolated from patients in this study are found in Table 8. *S.aureus* and *P.aeruginosa* were the most frequently isolated pathogens. *P.aeruginosa* was never found in early NP, but found in both VAP and non-VAP. Enterobacteriaceae, Gram negative afermenters and MRSA were almost exclusively seen in late NP and MSSA seen equally in early and late NPS. Non-pathogens included Candida species, coagulase-negative staphylococci, and enterococci.
Table 8. Microbiology of nosocomial pneumonia according to nosocomial pneumonia type

<table>
<thead>
<tr>
<th>Microorganism</th>
<th>VAP</th>
<th>Non-VAP</th>
<th>Early</th>
<th>Late</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. aureus</td>
<td>10</td>
<td>7</td>
<td>6</td>
<td>11</td>
</tr>
<tr>
<td>MSSA</td>
<td>7</td>
<td>6</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>MRSA</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>P. aeruginosa</td>
<td>6</td>
<td>7</td>
<td>0</td>
<td>13</td>
</tr>
<tr>
<td>H. influenzae</td>
<td>5</td>
<td>3</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>K. pneumoniae</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>E. coli</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Other enterobacteriaceae</td>
<td>6</td>
<td>3</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>Other afermenters</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>S. pneumoniae</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Non-pathogens</td>
<td>3</td>
<td>10</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>Other</td>
<td>4</td>
<td>3</td>
<td>1</td>
<td>6</td>
</tr>
</tbody>
</table>

A high-risk bacterium was present in 21.6% of patients (Table 9). Individuals with a high-risk microorganism experienced a longer time to initiation of appropriate antimicrobial therapy. They also tended to be older, have a higher APACHE score, and have more pre-pneumonia hospital, ventilator, and ICU days (not statistically significant).

Table 9. Characteristics of patients with and without a high-risk bacterium

<table>
<thead>
<tr>
<th>Variable</th>
<th>High-risk bacterium n=16</th>
<th>No high-risk bacterium n=58</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years (mean±SD)</td>
<td>66.4±12.2</td>
<td>60.2±17.0</td>
<td>0.18</td>
</tr>
<tr>
<td>LOS in days (mean±SD)</td>
<td>65.8±47.0</td>
<td>57.8±63.3</td>
<td>0.64</td>
</tr>
<tr>
<td># days before pneumonia (mean±SD)</td>
<td>21.7±24.2</td>
<td>12.3±13.7</td>
<td>0.15</td>
</tr>
<tr>
<td># days after pneumonia (mean±SD)</td>
<td>43.1±32.7</td>
<td>44.5±60.8</td>
<td>0.90</td>
</tr>
<tr>
<td># ventilator days (mean±SD)</td>
<td>18.3±20.2</td>
<td>9.0±10.0</td>
<td>0.15</td>
</tr>
<tr>
<td>#ICU days (mean±SD)</td>
<td>20.9±23.1</td>
<td>8.1±8.0</td>
<td>0.08</td>
</tr>
<tr>
<td>---------------------</td>
<td>------------</td>
<td>---------</td>
<td>------</td>
</tr>
<tr>
<td>Variable</td>
<td>High-risk bacterium n=16</td>
<td>No high-risk bacterium n=58</td>
<td>p</td>
</tr>
<tr>
<td>Apache score (mean±SD)</td>
<td>57.8±21.8</td>
<td>49.9±20.4</td>
<td>0.18</td>
</tr>
<tr>
<td># days between pneumonia &amp; survey (mean±SD)</td>
<td>8.3±7.7</td>
<td>7.2±6.1</td>
<td>0.55</td>
</tr>
<tr>
<td># days before treatment (mean±SD)</td>
<td>1.9±2.1</td>
<td>0.5±1.3</td>
<td>0.04</td>
</tr>
</tbody>
</table>

n= number  SD = standard deviation

The 15-day, 28-day, and discharge mortality rates, were 14.0%, 23.7%, and 29.8% respectively, with most deaths (79.4%) within 28 days of NP. There was no difference in 28-day mortality for patients with (18%) and without (26%) VAP (RR= 1.49 (95% CI 0.68-3.23; p=0.30) or with (20%) and without ICU/CCU admission (26.6%) (RR= 1.09 (95% CI 0.89-1.33; p=0.50). Non-ICU NP accounted for 63% of deaths.

5.2 Predictors for survival

On univariate analysis (Table 10), survival was significantly associated with a more favourable McCabe score, surgery, ICU admission, non-medicine service, absence of a high-risk microorganism, and greater number of ventilator days prior to NP. Survival tended (0.05<p≤0.10) to be associated with younger age, male gender, lower APACHE, more days in ICU before NP, absence of a secondary bacteremia, and having a respiratory specimen taken. There was no survival difference between those who did and did not receive the IDSA recommended empiric antibiotics and duration of treatment. Appropriate antibiotic therapy was started earlier in survivors than non-survivors, although this did not meet statistical significance (0.5 ± 1.1 vs. 0.9 ± 1.8 days, p=0.23).
Table 10. Patient characteristics stratified by 28-day and discharge outcome

<table>
<thead>
<tr>
<th>Variable</th>
<th>Alive(n=87) mean±SD</th>
<th>Dead(n=27) mean±SD</th>
<th>p</th>
<th>Alive(n=80) mean±SD</th>
<th>Dead(n=34) mean±SD</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years</td>
<td>62.6±15.9</td>
<td>68.4±14.3</td>
<td>0.09</td>
<td>62.1±15.9</td>
<td>68.5±14.2</td>
<td>0.05</td>
</tr>
<tr>
<td># conditions</td>
<td>2.8±1.6</td>
<td>3.3±1.5</td>
<td>0.18</td>
<td>2.7±1.5</td>
<td>3.5±1.7</td>
<td>0.02</td>
</tr>
<tr>
<td>LOS in days</td>
<td>59.4±59.7</td>
<td>28.1±13.4</td>
<td>&lt;0.0001</td>
<td>52.9±47.7</td>
<td>49.5±67.4</td>
<td>0.79</td>
</tr>
<tr>
<td># days before pneumonia</td>
<td>13.8±16.3</td>
<td>13±10.7</td>
<td>0.76</td>
<td>14±16.9</td>
<td>12.7±10.2</td>
<td>0.63</td>
</tr>
<tr>
<td># days after pneumonia</td>
<td>44.6±54.7</td>
<td>14.1±8.3</td>
<td>&lt;0.0001</td>
<td>37.9±39.9</td>
<td>35.8±67.7</td>
<td>0.86</td>
</tr>
<tr>
<td># ventilator days</td>
<td>12.3±14.5</td>
<td>6.5±2.6</td>
<td>0.02</td>
<td>12.6±14.9</td>
<td>7.2±3.7</td>
<td>0.05</td>
</tr>
<tr>
<td>#ICU days</td>
<td>11.9±14.8</td>
<td>7.2±4.4</td>
<td>0.08</td>
<td>12.1±15.3</td>
<td>7.8±5.4</td>
<td>0.12</td>
</tr>
<tr>
<td>Apache score</td>
<td>47.1±20.8</td>
<td>55.1±20.2</td>
<td>0.08</td>
<td>46.1±20.8</td>
<td>55.9±19.7</td>
<td>0.02</td>
</tr>
<tr>
<td># days before treatment</td>
<td>0.5±1.1</td>
<td>0.9±1.8</td>
<td>0.23</td>
<td>0.4±1.1</td>
<td>0.9±1.6</td>
<td>0.17</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variable</th>
<th>Alive</th>
<th>Dead</th>
<th>RR (death) (95% CI)</th>
<th>p</th>
<th>Alive</th>
<th>Dead</th>
<th>RR (death) (95% CI)</th>
<th>p</th>
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</thead>
<tbody>
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<tr>
<td>Male</td>
<td>63</td>
<td>15</td>
<td>0.58 (0.30-1.10)</td>
<td>0.10</td>
<td>57</td>
<td>21</td>
<td>0.75 (0.42-1.32)</td>
<td>0.30</td>
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<td>Female</td>
<td>24</td>
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<td></td>
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<td>McCabe</td>
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<td>0.30</td>
<td>11</td>
<td>3</td>
<td>0.65</td>
<td>0.62</td>
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</table>

28-day outcome | Discharge outcome
<table>
<thead>
<tr>
<th>Variable</th>
<th>Alive</th>
<th>Dead</th>
<th>RR (death) (95% CI)</th>
<th>p</th>
<th>Alive</th>
<th>Dead</th>
<th>RR (death) (95% CI)</th>
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<tr>
<td>Surgery</td>
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</tr>
<tr>
<td>No</td>
<td>32</td>
<td>18</td>
<td>2.56 (1.26-5.20)</td>
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<td>23</td>
<td>2.68 (1.45-4.96)</td>
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<tr>
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<td>18</td>
<td>1.62 (0.80-3.29)</td>
<td>0.17</td>
<td>41</td>
<td>22</td>
<td>1.48 (0.82-2.70)</td>
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<tr>
<td>No</td>
<td>37</td>
<td>18</td>
<td>2.15 (1.05-4.37)</td>
<td>0.03</td>
<td>34</td>
<td>21</td>
<td>1.73 (0.96-3.11)</td>
<td>0.06</td>
</tr>
<tr>
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<td>50</td>
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<td>46</td>
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<td>Other NI</td>
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<tr>
<td>No</td>
<td>70</td>
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<td>0.88 (0.40-1.94)</td>
<td>0.76</td>
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n= number    SD = standard deviation    U/K = unknown    N/A = not applicable

Variables entered into the first multivariable analysis model were age, gender, McCabe score, APACHE score, surgery, ICU admission, service type, whether a specimen was taken, and number of days before appropriate antimicrobial treatment was initiated. Although the presence
of secondary bacteremia was statistically associated with 28-day mortality (p=0.09), there were only 2 bacteremias and the model used to investigate this variable showed questionable fit. Bacteremia was therefore not included in the final model. Variables in the second model were McCabe score, surgery, ICU admission, service, and number of days before adequate treatment started. Both models were run with and without the presence of the high-risk bacteria variable.

On multivariable analysis that included the high-risk bacteria variable in the analysis (Table 11), the only predictors for survival were lower McCabe score (RR 0.24; 95% CI 0.08-0.67, p=0.006) and earlier treatment with an appropriate antibiotic (RR 0.68; 95% CI 0.46-1.00, p=0.05). On multivariable analysis that excluded the high-risk bacteria variable (Table 12), predictors for survival were lower McCabe score, male gender, and ICU admission. There were no interactions with age, APACHE score, whether a specimen was collected, or the presence of a high-risk bacterium. None of the analyses where other variations of the McCabe score were entered as independent variables had a good fit for the models tested.

Table 11. Results of multivariable analysis (including risk bacteria variable)

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<th>Wald chi-square</th>
<th>Pr &gt; chi-square</th>
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Table 12. Results of multivariable analysis (excluding risk bacteria variable)

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Chapter 6
Discussion

6.1 Study findings

6.1.1 Prevalence of nosocomial pneumonia

During the Canadian Point Prevalence Survey in February 2002, 10.5% of hospitalized adults had at least one NI, of which 26% were reported to be NP, indicating a NP prevalence rate of 3% in the hospitalized adults surveyed. The prevalence of NI was higher in critical care units (33%) where 15.6% of patients had NP. In the critical care setting, NP accounted for 47.1% of all NIs. The prevalence rate of NP in surgical patients was 1.9%; and in medical patients it was 1.8%.

There is very little literature from which we can draw comparisons. Most NI studies are incidence studies, in contrast to this point prevalence survey. Eggiman et al demonstrated that the method of reporting VAP rates has a significant impact on risk estimates. Hence, it is important that rates not be directly compared when methodologies differ. However, a similar 1-day point prevalence survey among European ICUs in 1992 found that 20.6% of 10,038 patients had an ICU-acquired infection and that 46.9% of these infections were NP. The proportion of NIs accounted for by NP are highly comparable in the European and Canadian studies. An incidence study in a single Scandinavian mixed medical and surgical ICU in 2002 found that VAP and other nosocomial lower respiratory tract infections accounted for 53.8% of ICU-acquired NIs, with 23.9% of patients who had been in the ICU for at least 48 hours developing a NI.

Our higher overall critical care NI rate could be related to two factors. In the European study, there is no indication that patients in the ICU for less than 48 hours were excluded. If this were the case, that study would have included patients who, by definition, are not at risk of NI, thereby incorrectly deflating the infection risk. In contrast, our study explicitly included only patients who had been in a critical care unit for at least 48 hours. The other factor to consider when comparing the Canadian point prevalence study results with incidence studies is that prevalence rates tend to overestimate risk in comparison to incidence rates.
In terms of non-critical care patients, the only prevalence study found in the literature review was one conducted in 72 German hospitals in 1994. Comparing rates, our prevalence was somewhat higher (1.8% vs. 0.51% in medical patients and 1.9% vs. 0.26% in surgical patients). However, the German study included all patients, regardless of duration of hospitalization, which could have resulted in a factitiously low prevalence rate.

Overall, comparing results from the Canadian point prevalence survey with these other studies suggests that our hospitals have a similar experience in terms of NP rates.

6.1.2 Characteristics of the Study Population

A number of studies have described the characteristics of patients who develop NP and identified risk factors for its occurrence. Findings have been summarized in several review articles. The results in the various publications have sometimes been inconsistent, no doubt reflecting the patient populations and specific potential risk factors examined, variable definitions and diagnostic criteria for NP, and different sample sizes and analytical methods.

Table 2 summarizes the various factors that have been reported as representing independent risks for acquiring NP. Several themes emerge. Some risk factors for NP that have been identified are patient demographic factors that cannot be modified, such as male gender, increasing age, and advanced severity of illness. Certain underlying medical or surgical conditions and their treatments, which may or may not be modifiable, may also increase the risk for NP. These include neurologic conditions, impaired airway reflexes, surgery, chronic lung disease, ARDS, and use of gastric-pH altering agents. By far the most consistently reported risk factors, however, are intubation/mechanical ventilation and reintubation. While the prior receipt of antimicrobials has been identified as a risk factor for NP, other studies have found it to have a protective effect.

There was a disproportionate number of men (68.4%) compared to women (31.6%) in this retrospective cohort study of patients with NP. Although the study was not designed to identify risks for NP, this observation suggests that men are at higher risk, a phenomenon that has been observed previously. The average ages for men and women in this study were similar (64±15.6 years vs. 65±17 years).
The characteristics of our cohort reflect what one would associate with a generally sicker hospitalized population of patients. They tended to have a number of underlying co-morbidities (mean 3± 1.6) and the majority (70.2%) had an ultimately or rapidly fatal condition on admission. Where smoking information was available, 80.6% were current or ex-smokers. This is somewhat higher than a 2005 Government of Canada survey that found that 68% of respondents to the Canadian Community Health Survey (n=65,000) who were aged ≥ 55 years self-identified as a smoker or former smoker (http://www4.hrsdc.gc.ca/3ndic.1t.4r@-eng.jsp?iid=12; accessed December 12, 2010), and likely reflects that these individuals are at higher risk for a number of chronic medical conditions, which in all likelihood also increase their risk of developing NP. Almost one-third (30.7%) were immune suppressed as a consequence of medical therapy, almost half (44.7%) had been ventilated during their admission, and just over half (51.8%) had spent some time in the ICU. The average number of days ventilated and in the ICU prior to the onset of NP was approximately 11 days.

6.1.3 Pneumonia factors

ICU-acquired NP and VAP constituted a considerable proportion of the NI cohort, representing 36.8% and 35.1% of NP cases. However, almost two-thirds of NP cases were not associated with mechanical ventilation. Thus, while ventilated patients may be at the greatest risk for NP, from an overall perspective, non-ventilator associated NP may pose as great a burden to the health care system as VAP, and its occurrence and prevention warrant further study.

NP in our study occurred almost equally among medical and surgical patients. This is in contrast to other studies that suggest that NP is more common on surgical services and the point prevalence study that showed medical patients to be at a lower overall risk of NI, but similar to the findings of Greenaway et al who evaluated NP in patients on general medicine and surgery wards. Given that prevalence studies tend to identify disease in patients with longer hospital stays, and medical patients tend to experience greater lengths of stay than surgical patients, the nature of our sampling population may spuriously explain the higher frequency of NP seen in medical patients. On the other hand, this observation may represent a true risk and point to the need to reconsider the risk to medical patients of acquiring a NP.
A respiratory specimen was obtained from 64.9% of patients. Given the difficulty in obtaining respiratory tract specimens on patients who are not intubated, it is not unexpected that specimens were not obtained from all patients. A high proportion of patients (67.6%) were on antibiotics when the specimen was taken. Findings from the literature have shown that patients receiving antibiotic therapy at the time of specimen collection are more likely to grow a Gram-negative than a Gram-positive bacterium. It is therefore difficult to know how reliably the culture result reflects the true etiologic agent(s), and whether the microorganisms isolated are pathogens or colonizers that have arisen as a result of the antimicrobials. The microorganisms isolated from patients in this study, and their occurrence with early or late NP, reflects findings in the published literature. There was a preponderance of Gram negative bacteria among the isolates, which were seen primarily in late NP.

A high-risk bacterium (defined as MRSA, *Acinetobacter* sp, or *P. aeruginosa*) was present in 21.6% of patients who had a respiratory tract specimen collected for culture. These patients tended to be older, have a higher Apache score, and have more pre-pneumonia hospital, ventilator, and ICU days. This is in keeping with the many studies showing that MRSA and *P. aeruginosa* are the predominant pathogens in later onset VAP. Similar to these other studies, a large proportion of our patients had received antimicrobials within a month of their pneumonia, which in all likelihood contributed to the presence of more resistant bacteria, the more susceptible bacteria having been eradicated by the earlier course(s) of antimicrobials. It is instructive to note that it took longer to start patients with a high-risk bacterium on appropriate antibiotics, suggesting that clinicians underestimated the occurrence of these microorganisms, were not familiar with factors predictive of their presence, and/or discounted these microorganisms as colonizers and not pathogens for the patient in question. It is also interesting to note that patients from whom a specimen was collected had a delay in the initiation of antimicrobial therapy that appropriately covered the isolated bacteria. While this may have been entirely a definition phenomenon, it may point to a general under-appreciation of the potential presence of high-risk bacteria in patients with NP. This is an important finding for clinicians and one worth emphasizing since these high-risk bacteria and delayed effective treatment are both associated with a poorer prognosis.
Only two patients (1.8%) in this study developed bacteremia secondary to NP. In the literature the occurrence of bacteremia secondary to NP ranges from 0-16.7% of cases. Secondary bacteremia has been identified as a risk factor for death in some studies, but not in others. It remains to be determined whether the presence of bacteremia secondary to NP provides prognostic information and assists in optimizing antimicrobial therapy where respiratory tract specimens have not been obtained or are culture negative.

Less than one-fifth of patients were treated with a short-course (≤ 7 days) of antimicrobials, a strategy supported by the current IDSA treatment guidelines. These guidelines were published after this study was conducted, and so adherence to their recommendations cannot be evaluated. However, our finding of a tendency to use longer courses of antimicrobial therapy for NP suggests that there is substantial opportunity for decreasing antimicrobial use by shortening the course of therapy to that recommended in the IDSA guidelines. It will be interesting whether, in the future, shorter antimicrobial courses for NP become standard practice in Canada.

6.1.4 Nosocomial pneumonia outcomes

The overall 28-day mortality rate in this study was 23.7%. This is similar to the findings of an earlier study in Manitoba in which 25% of patients with NP (the ICU/non-ICU breakdown was not provided) died and considerably lower than the 48.5% mortality reported from a single hospital in Taiwan. This difference could well be accounted for by different patient populations and risk factors. The lower mortality in our study could also be attributed to the methodology. Prevalence surveys may underestimate the death rate because they include both existing and new cases. Survival has already been demonstrated in existing cases. This possibility is underscored by the presence in this cohort of patients with NP onset more than 2 weeks prior to the survey. It is likely that most, if not all, of these 5 patients were actually recovered from their pneumonia despite the persistence of antimicrobial therapy. Most deaths (79.4%) occurred within 28 days of the NP. On the other hand, fewer than half of the deaths (47.1%) occurred within 15 days of the NP. This supports our decision that 28-day survival represents a reasonable endpoint at which to measure outcomes.

The 26% mortality rate for VAP that we found is lower than that generally reported in the literature, which ranges from 25.1-58%.


mortality rate of 18% for non-VAP NP seen in this cohort. While the published reported mortality rates (6.5%-36.5% \cite{28,31,61,67}) for non-ICU NP tend to be lower than those associated with VAP, it is obvious that a considerable range exists, one that overlaps with the mortality from VAP NP. We would hypothesize that similar NP mortality rates in non-VAP and VAP subgroups reflect a situation where patients outside of ICU have almost the same extent and severity of underlying illness as patients in ICU. It may also be that the non-VAP patients were not considered candidates for ICU care, and therefore received less aggressive supportive care for their NP. This hypothesis is supported by the finding that ICU care was associated with improved survival on univariable analysis, and on multivariable analysis where infection with high-risk bacteria was not included as an independent variable. This study did not collect information on resuscitation status. While the most likely reason for our inability to find a mortality difference between VAP and non-VAP in this study is insufficient power (less than 50% with the mortality rates observed), it may be that there are no mortality differences between ICU and non-ICU NP, and that NP in the non-ICU setting warrants further attention.

Even though the mortality rate in this study might be considered relatively low compared to that reported in the literature, the average length of hospital stay was long (mean of 59 days), similar to other studies’ findings \cite{9,22,29,37,56,64}. The majority of the hospital stay (75% for survivors and 50% for non-survivors) was accounted for by post-NP days. This is in keeping with the literature, which generally is in agreement that NP prolongs hospital stay, thereby contributing to the burden of illness \cite{9,22,29,55-57,99}.

### 6.1.5 Predictors of nosocomial pneumonia survival

While a number of patient factors associated with death were identified on univariable analysis, only one of these, the McCabe score, remained significant on multivariable analysis that included high risk bacteria as an independent variable. This is in keeping with studies that have identified a number of different factors that may be associated with a poorer outcome, factors that may not bear out on multivariable analysis or be confirmed from study to study.

A staggering proportion (86.8%) of patients received an antibiotic in the month prior to their pneumonia. In the absence of a control group, we do not know whether our study population received disproportionately more antimicrobial therapy than the general hospitalized patient
population. Neither do we know what the indications for these antibiotics were. What appears to be an excessive use of antibiotics may reflect a group of patients whose underlying illnesses required antibiotic treatment or prophylaxis and put them at risk of NP. Whatever the reason for prior antibiotic use, in addition to increasing the risk of NP with high-risk or other multi-resistant microorganisms, prior antibiotic use has been shown to increase the risk of NP-attributable death. The extent to which antibiotics contribute to this increased mortality risk, independent of other host factors, through a mechanism of facilitating colonization by high-risk microorganisms remains to be investigated. We were unable to identify prior use of antibiotics as a mortality risk factor, no doubt related to their widespread use.

Only 23% of patients in our study received the IDSA recommended empirical antibiotic therapy. In many instances this was related to patients receiving only one agent when two should have been given according to the IDSA guideline. However, failure to receive the recommended empirical agents was not associated with a poorer outcome in our study. This is in keeping with the premise that two active agents are not required to treat most infections, and hence survival is not improved by using two antibacterials when one appropriate agent will do. In our study, a microorganism that was not susceptible to the prescribed antimicrobial was isolated in only 8.8% of cases where that information was available. It appears that most antimicrobials selected on an empirical basis proved to be active against the pathogens isolated.

Delay in initiating appropriate antimicrobial therapy was associated with higher mortality risk on multivariable analysis that included high risk bacteria as an independent variable. On the other hand, in multivariate analysis where observations were not limited to patients where the presence or absence of a high risk bacterium was known, the time to appropriate antimicrobial therapy was no longer a predictor of survival. It is interesting to hypothesize from this observation that early initiation of appropriate therapy is most important in the presence of pathogens that are likely to be associated with a poorer outcome. Other studies have identified the importance of timely initiation of antibiotics in critically ill patients. Luna et al in their study of VAP found that the mortality rate was reduced when the initial empirical antibiotic therapy was active against the microorganisms grown from a BAL sample. These findings were confirmed by Lee et al, who demonstrated that the benefit of appropriate initial empiric therapy held, even when therapy was later modified to ensure appropriate coverage. Furthermore, Zavascki et al found that appropriate therapy improved the likelihood of survival in patients with hospital-acquired
P. aeruginosa pneumonia. Similar findings of poorer prognosis where an inappropriate antimicrobial therapy was initially used, or conversely, an improved outcome where an appropriate initial therapy was administered have been demonstrated by other investigators. Appropriate empirical therapy is a prognostic factor that warrants enhanced recognition. The observation that age and APACHE III score were not predictors of fatal outcome suggests that with appropriate therapy even elderly and acutely, severely ill patients may be cured of NP. There have been recent publications that demonstrate the benefit of pre-printed orders and/or standardized care pathways for patients with sepsis. No doubt patients with NP would benefit from such a strategy given the importance of prompt initiation of appropriate initial antimicrobial therapy.

6.2 Limitations

There are several potential limitations that could cause the results of the study to be influenced through bias, confounding, or chance. The limitation of greatest concern is sample size. It is recommended that the sample size for multiple regression analysis be considerably more (5-10 times more) than the number of variables. Our inability to identify additional mortality risk factors on multivariable analysis is likely related, in part, to the small sample size. The number of variables entered into the regression analyses in this study ranged from 5-11 and the number of observations on which the analyses were performed ranged from 37-54, depending on the variables included. Several of the models tested were of poor or questionable fit, likely due to the small sample size for the number of variables tested. As a result, the relative contributions of the individual components of the McCabe score could not be tested in multivariate analysis. At 114 patients in total, we are likely underpowered to identify small, but clinically significant, differences in factors that predict survival.

Selection bias may have been introduced if participating centres and their patients differ systematically from non-participating centres, by virtue of higher (or lower) NP rates related to site-specific risk factors. We have no reason to believe that this was the case for the CNISP participating hospitals. Additionally, the patients included in this study represented 76% of the entire NP cohort.

Another potential limitation was the nature of the methodology, and hence of the cohort. In a prevalence survey, there is concern that patients who have survived will outnumber those who
have not survived and thereby bias the survival analysis. In our study, almost one third of the patients had their NP onset within 3 days of the survey. However, there were outliers, with 5 patients having the onset of their pneumonia more than 2 weeks before the survey. There were no demographic or outcome differences between patients with prevalent and incident NP, suggesting that this factor did not play a role and that prevalence surveys give an accurate reflection of the impact of NP.

Another potential limitation was the precision of the pneumonia diagnosis and, hence, for our study, including patients who really did not have pneumonia (misclassification bias). The questionable ability to accurately diagnose NP has long been recognized in terms of both surveillance and clinical management. In this study, patients included in the cohort were identified with NP during the course of a single day point prevalence survey. With detailed chart data abstraction, not all of the patients were subsequently verified to meet criteria for the surveillance definition of pneumonia. In the vast majority of instances this was because there was no purulent sputum or appropriate confirmatory diagnostic specimen to accompany an abnormal chest radiograph. It is well recognized that many patients with pneumonia are unable to produce sputum, secondary bacteremia and empyema are uncommon, and the invasive diagnostic techniques required to support a surveillance definition are not routinely performed. This suggests that the surveillance criteria in use at the time of the prevalence survey would misclassify a number of patients with bona fide NP. In our study, the clinical features and outcomes of patients who did not meet all the criteria for diagnosis of NP were similar to those of NP patients who did meet the criteria. Given the lack of a validated gold standard for NP diagnosis and the rigor with which charts of patients suspected to have NP were reviewed, taking into account clinical course and response to antimicrobial therapy, it is felt that all patients included in this case cohort study had similar likelihood of NP. As noted in the literature review, similar mortality risk has been attributed to suspected and confirmed VAP, and there may be less misclassification than previously thought26. Alternatively, these 2 subpopulations experience similar mortality related to factors other than the presence of NP. Including patients who did not have NP would have impacted negatively on our ability to identify prognostic indicators for survival.

The potential for observer bias is felt to be relatively low. The exposure had already been determined, well in advance of assessing the outcome or posing the question to be addressed by
this study. The outcome of mortality at 4 weeks is objective. It is possible that collection of information other than exposure and outcome could have been affected by observer bias that could influence data abstractors in the completeness and accuracy of data collection. We employed several strategies to minimize this. The first was that the data abstractors were not aware of specific prognostic factors that were being investigated. Standard definitions were used and the ICPs were trained to complete the questionnaire in the same manner and with the same care for all the study subjects. Comparability of data collection was evaluated by examining the frequency with which observations were made and the degree of completeness and detail of the observations for both survivors and non-survivors.

Confounding was addressed through multivariable analyses. It is possible that some potential confounding factors remain unrecognized, although that is unlikely given the number and variety of published studies.

The validity and reliability of the predictor variables may pose a problem. This relates primarily to the nature of chart reviews, where we are reliant on data that has been obtained and recorded by individuals who have generally not collected the information using standard definitions and interview techniques. However, many previous studies have used the same or similar predictor variables as markers of patient risk. The questionnaires were reviewed in detail by the PI to determine completeness, as a surrogate for accuracy.

Finally, even if the findings from this study are valid, they may not be generalizable to all Canadian hospitals. The majority of CNISP hospitals are large, tertiary care teaching centres, which are not representative of most Canadian hospitals. While these hospitals are not representative of hospitals throughout Canada, it is expected that the patients are representative of patients in secondary and tertiary care hospitals. It is difficult to predict whether rates in other situations might be higher or lower than in this study. However, the message of prompt initiation of appropriate antibiotics is likely to apply generally.
Chapter 7
Summary of Key Findings and Recommendations

7.1 Key findings

- The prevalence of NP, defined as development of pneumonia 48 hours or more post-admission, in adults in hospitals participating in the CNISP appears similar to rates reported in the literature.

- A high proportion of patients with NP have more than 1 co-morbid illness, and have a rapidly or ultimately fatal underlying illness, supporting the notion that these types of patients are at increased risk for a nosocomial infection and death.

- While ICU patients are at higher risk for NP than non-ICU patients, NP in non-ICU patients accounts for the larger proportion of these infections in the hospitalized population.

- Patients infected with a ‘high risk’ microorganism reflected findings in the literature: they tended to be older, have higher APACHE III scores, and longer hospitalization, ICU, and ventilator-days; and experienced delayed administration of effective antimicrobial therapy.

- There was a very high rate (86.8%) of recent prior antimicrobial use in this cohort, a variable that the literature suggests is associated with an increased risk of infection with a ‘risk’ microorganism and higher mortality.

- Delayed initiation of appropriate antimicrobial therapy was associated with poorer outcome in multivariable analysis.

7.2 Recommendations

- NP prevalence rates identified during the 2002 point prevalence survey could be used as benchmark rates for similar Canadian acute care hospitals, limitations inherent to prevalence studies support the need to conduct incidence surveys to allow calculation of incidence density rates, which better reflect risk.
• Further research should reexamine the impact of NP in non-ICU hospital settings, and investigate risk factors for both its occurrence and outcome in this specific setting.

• Physicians should be aware of local trends in nosocomial microorganisms and their susceptibility patterns, as well as in their hospitals and patient populations, and use that knowledge to promptly prescribe appropriate empiric therapy for NP.

• Hospitals should identify mechanisms whereby information regarding contemporaneous microorganisms and their susceptibility patterns is readily available to physicians.

• Strategies and/or interventions that result in the timely administration of appropriate antimicrobial therapy should be investigated.
References


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22. Bercault N, Boulain T. Mortality rate attributable to ventilator-associated nosocomial  
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5.

66.


Appendix I – Patient Information Form

1. Patient identifier: ______ - _________________

**Part 1: Patient demographic information**

2. Date of birth: _____ / _____ / ________  3. Sex: □ Male □ Female
   
   MM         DD       YYYY

4. Date of hospital admission:       ______ / ______ / _____
   
   MM        DD           YY

5. Date of hospital discharge:        ______ / ______ / _____
   
   MM          DD         YY

6. Status at time of discharge:      Alive □    Deceased □

7. Discharged to: □ Home □ Other hospital □ Rehab □ Nursing home □ Unknown □
   
   Other____________________________________

**Part 2: Patient underlying health status**

8. Most responsible admission diagnosis: _________________________________

9. Concurrent conditions ( □ all that apply ):
   
   □ Acute renal failure    □ AIDS
   □ Bone marrow transplant □ Burn
   □ Cirrhosis             □ Community-acquired bacteremia
   □ Community-acquired pneumonia □ Congestive heart failure
   □ COPD                  □ Diabetes mellitus
   □ Dialysis-dependent CRF □ Hepatic failure
   □ HIV                   □ Ischemic heart disease
   □ Leukemia/multiple myeloma □ Lymphoma
   □ Metastatic cancer     □ Non-metastatic cancer
   □ Neuromuscular disease □ Solid organ transplant
   □ Stroke with deficit   □ Trauma
   □ Other (specify): _________________________________

10. McCabe and Jackson classification:

   □ Rapidly fatal    □ Ultimately fatal    □ Nonfatal

11. Smoking status: Current smoker: □ Yes □ No □ Unknown    If not a current smoker:
   
   □ Ex-smoker □ Never smoked □ Unknown
   
   Total number of pack-years smoked: _________________________________
Part 3: Factors related to hospitalization

12. Surgery during admission: □ No □ Yes Date: ____ / ____ / ____

If the patient had surgery, was it elective?: □ No □ Yes

13. Patient received invasive mechanical ventilation for > 48 hours:

□ No □ Yes

Start date 1: ____ / ____ / ____ Stop date 1: ____ / ____ / ____

Start date 2: ____ / ____ / ____ Stop date 2: ____ / ____ / ____

Start date 3: ____ / ____ / ____ Stop date 3: ____ / ____ / ____

Start date 4: ____ / ____ / ____ Stop date 3: ____ / ____ / ____

14. Patient received non-invasive mechanical ventilation for > 12 hours:

□ No □ Yes

Start date 1: ____ / ____ / ____ Stop date 1: ____ / ____ / ____

Start date 2: ____ / ____ / ____ Stop date 2: ____ / ____ / ____

Start date 3: ____ / ____ / ____ Stop date 3: ____ / ____ / ____

Start date 4: ____ / ____ / ____ Stop date 3: ____ / ____ / ____

15. If ventilated, the main indication for mechanical ventilation ( [ only one ]);

□ acute respiratory failure □ adult respiratory distress syndrome
□ exacerbation COPD □ cardiogenic pulmonary edema
□ multiple trauma □ neurologic illness
□ postoperative control

16. Patient had a tracheostomy: □ No □ Yes Date: ____ / ____ / ____

17. Patient was in intensive care: □ No □ Yes

Start date 1: ____ / ____ / ____ Stop date 1: ____ / ____ / ____

Start date 2: ____ / ____ / ____ Stop date 2: ____ / ____ / ____

Start date 3: ____ / ____ / ____ Stop date 3: ____ / ____ / ____

Start date 4: ____ / ____ / ____ Stop date 3: ____ / ____ / ____
18. Patient had a nosocomial infection other than pneumonia:
   □ No □ Yes

   □ Bloodstream infection 1 Date: ____ / ____ / ____
       MM  DD  YY
   □ Bloodstream infection 2 Date: ____ / ____ / ____
       MM  DD  YY
   □ Surgical site infection 1 Date: ____ / ____ / ____
       MM  DD  YY
   □ Surgical site infection 2 Date: ____ / ____ / ____
       MM  DD  YY
   □ Urinary tract infection 1 Date: ____ / ____ / ____
       MM  DD  YY
   □ Urinary tract infection 2 Date: ____ / ____ / ____
       MM  DD  YY
   □ C. difficile diarrhea 1 Date: ____ / ____ / ____
       MM  DD  YY
   □ C. difficile diarrhea 2 Date: ____ / ____ / ____
       MM  DD  YY

**Part 4: Medications prior to and during hospitalization:**

19. Corticosteroids: □ No □ Yes

20. Antimicrobials: □ No □ Yes

21. Chemotherapy within the past 45 days: □ No □ Yes

22. Immunosuppressive therapy: □ No □ Yes

**Part 5: Factors related to the nosocomial pneumonia**

23. Patient had nosocomial pneumonia: □ No □ Yes

   Date: ____ / ____ / ____
       MM  DD  YY

   If no, go to part 6

   If yes, proceed with question 24.
24. Diagnostic criteria (all that apply):
   - rales or dullness to percussion on physical exam
   - chest imaging shows new or progressive infiltrate, consolidation, cavitation, or pleural effusion
   - new onset of purulent sputum or change in the character of the sputum
   - organism isolated from blood culture
   - isolation of an etiologic agent from a specimen obtained by transtracheal aspirate, bronchial brushing, or biopsy
   - isolation of virus from or detection of viral antigen from respiratory secretions
   - diagnostic single antibody titre (IgM) or fourfold increase in paired sera(IgG) for a respiratory pathogen
   - histopathologic evidence of pneumonia

25. Chest imaging findings: number of lobes involved ____________

26. Service where the pneumonia was acquired (only one):
   - Medicine
   - Surgery
   - Intensive care unit
   - Coronary care unit

27. Was this a ventilator-acquired pneumonia?  No  Yes

28. There was a secondary bacteremia related to the pneumonia:
   - No
   - Yes

29. A respiratory tract specimen was collected:  No  Yes
   If yes, date ___ / ___ / ___
   MM  DD  YY

30. Was the patient on systemic antibacterials ≥ 24 hours when the specimen was obtained?  No  Yes

31. Source of respiratory tract specimen:
   - sputum
   - lung biopsy
   - transtracheal aspirate
   - pleural fluid
   - ETT or tracheostomy suction
   - Bronchoscopy with protected BAL or brush
   - Bronchoscopy with unprotected BAL or brush

32. Was the specimen cultured quantitatively?  Yes  No
### 33. Pneumonia and secondary bacteremia organisms:

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<th>Antimicrobial</th>
<th>Pneumonia organism 1</th>
<th>Pneumonia organism 2</th>
<th>Pneumonia organism 3</th>
<th>Secondary bacteremia organism 1</th>
<th>Secondary bacteremia organism 2</th>
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<td>tetracycline</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ticar/clav</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug</td>
<td>Route</td>
<td>Dose</td>
<td>Start</td>
<td>Stop</td>
<td></td>
</tr>
<tr>
<td>----------</td>
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<td></td>
<td></td>
<td>MM DD YY</td>
<td>MM DD YY</td>
<td></td>
</tr>
</tbody>
</table>

34. Empiric antimicrobial(s):

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route</th>
<th>Dose</th>
<th>Start</th>
<th>Stop</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>MM DD YY</td>
<td>MM DD YY</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route</th>
<th>Dose</th>
<th>Start</th>
<th>Stop</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>MM DD YY</td>
<td>MM DD YY</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route</th>
<th>Dose</th>
<th>Start</th>
<th>Stop</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>MM DD YY</td>
<td>MM DD YY</td>
</tr>
</tbody>
</table>

35. Definitive antimicrobial(s):

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route</th>
<th>Dose</th>
<th>Start</th>
<th>Stop</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>MM DD YY</td>
<td>MM DD YY</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route</th>
<th>Dose</th>
<th>Start</th>
<th>Stop</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>MM DD YY</td>
<td>MM DD YY</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route</th>
<th>Dose</th>
<th>Start</th>
<th>Stop</th>
</tr>
</thead>
<tbody>
<tr>
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<td></td>
<td>MM DD YY</td>
<td>MM DD YY</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route</th>
<th>Dose</th>
<th>Start</th>
<th>Stop</th>
</tr>
</thead>
<tbody>
<tr>
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<td></td>
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<td>MM DD YY</td>
<td>MM DD YY</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route</th>
<th>Dose</th>
<th>Start</th>
<th>Stop</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>MM DD YY</td>
<td>MM DD YY</td>
</tr>
</tbody>
</table>
### Part 6. Vital signs and laboratory values

36.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>On admission</th>
<th>72 hours prior</th>
<th>At onset</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>lowest</td>
<td>highest</td>
<td>lowest</td>
</tr>
<tr>
<td>respiratory rate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pulse</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean BP (if available)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>temperature, °C</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>urine output, cc/day</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( F_1O_2 )</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( p_aO_2 )</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( p_aCO_2 )</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>total WBC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hematocrit</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Na⁺</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>glucose</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BUN</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>creatinine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>albumin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>total bilirubin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eyes open spontaneously or to verbal or painful stimuli</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Motor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obeys verbal command</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Localizes pain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flexion withdrawal or decorticate rigidity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decerebrate rigidity or no response</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verbal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oriented converses</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Confused conversation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inappropriate words or incomprehensible sounds</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No response</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient sedated/paralyzed</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Put comments re: section 36 on back of page.
37. Today’s date: ____ (MM) / ____ (DD)

38. Data abstractor: ________________
Appendix II - Definitions

- **Adequate antimicrobial therapy** – each organism isolated is susceptible to at least one of the antimicrobials that the patient is started on (2 for *P. aeruginosa*) at the time the pneumonia is diagnosed by the physician and the timing, route, dosage, and duration are considered adequate

- **APACHE III score** – a score quantitating degree of acute and chronic illness

- **Bronchoscopy with a protected specimen brush (PSB) or bronchoalveolar lavage (PBAL)** – a bronchoscopic procedure to collect respiratory specimens uncontaminated by upper airway secretions

- **High risk organisms** – *P. aeruginosa, Acinetobacter sp., Aspergillus sp.*, methicillin-resistant *S. aureus*

- **Immunosuppression** – receiving corticosteroids as above, cancer chemotherapy or other immunosuppressive therapy within 45 days of the diagnosis of chemotherapy, HIV, granulocytes < 1000/mm³, hematologic malignancy, solid organ or bone marrow transplant

- **McCabe and Jackson categories** – rapidly fatal (death anticipated during hospitalization), ultimately fatal (death anticipated within 5 years), nonfatal as determined at the time of hospitalization

- **Multiorgan failure** – dysfunction of > 2 organ systems as defined by:
  - **renal**: a twofold increase in baseline Cr or absolute increase by 176.8μmol/L
  - **hepatic**: rise in total bilirubin to > 34.2 μmol/L
  - **pulmonary**: requiring mechanical ventilation or PaO₂ < 60 while receiving FiO₂ ≥ 50% or the use of 10 cm PEEP
  - **bone marrow**: DIC, WBC < 1000/mm³, or platelets < 75,000/L
  - **neurologic**: new focal deficit or new generalized process (eg. coma or seizures)
  - **cardiac**: acute MI, cardiac arrest or new onset CHF

- **Neutropenia** – granulocytes < 1000/mm³

- **Nosocomial pneumonia** – at least 48 hours after admission the onset of: A) rales or dullness to percussion on physical exam and at least one of a) new onset purulent sputum or change in the character of the sputum, b) organism isolated from blood culture, c) isolation of an etiologic agent from a specimen obtained by transtracheal aspirate, bronchial brushing, or biopsy OR B) chest imaging shows new or progressive infiltrate, consolidation, cavitation, or pleural effusion and at least one of: a) new onset of purulent sputum or change in the character of sputum, b) organism isolated from blood culture, c) isolation of an etiologic agent from a specimen obtained by transtracheal aspirate, bronchial brushing, or biopsy, d) isolation of virus from or detection of viral antigen in respiratory secretions, e) diagnostic single antibody titer (IgM) or fourfold increase in paired sera (IgG) for a pathogen, f) histologic evidence of pneumonia

- **Pneumonia service** – the service the patient was on when the pneumonia was acquired

- **Postsurgical** – patients after elective or emergency surgery or admitted because of severe postoperative complications

- **Prior antimicrobial therapy** – intravenous or oral administration of at least one antimicrobial for > 24 hours during any portion of the hospitalization or within two weeks prior to hospital admission
- **Shock** – systolic blood pressure < 80 mm Hg or requirement for vasopressors to maintain BP > 80 mm Hg for > 4 hours
- **Trauma** – category for patient even if surgery performed during the admission (eg. hip fracture, MVA)
Appendix III – Patient Information Form Instructions

1. The patient identifier is the number given to the patient for the point prevalence survey in February 2002. It consists of the CHEC number and the patient unique identifier (eg. 15A-0000000).

2. The patient’s date of birth as identified on the admission sheet.

3. The patient’s biological sex.

4. The date of the hospital admission for which the patient was part of the point prevalence survey.

5. The date of the hospital discharge for which the patient was part of the prevalence survey. If the patient is still in hospital from that admission, leave blank.

6. Was the patient dead or alive at the time of discharge? If the patient is still in hospital, check alive.

7. Indicate where the patient was discharged to.

8. Indicate the main medical or surgical diagnosis for which the patient was hospitalized as written in the admission history.

9. Indicate all the chronic medical and surgical conditions that the patient had on or during the admission, even if they were only diagnosed during that admission. Include the admission diagnosis given in question 8.
   a. Acute renal failure: the patient has been identified by a physician as having acute renal failure. Renal failure is defined as a twofold increase in baseline creatinine or absolute increase by 176.8μmol/L. It must have been present prior to and at the onset of the nosocomial pneumonia; the patient cannot have chronic renal failure.
b. AIDS: the patient is identified as having an AIDS defining diagnosis

c. Bone marrow transplant: the patient has had a bone marrow transplant for any indication prior to the onset of the pneumonia

d. Burn: the patient has a burn as one of the admission diagnoses

e. Cirrhosis: the patient has a diagnosis of cirrhosis, with or without hepatic failure, from any etiology (eg. hepatitis C, hepatitis B, alcohol, primary biliary cirrhosis, etc)

f. Community-acquired bacteremia: the patient is diagnosed with and treated for a community-acquired bloodstream infection on admission

g. Community-acquired pneumonia: the patient is diagnosed with and treated for a community-acquired pneumonia on admission

h. Congestive heart failure: the patient has chronic congestive heart failure from any cause

i. COPD: the patient is noted to have chronic bronchitis and/or emphysema as recorded in the chart; does not include asthma; does not require confirmation by pulmonary function tests

j. Diabetes mellitus: the patient has diabetes requiring treatment with oral medications and/or insulin; does not include diabetes controlled with diet alone

k. Dialysis-dependent renal failure: the patient has chronic renal failure requiring either hemodialysis or peritoneal dialysis; does not include acute renal failure

l. Hepatic failure: the patient has a diagnosis of hepatic failure (eg. hepatic coma, encephalopathy or coagulopathy) with or without cirrhosis, from any etiology; if it is diagnosed during the hospitalization its manifestations must have been present before the onset of the pneumonia

m. HIV: the patient is HIV infected with/without AIDS

n. Ischemic heart disease: the patient has stable or unstable angina, previous or current myocardial infarction, coronary insufficiency, or is otherwise identified as having ischemic heart disease

o. Leukemia/multiple myeloma: does not include leukemia or myeloma considered to be cured (eg. by bone marrow transplant or curative chemotherapy in the past)

p. Lymphoma: does not included lymphoma considered to be cured (eg. by bone marrow transplant or curative chemotherapy in the past)
q. Metastatic cancer: the patient has documented metastatic cancer
r. Non-metastatic cancer: the patient has cancer within 3 months of the point prevalence survey but no documentation of cancer metastases; exclude non-melanoma skin cancer
s. Neuromuscular disease: the patient has a chronic neurological disease such as myasthenia gravis, amyotrophic lateral sclerosis, supranuclear bulbar palsy, Parkinson’s disease, etc, with associated nerve and/or muscle
t. Solid organ transplant: the patient has had a heart, heart-lung, kidney, liver, or pancreas transplant prior to the pneumonia
u. Stroke with deficit: the patient has been left with residual neurologic deficit from a stroke which must have occurred prior to the nosocomial pneumonia
v. Trauma: the patient has had trauma as one of the diagnoses whether or not surgery is required (eg. MVA, fractured hip
w. Other: specify other conditions that the patient had on admission or chronic conditions the patient had which were first diagnosed on admission

10. At the time of admission, based on the patient’s admission diagnosis and concurrent diagnoses, the patient’s death is anticipated during the admission (rapidly fatal) or within 5 years (ultimately fatal) or is not anticipated (nonfatal).

11. The patient has been smoking within 6 weeks of admission (current), stopped smoking at least 6 weeks ago (ex-smoker), has never smoked, or status is unknown. Pack years = number of packs smoked/day x number years smoked.

12. Includes any surgery (except tracheostomy) involving an incision and requiring general or regional anaesthesia during the admission; does not include surgery under local. For a patient with nosocomial pneumonia, the surgery must have occurred prior to the pneumonia. If the nosocomial pneumonia patient has had more than one surgical procedure during the hospitalization, give the date for the procedure closest in time to the pneumonia. If the non-pneumonia patient has had more than one surgical procedure, give the date of the first surgical procedure.
13. Invasive mechanical ventilation includes ventilation with an endotracheal tube (nasotracheal or orotracheal) or tracheostomy. For the nosocomial pneumonia patient, the invasive mechanical ventilation must have been in use prior to the diagnosis of pneumonia. If the invasive mechanical ventilation is ongoing at the time of onset of the nosocomial pneumonia, the stop date is not required. Start and stop dates are required for invasive mechanical ventilations occurring prior to but not ongoing at the time of the onset of the pneumonia. This question does not include mechanical ventilation given for anaesthesia.

14. Non-invasive mechanical ventilation involves ventilation by face-mask (there is no endotracheal tube or tracheostomy). For the nosocomial pneumonia patient, the non-invasive mechanical ventilation must have been in use prior to the diagnosis of pneumonia. If the non-invasive mechanical ventilation is ongoing at the time of onset of the nosocomial pneumonia, the stop date is not required. Start and stop dates are required for non-invasive mechanical ventilations occurring prior to but not ongoing at the time of the onset of the pneumonia.

15. Choose the major indication for initiating the invasive or non-invasive mechanical ventilation.

16. For the nosocomial pneumonia patient, the tracheostomy must be present prior to the pneumonia. Give the date that the tracheostomy was done, if done during this hospitalization.

17. The patient was admitted to an intensive care unit at any time during the admission and, for the nosocomial pneumonia patient, prior to the pneumonia. If the patient was still in the ICU at the onset of the pneumonia, the stop date is not required.

18. The patient had a nosocomial infection(s) other than nosocomial
pneumonia. For the nosocomial pneumonia patient, the infection(s) must have been diagnosed prior to the pneumonia. This does not include bacteremia secondary to the nosocomial pneumonia (this is question 28). Only symptomatic UTIs are included.

19. Prior to or during the hospital admission the patient received a systemic corticosteroid at a dose equivalent to prednisone $\geq 20$ mg/day for $\geq 2$ weeks or $\geq 30$ mg/day for $\geq 1$ week. Does not include topical steroids. Dose equivalencies are:

<table>
<thead>
<tr>
<th>Steroid</th>
<th>Equivalent dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortisone</td>
<td>25 mg.</td>
</tr>
<tr>
<td>Hydrocortisone</td>
<td>20 mg.</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>4 mg.</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>5 mg.</td>
</tr>
<tr>
<td>Prednisone</td>
<td>5 mg.</td>
</tr>
<tr>
<td>Triamcinolone</td>
<td>4 mg.</td>
</tr>
<tr>
<td>Betamethasone</td>
<td>0.6 mg.</td>
</tr>
<tr>
<td>Dexamethasone (Decadron)</td>
<td>0.75 mg.</td>
</tr>
<tr>
<td>Fludnocortisone</td>
<td>10 mg.</td>
</tr>
</tbody>
</table>

20. Within two weeks of or at any time during the hospital admission the patient received oral or intravenous antibacterials for more than 24 hours. In addition to the antibiotics listed in question 33, include clarithromycin, azithromycin, and norfloxacin.

21. The patient received oral or intravenous anticancer chemotherapy as an inpatient or outpatient within 45 days of admission to hospital.

22. The patient was on immunosuppressive therapy within 45 days of admission to hospital. Immunosuppressive therapies include azathioprine, methotrexate, cyclosporine, tacrolimus, sirolimus, cyclophosphamide, antithymocyte/antilymphocyte globulin.

23. The patient was diagnosed as having nosocomial pneumonia during the point prevalence survey in February 2002. Give the date of onset as recorded on the CHEC point prevalence survey.
24. Indicate all the criteria that were used to diagnose the nosocomial pneumonia. These are the criteria used for the diagnosis of nosocomial pneumonia during the point prevalence survey.

25. Indicate the number of lobes involved with the pneumonia as reported by the radiologist on chest imaging at the time the pneumonia is diagnosed. The number of lobes involved is 1-5. Chest Xray or CT scan may be used. If the two differ, use the results from the CT scan.

26. Indicate the service that the patient was on when the pneumonia was acquired. This may not be the service that the patient was on at the time the pneumonia was diagnosed or at the time of the prevalence survey. Generally, the ward the patient was on ~ 48 hours prior to the onset of the pneumonia is the one where it was acquired. Medicine includes all medical specialties (including bone marrow transplant, dialysis, etc.) and surgery includes all surgical specialties (including orthopedics, neurosurgery, etc.), urology, gynecology, and oromaxillofacial surgery provided the patient is not in an intensive or coronary care unit. Medicine and surgery refer to general and intermediate care units. Intensive care unit includes cardiovascular, medical, surgical and mixed medical/surgical intensive care units. Coronary care unit includes only coronary care (not cardiovascular intensive care).

27. The patient has received mechanical ventilation for at least 48 hours prior to the onset of the pneumonia and has received mechanical ventilation within 48 hours of the onset of nosocomial pneumonia.

28. The patient has bacteremia secondary to the nosocomial pneumonia. There must be no evidence that the bacteremia is secondary to another nosocomial infection.

29. Indicate whether a respiratory tract specimen was collected. To be included, the specimen must have been collected on the day of or within 48 hours prior to the onset of the pneumonia. Do not include specimens included after the diagnosis is made.
30. Indicate whether the patient was on oral or IV antibacterials for ≥ 24 hours at the time the specimen was collected. Question 33 has a detailed list of antibacterials. Also included as antibacterials are azithromycin, clarithromycin, and norfloxacin.

31. Indicate the type of respiratory tract specimen that the organisms listed in question 27 were isolated from. To be considered a PBAL or PSB (protected BAL or specimen brush), this must clearly be documented in the chart. The documentation may be found in the progress note, procedure sheet, or microbiology lab requisition. Protected (double catheter) specimens are meant to be cultured quantitatively. A laboratory specimen reported quantitatively (example: 3x10^4 colonies /ml of ….) is likely a protected BAL or brush.

32. If a specimen was cultured quantitatively, the report will be given as # cfu/ml. Semiquantitative measures (heavy, light, etc.) do not represent quantitative cultures.

33. Write the name of the organism (bacteria, virus, fungus) isolated from the respiratory tract or blood (only for bacteremia secondary to pneumonia) or identified by serology. Indicate the growth (eg: heavy, light, etc.) when available on the report. For identified bacteria, indicate ‘S’ (susceptible) or ‘R’ (resistant) for all susceptibility results reported by the laboratory. A missing value means that the antimicrobial was not tested. TMP/SMX=trimethoprim/sulfamethoxazole. For this table,
amoxicillin=ampicillin
oxacillin=nafcillin=methicillin=cloxacillin
penicillinG=penicillinV=penicillin
cephalothin=cefazolin
ceftriaxone=ceftizoxime=cefotaxime

34. Indicate the antimicrobial(s) that the patient was started on to treat the pneumonia before the laboratory results were available. If the patient was already on antimicrobial(s) when the pneumonia was diagnosed and if they were not changed when the pneumonia was diagnosed, these are the empiric antimicrobial(s).
35. Indicate the antimicrobial(s) that the patient was changed to in response to the laboratory results or because the patient failed to respond to empiric therapy. If the patient’s antimicrobials were not changed this question will be unanswered. In general, include only those changes made within the first 2-3 weeks after diagnosis.

36. Give the values for the 24 hour time frame indicated. The 24 hour time frame is midnight to midnight of the date indicated (ie, the calendar day). The day of admission is day 1. If only one result was available for the date, give it. Where the result was not available, leave blank.

   a. respiratory rate: lowest and highest
   b. pulse: lowest and highest
   c. BP: lowest and highest. This is not required if the lowest and highest mean BP are available.
   d. mean BP: when available from the chart. This is usually only available for ICU patients. Give lowest and highest
   e. temperature: lowest and highest
   f. urine output: total cc/24hours. If monitored < 24 hours, cannot be calculated
   g. FIO2: highest
   h. PaO2: lowest
   i. pH: lowest and highest
   j. PaCO2: corresponding value for lowest and highest pH
   k. total WBC: lowest and highest
   l. hematocrit: lowest and highest
   m. Na+: lowest and highest
   n. Glucose: lowest and highest
   o. BUN: highest
   p. creatinine: lowest and highest
   q. albumin: lowest and highest
   r. total bilirubin: highest
   s. Record the worst neurological status for the 24 hours. Use a time when the patient was not heavily sedated and/or paralyzed whenever available. Indicate whether the
patient was heavily sedated and/or paralyzed when the neurological evaluation was done.

For nosocomial pneumonia patients, 72 hours prior is 72 hours before the onset of nosocomial pneumonia. For the non-pneumonia patients, 72 hours prior is 72 hours before the ‘index date’. The ‘index date’ is the hospitalization day that corresponds to the hospitalization day that the case had the onset of nosocomial pneumonia. As an example, if the case patient developed nosocomial pneumonia on day 7 of hospitalization then the index date is day 7 for the nonpneumonia patient and 72 hours prior is day 4. At diagnosis is the date of the onset of the nosocomial pneumonia for the case patient and the corresponding hospitalization day for the nonpneumonia patient.

When a value is blank we are assuming that it is normal (and therefore not ordered). Comment in the space available if you believe that the result might be abnormal but the test was not ordered for a specific reason such as therapy and/or active care had been withdrawn or bloodwork was being ordered only every few days.

37. Today’s date is the date the patient information form was completed.

38. Data abstractor is the name of the person completing the patient information form.
Appendix IV – SAS Codes

*-----------------------------------------------------*

Program Name: PNEUMO_July4 stored in "P\my documents"

Purpose: To analyze nosocomial pneumonia data

Number of additional variables defined,

graphs removed compared to earlier data analyses, and

various regression analyses run.

Lynn Johnston

July 31, 2011

*-----------------------------------------------------*;

* To summarize contents of the database;

   proc contents data=sasuser.pneumo_july4 varnum;

   run;

* To add value labels;

   proc format;

   value sex 0='male' 1='female';

   value Mcabe 1='nonfatal' 2='ultimately fatal' 3='rapidly fatal';

   value smoke 1='never' 2='exsmoker' 3='current' 4='unknown';

   value smoker 0='never smoked/unknown' 1='ever smoked';

   value service 1='medicine' 2='surgery' 3='ICU' 4='CCU';

   value spec 1='sputum' 2='biopsy' 3='ETT' 4='PBAL' 5='BAL'

     6='TTA' 7='pleural fluid' 8='none';

   run;

*-----------------------------------------------------*
value treatdays 1='< 5 days' 2='5-7 days' 3='8-14 days' 4='> 14 days';

value yesno 0='no' 1='yes';

value outcome 0='dead' 1='alive';
un;

* To 1) create new variables LOS, prepnu, postpnu, test incident, smoker, early, short, morbid, earlymort, fatalMcCabe, rapidMcCabe, slowMcCabe and

2) add variable labels;

data sasuser.pneumo_july4a;

set sasuser.pneumo_july4;

LOS=(datepart(DOD)-datepart(DOA))+1;

prepnu=(datepart(PDATE)-datepart(DOA));

postpnu=(datepart(DOD)-datepart(PDATE));

If postpnu LE 15 and status = 0 then earlymort=0;

else earlymort=1;

If conds LE 3 then morbid=0;

else if conds GT 3 then morbid=1;

If service GT 1 then medical=0;

else if service EQ 1 then medical=1;

If spec EQ 8 then test =0;

else if spec NE 8 then test = 1;

If prev GT 3 then incident = 0;

else if prev LE 3 then incident = 1;
If prepnu GT 4 then early = 0;
else if prepnu LE 4 then early = 1;

If smoke = 1 then smoker = 0;
else if 2 LE smoke LE 3 then smoker = 1;

If treatdays GE 3 then short = 0;
else if treatdays LT 3 then short = 1;

If Mcape LT 2 then fatalMcCabe = 0;
else if Mcape GE 2 then fatalMcCabe = 1;

If Mcape LT 3 then rapidmccabel = 0;
else if Mcape EQ 3 then rapidmccabel = 1;

If Mcape LT 2 then rapidmccabe = 0;
else if Mcape EQ 3 then rapidmccabe = 1;

If Mcape LT 2 then slowmccabe = 0;
else if Mcape EQ 2 then slowmccabe = 1;

Format morbid medical smoker surg esurg vent CPAP trach ICU NI steroid antibiotic
chemo immsupp suppress pneumo crit VAP BSI prebiotic
riskbug IDSTreat IDSAdura Orgcover test incident early short fatalMcCabe rapidmccabe
slowmccabe rapidMcCabel yesno.
status mortal earlymort outcome.;

label sex='gender'
status='discharge status'
conds='number of admission comorbid illnesses'
morbid='more than 3 comorbidities'

MCabe='McCabe score on admission'

fatalMcCabe='McCabe score of 2 or 3'

rapidMcCabe='McCabe score of 3 vs 1'

rapidMcCabe1='McCabe score of 3 vs 1+2'

slowMcCabe='McCabe score of 2'

smoke='smoking status on admission'

smoker='ever smoked'

surg='surgery during admission'

vent='ventilated during admission'

CPAP='CPAP during admission'

trach='trach during admission'

ICU='ICU stay during admission'

NI='nosocomial infection other than pneumonia'

steroid='had received steroids'

antibiotic='had received an antibiotic'

chemo='had received chemotherapy'

immsupp='had received an immunosuppressant'

suppress='any immunosuppression'

crit='met nosocomial pneumonia definition'

service='service where pneumonia acquired'

medical='medical patient'

VAP='ventilator-acquired pneumonia'
BSI='secondary bloodstream infection'

spec='type of respiratory specimen'

test='respiratory specimen obtained'

prebiotic='on antibiotic when specimen taken'

riskbug='MRSA, P.aeruginosa,or Acinetobacter isolated'

IDSAtrat='patient received recommended empiric drugs'

IDSAdura='patient received recommended duration of therapy'

Orgcover='antibiotics covered bacteria grown'

Treatdays='duration of pneumonia treatment'

mortal='28 day outcome'

earlymort='outcome at 15 days'

incident='pneumonia onset within 3 days of survey'

early='pneumonia onset within 4 days of admission'

short='treatment less that 8 days'

site='hospital';

Format sex sex. mcabe mcabe. smoke smoke. service service.

spec spec. treatdays treatdays.;

run;

* To summarize contents of the labelled database;

   proc contents data=sasuser.pneumo_july4a varnum;

run;

* To sort the data by gender;

   Proc sort data=sasuser.pneumo_july4a;
by sex;

run;

* To sort the data by mortal;

   proc sort data=sasuser.pneumo_july4a;
   by mortal;
   run;

* To sort the data by status;

   proc sort data=sasuser.pneumo_july4a;
   by status;
   run;

* to generate descriptive statistics for pneumonia study;

   proc univariate data=sasuser.pneumo_july4a normal plot;
   title'Descriptive Statistics - Entire Group';
   var age conds LOS prepnu postpnu vdays icudays apache prev pretreatdays
       RR pulse MBP temp O2 hct WBC Cr alb glu;

   id ID;
   run;

* to generate descriptive statistics by day 28 outcome;

   proc univariate data=sasuser.pneumo_july4a normal plot;
   title'Descriptive Statistics - 28 Day Outcome';
   by mortal;
   var age conds LOS prepnu postpnu vdays icudays apache prev pretreatdays;
   run;
* to generate descriptive statistics by discharge outcome;

```sas
proc univariate data=sasuser.pneumo_july4a normal plot;

Title'Descriptive Statistics - Discharge Outcome';

by status;

var age conds LOS prepnu postpnu vdays icudays apache prev pretreatdays;

run;
```

* to compare age, etc. among various groups;

```sas
proc ttest data=sasuser.pneumo_july4a;

title' continuous variables by discharge status';

class status;

var age conds LOS prepnu postpnu vdays icudays apache prev pretreatdays;

run;
```

* to compare age, etc. among various groups;

```sas
proc ttest data=sasuser.pneumo_july4a;

title' continuous variables by 28 day status';

class mortal;

var age conds LOS prepnu postpnu vdays icudays apache prev pretreatdays;

run;
```

* to compare age, etc. among various groups;

```sas
proc ttest data=sasuser.pneumo_july4a;

title' continuous variables by sex';

class sex;
```
var age conds LOS prepnu postpnu vdays icudays apache prev pretreatdays;

run;

* to compare age, etc. among various groups;

proc ttest data=sasuser.pneumo_july4a;

title 'continuous variables by presence of risk bug';

class riskbug;

var age conds LOS prepnu postpnu vdays icudays apache prev pretreatdays;

run;

* to compare age, etc. among various groups;

proc ttest data=sasuser.pneumo_july4a;

title 'continuous variables by treated according to IDSA criteria';

class IDSAtreat;

var age conds LOS prepnu postpnu vdays icudays apache prev pretreatdays;

run;

* to compare age, etc. among various groups;

proc ttest data=sasuser.pneumo_july4a;

title 'continuous variables by whether pneumonia criteria met';

class crit;

var age conds LOS prepnu postpnu vdays icudays apache prev pretreatdays;

run;

* to compare age, etc. among various groups;

proc ttest data=sasuser.pneumo_july4a;

title 'continuous variables by whether a specimen was sent';
class test;

var age conds LOS prepnu postpnu vdays icudays apache prev pretreatdays;
run;

* to compare age, etc. among various groups;

proc ttest data=sasuser.pneumo_july4a;
title' continuous variables by whether it was an incident pneumonia';
class incident;
var age conds LOS prepnu postpnu vdays icudays apache prev pretreatdays;
run;

* to compare age, etc. among various groups;

proc ttest data=sasuser.pneumo_july4a;
title' continuous variables by presence of early pneumonia';
class early;
var age conds LOS prepnu postpnu vdays icudays apache prev pretreatdays;
run;

* to compare age, etc. among various groups;

proc ttest data=sasuser.pneumo_july4a;
title' continuous variables by presence of medical patient';
class medical;
var age conds LOS prepnu postpnu vdays icudays apache prev pretreatdays;
run;

* to compare age, etc. among various groups;

proc ttest data=sasuser.pneumo_july4a;
title' continuous variables by 15 day status';

class earlymort;

var age conds LOS prepnu postpnu vdays icudays apache prev pretreatdays;

run;

* to compare pretreatment days among surgery vs non-surgery patients;

proc ttest data=sasuser.pneumo_july4a;

  title' pretreatment days by whether surgery patient';

  class surg;

  var pretreatdays;

run;

* to compare pretreatment days among ICU vs non-ICU patients;

proc ttest data=sasuser.pneumo_july4a;

  title' pretreatment days by whether ICU patient';

  class ICU;

  var pretreatdays;

run;

* to compare pretreatment days among fatal and non-fatal McCabe patients;

proc ttest data=sasuser.pneumo_july4a;

  title' pretreatment days by whether fatal or nonfatal McCabe patient';

  class fatalMcCabe;

  var pretreatdays;

run;

* to compare the number of conditions among various groups;
proc npar1way data=sasuser.pneumo_july4a wIlcoxon;
title' comparison of number of conditions by sex';
class sex;
var conds; exact wilcoxon;
run;

* to compare the number of conditions among various groups;
proc npar1way data=sasuser.pneumo_july4a wIlcoxon;
title' comparison of number of conditions by discharge status ';
class status;
var conds; exact wilcoxon;
run;

* to compare the number of conditions among various groups;
proc npar1way data=sasuser.pneumo_july4a wIlcoxon;
title' comparison of number of conditions by 28 day outcome ';
class mortal;
var conds; exact wilcoxon;
run;

* to compare the number of conditions among various groups;
proc npar1way data=sasuser.pneumo_july4a wIlcoxon;
title' comparison of number of conditions by whether pneumonia criteria met ';
class crit;
var conds; exact wilcoxon;
run;

* to compare the number of conditions among various groups;

    proc npar1way data=sasuser.pneumo_july4a wilcoxon;

    title 'comparison of number of conditions by whether pneumonia criteria met';

    class early;

    var conds; exact wilcoxon;

run;

* to compare the number of conditions among various groups;

    proc npar1way data=sasuser.pneumo_july4a wilcoxon;

    title 'comparison of number of conditions by whether pneumonia criteria met';

    class medical;

    var conds; exact wilcoxon;

run;

* to compare the number of conditions among various groups;

    proc npar1way data=sasuser.pneumo_july4a wilcoxon;

    title 'comparison of number of conditions by presence of a risk bug';

    class riskbug;

    var conds; exact wilcoxon;

run;

* to compare the number of conditions among various groups;

    proc npar1way data=sasuser.pneumo_july4a wilcoxon;

    title 'comparison of number of conditions by presence of a risk bug';

    class riskbug;

    var conds; exact wilcoxon;

run;
title' comparison of number of conditions by whether treated according to IDSA guidelines ';

class IDSAtreat;

var conds; exact wilcoxon;

run;

* to compare number of pretreatment days among McCabe classes;

proc npar1way data=sasuser.pneumo_july4a wilcoxon;
title' comparison of pretreatment days among McCabe classes ';
class McCabe;

var pretreatdays; exact wilcoxon;

run;

* to generate frequency counts for categorical variables;

proc freq data=sasuser.pneumo_july4a;
title ' Frequency Counts for Categorical Variables';

Tables sex status mortal earlymort McCabe morbid smoker surg vent CPAP trach ICU NI steroid antibiotic

        chemo suppress immsupp crit service medical VAP early incident BSI test prebiotic riskbug IDSAtreat

        IDSAdura orgcover treatdays short site;

run;

* to determine correlations between age, number of conditions, number of ventilator days,
number of ICU days, and APACHE score;

proc corr data=sasuser.pneumo_july4a pearson spearman nosimple Best=8;
title' Correlations between continuous variables';
**to determine correlations between age, pretreatment days and APACHE score;**

```sas
proc corr data=sasuser.pneumo_july4a pearson spearman nosimple;
  title 'Correlations between age, Apache, and pretreatment days';
  var age apache pretreatdays;
run;
```

* To evaluate partial correlations;

```sas
proc corr data=sasuser.pneumo_july4a nosimple;
  title 'Role of age in correlation between LOS, prepnu, postpnu, vdays, ICUdays, pretreatdays and APACHE';
  var LOS prepnu postpnu vdays ICUdays pretreatdays;
  with APACHE;
  partial age;
run;
```

* to examine whether outcome is affected by number of conditions;

```sas
proc freq data=sasuser.pneumo_july4a;
  title 'chi-square test for trend';
  tables (status mortal)* conds/chisq;
run;
```

* to analyze discharge and 28 day outcomes according to key variables;

```sas
proc freq data=sasuser.pneumo_july4a;
```
tables (sex fatalMcCabe rapidMcCabe slowMcCabe rapidMccabel MCabe morbid smoker surg vent ICU NI steroid antibiotic chemo immsupp incident suppress crit service medical VAP early BSI test riskbug IDSTreat IDSAdura orgcover
treatdays short site)* (status mortal earlymort)/chisq CMH;
run;

* to compare key variables between men and women;

proc freq data=sasuser.pneumo_july4a;
tables (MCabe morbid smoker surg vent ICU NI steroid antibiotic chemo immsupp incident suppress crit service medical VAP early BSI test riskbug IDSTreat IDSAdura orgcover
treatdays short site)* (sex)/chisq CMH;
run;

* to run regression analysis: predictors of 28 day outcome;

proc logistic data=sasuser.pneumo_july4a;
title 'Model 1 McCabe:28 day outcome; p<0.10 excluding riskbug';
model mortal=age sex apache pretreatdays mcabe surg ICU BSI spec service/
   selection=forward
table pprob = (0 to 1 by 0.1)
lackfit
risklimits;
run;

* to run regression analysis: predictors of 28 day outcome;
**proc logistic data=sasuser.pneumo_july4a;**

*title* 'Model 2 McCabe: 28 day outcome; p<0.10 including riskbug;*

  model mortal=age sex apache pretreatdays mcabe
  surg ICU BSI spec service riskbug/

  selection=forward
  ctable pprob = (0 to 1 by 0.1)
  lackfit
  risklimits;

*run;*

* to run regression analysis: predictors of 28 day outcome;*

**proc logistic data=sasuser.pneumo_july4a;**

*title* 'Model 3 McCabe: 28 day outcome; p<0.05 excluding riskbug;*

  model mortal=mcabe surg ICU service pretreatdays/

  selection=forward
  ctable pprob = (0 to 1 by 0.1)
  lackfit
  risklimits;

*run;*

* to run regression analysis: predictors of 28 day outcome;*

**proc logistic data=sasuser.pneumo_july4a;**

*title* 'Model 4 McCabe: 28 day outcome; p<0.05 including riskbug;*

  model mortal=mcabe surg ICU service pretreatdays riskbug/

  selection=forward
ctable pprob = (0 to 1 by 0.1)

lackfit

risklimits;

run;

* to run regression analysis: predictors of 28 day outcome;

proc logistic data=sasuser.pneumo_july4a;

title 'Model 5 McCabe: 28 day outcome; p<0.10 include riskbug/exclude BSI';

model mortal=age sex apache pretreatdays mcabe

surg ICU spec service riskbug/

selection=forward

ctable pprob = (0 to 1 by 0.1)

lackfit

risklimits;

run;

* to run regression analysis: predictors of 28 day outcome;

proc logistic data=sasuser.pneumo_july4a;

title 'Model 6 McCabe: 28 day outcome; p<0.10 include riskbug/exclude BSI,service';

model mortal=age sex apache pretreatdays mcabe

surg ICU spec service riskbug/

selection=forward

ctable pprob = (0 to 1 by 0.1)

lackfit
risklimits;

run;

* to run regression analysis: predictors of 28 day outcome;

proc logistic data=sasuser.pneumo_july4a;

title 'Model 7 McCabe: 28 day outcome; p<0.10 excluding riskbug and BSI';

model mortal=age sex apache pretreatdays mcabe surg ICU spec service/
selection=forward
ctable pprob = (0 to 1 by 0.1)
lackfit
risklimits;

run;

* to run regression analysis: predictors of 28 day outcome;

proc logistic data=sasuser.pneumo_july4a;

title 'Model 8 McCabe: 28 day outcome; with potential interactions';

model mortal=age sex apache pretreatdays mcabe surg ICU spec riskbug age*pretreatdays apache*pretreatdays spec*pretreatdays riskbug*pretreatdays/
selection=forward
ctable pprob = (0 to 1 by 0.1)
lackfit
risklimits;

run;
* to run regression analysis: predictors of 28 day outcome;

```sas
proc logistic data=sasuser.pneumo_july4a;
  title 'Model 1 Rapid: 28 day outcome; p<0.10 excluding riskbug';
  model mortal=age sex apache pretreatdays rapidmccabe surg ICU BSI spec service/
    selection=forward
c    ctable pprob = (0 to 1 by 0.1)
lackfit
  risklimits;
run;
```

* to run regression analysis: predictors of 28 day outcome;

```sas
proc logistic data=sasuser.pneumo_july4a;
  title 'Model 2 Rapid: 28 day outcome; p<0.10 including riskbug';
  model mortal=age sex apache pretreatdays rapidmccabe surg ICU BSI spec service riskbug/
    selection=forward
c    ctable pprob = (0 to 1 by 0.1)
lackfit
  risklimits;
run;
```

* to run regression analysis: predictors of 28 day outcome;

```sas
proc logistic data=sasuser.pneumo_july4a;
  title 'Model 3 Rapid: 28 day outcome; p<0.05 excluding riskbug';
```
model mortal=rapidmccabe surg ICU service pretreatdays/
  selection=forward
  ctable pprob = (0 to 1 by 0.1)
  lackfit
  risklimits;
run;

* to run regression analysis: predictors of 28 day outcome;

proc logistic data=sasuser.pneumo_july4a;
title 'Model 4 Rapid: 28 day outcome; p<0.05 including riskbug';
  model mortal=rapidmccabe surg ICU service pretreatdays riskbug/
    selection=forward
    ctable pprob = (0 to 1 by 0.1)
    lackfit
    risklimits;
run;

* to run regression analysis: predictors of 28 day outcome;

proc logistic data=sasuser.pneumo_july4a;
title 'Model 5 Rapid: 28 day outcome; p<0.10 include riskbug/exclude BSI';
  model mortal=age sex apache pretreatdays rapidmccabe surg ICU spec service riskbug/
    selection=forward
    ctable pprob = (0 to 1 by 0.1)
lackfit

risklimits;

run;

* to run regression analysis: predictors of 28 day outcome;

proc logistic data=sasuser.pneumo_july4a;

title 'Model 6 Rapid: 28 day outcome; p<0.10 include riskbug/exclude BSI, service';

   model mortal=age sex apache pretreatdays rapidmccabe surg ICU spec riskbug/

   selection=forward

   ctable pprob = (0 to 1 by 0.1)

   lackfit

   risklimits;

run;

* to run regression analysis: predictors of 28 day outcome;

proc logistic data=sasuser.pneumo_july4a;

title 'Model 7 Rapid: 28 day outcome; p<0.10 excluding riskbug and BSI';

   model mortal=age sex apache pretreatdays rapidmccabe surg ICU spec service/

   selection=forward

   ctable pprob = (0 to 1 by 0.1)

   lackfit

   risklimits;
run;
* to run regression analysis: predictors of 28 day outcome;

proc logistic data=sasuser.pneumo_july4a;
title'Model 8 Rapid: 28 day outcome; with potential interactions';
   model mortal=age sex apache pretreatdays rapidmccabe surg ICU spec riskbug age*pretreatdays apache*pretreatdays spec*pretreatdays riskbug*pretreatdays/
           selection=forward
ctable pprob = (0 to 1 by 0.1)
lackfit
risklimits;
run;

* to run regression analysis: predictors of 28 day outcome;

proc logistic data=sasuser.pneumo_july4a;
title'Model 1 Slow: 28 day outcome; p<0.10 excluding riskbug';
   model mortal=age sex apache pretreatdays slowmccabe surg ICU BSI spec service/
           selection=forward
ctable pprob = (0 to 1 by 0.1)
lackfit
risklimits;
run;

* to run regression analysis: predictors of 28 day outcome;
proc logistic data=sasuser.pneumo_july4a;

   title 'Model 2 Slow: 28 day outcome; p<0.10 including riskbug';

   model mortal=age sex apache pretreatdays slowmccabe surg ICU BSI spec service riskbug/
       selection=forward
       ctable pprob = (0 to 1 by 0.1)
       lackfit
       risklimits;

run;

* to run regression analysis: predictors of 28 day outcome;

proc logistic data=sasuser.pneumo_july4a;

   title 'Model 3 Slow: 28 day outcome; p<0.05 excluding riskbug';

   model mortal=slowmccabe surg ICU service pretreatdays/
       selection=forward
       ctable pprob = (0 to 1 by 0.1)
       lackfit
       risklimits;

run;

* to run regression analysis: predictors of 28 day outcome;

proc logistic data=sasuser.pneumo_july4a;

   title 'Model 4 Slow: 28 day outcome; p<0.05 including riskbug';

   model mortal=slowmccabe surg ICU service pretreatdays riskbug/
       selection=forward
* to run regression analysis: predictors of 28 day outcome;

```sas
proc logistic data=sasuser.pneumo_july4a;
title 'Model 5 Slow: 28 day; p<0.10 include riskbug/exclude BSI';
model mortal=age sex apache pretreatdays slowmccabe surg ICU spec service riskbug/
   selection=forward
   ctable pprob = (0 to 1 by 0.1)
lackfit
risklimits;
run;
```

* to run regression analysis: predictors of 28 day outcome;

```sas
proc logistic data=sasuser.pneumo_july4a;
title 'Model 6 Slow: 28 day outcome; p<0.10 include riskbug/exclude BSI,service';
model mortal=age sex apache pretreatdays slowmccabe surg ICU spec service riskbug/
   selection=forward
   ctable pprob = (0 to 1 by 0.1)
lackfit
risklimits;
run;
```
* to run regression analysis: predictors of 28 day outcome;

**proc logistic** data=sasuser.pneumo_july4a;

title'Model 7 Slow:28 day outcome; p<0.10 excluding riskbug and BSI';

   **model** mortal=age sex apache pretreatdays slowmcabe

   surg ICU spec service/

   selection=forward

   ctable pprob = (0 to 1 by 0.1)

   lackfit

   risklimits;

run;

* to run regression analysis: predictors of 28 day outcome;

**proc logistic** data=sasuser.pneumo_july4a;

title'Model 8 Slow:28 day outcome; with potential interactions';

   **model** mortal=age sex apache pretreatdays slowmccabe

   surg ICU spec riskbug age*pretreatdays apache*pretreatdays

   spec*pretreatdays riskbug*pretreatdays/

   selection=forward

   ctable pprob = (0 to 1 by 0.1)

   lackfit

   risklimits;

run;
* to run regression analysis: predictors of 28 day outcome;

    proc logistic data=sasuser.pneumo_july4a;
    title 'Model 1 Rapid1:28 day outcome; p<0.10 excluding riskbug';
    model mortal=age sex apache pretreatdays rapidmccabe1
        surg ICU BSI spec service/
            selection=forward
            ctable pprob = (0 to 1 by 0.1)
            lackfit
            risklimits;
    run;

* to run regression analysis: predictors of 28 day outcome;

    proc logistic data=sasuser.pneumo_july4a;
    title 'Model 2 Rapid1:28 day outcome; p<0.10 including riskbug';
    model mortal=age sex apache pretreatdays rapidmccabe1
        surg ICU BSI spec service riskbug/
            selection=forward
            ctable pprob = (0 to 1 by 0.1)
            lackfit
            risklimits;
    run;

* to run regression analysis: predictors of 28 day outcome;

    proc logistic data=sasuser.pneumo_july4a;
    title 'Model 3 Rapid1:28 day outcome; p<0.05 excluding riskbug';
model mortal=rapidmccabel surg ICU service pretreatdays/

    selection=forward

catable pprob = (0 to 1 by 0.1)

lackfit

risklimits;

run;

* to run regression analysis: predictors of 28 day outcome;

proc logistic data=sasuser.pneumo_july4a;

title 'Model 4 Rapid1: 28 day outcome; p<0.05 including riskbug';

    model mortal=rapidmccabel surg ICU service pretreatdays riskbug/

        selection=forward

catable pprob = (0 to 1 by 0.1)

lackfit

risklimits;

run;

* to run regression analysis: predictors of 28 day outcome;

proc logistic data=sasuser.pneumo_july4a;

title 'Model 5 Rapid1: 28 day outcome; p<0.10 include riskbug/exclude BSI';

    model mortal=age sex apache pretreatdays rapidmccabel surg ICU spec service riskbug/

        selection=forward

catable pprob = (0 to 1 by 0.1)
* to run regression analysis: predictors of 28 day outcome;

```sas
proc logistic data=sasuser.pneumo_july4a;
title 'Model 6 Rapid1:28 day outcome; p<0.10 include riskbug/exclude BSI,service';
model mortal=age sex apache pretreatdays rapidmccabe1 surg ICU spec riskbug/
            selection=forward
ctable pprob = (0 to 1 by 0.1)
lackfit
risklimits;
run;
```

* to run regression analysis: predictors of 28 day outcome;

```sas
proc logistic data=sasuser.pneumo_july4a;
title 'Model 7 Rapid1:28 day outcome; p<0.10 excluding riskbug and BSI';
model mortal=age sex apache pretreatdays rapidmccabe1 surg ICU spec service/
            selection=forward
ctable pprob = (0 to 1 by 0.1)
lackfit
risklimits;
run;
```
run;

* to run regression analysis: predictors of 28 day outcome;

proc logistic data=sasuser.pneumo_july4a;

title'Model 8 Rapid1: 28 day outcome; with potential interactions';

   model mortal=age sex apache pretreatdays rapidmccabe1

   surg ICU spec riskbug age*pretreatdays apache*pretreatdays
spec*pretreatdays riskbug*pretreatdays/

        selection=forward

        ctable pprob = (0 to 1 by 0.1)

        lackfit

        risklimits;

run;

* to run regression analysis: predictors of 28 day outcome;

proc logistic data=sasuser.pneumo_july4a;

title'Model 1 Fatal: 28 day outcome; p<0.10 excluding riskbug';

model mortal=age sex apache pretreatdays fatalmccabe

   surg ICU BSI spec service/

        selection=forward

        ctable pprob = (0 to 1 by 0.1)

        lackfit

        risklimits;

run;

* to run regression analysis: predictors of 28 day outcome;
proc logistic data=sasuser.pneumo_july4a;

  title 'Model 2 Fatal: 28 day outcome; p<0.10 including riskbug';

    model mortal=age sex apache pretreatdays fatalmccabe surg ICU BSI spec service riskbug/
          selection=forward
          ctable pprob = (0 to 1 by 0.1)
          lackfit
          risklimits;

run;

* to run regression analysis: predictors of 28 day outcome;

proc logistic data=sasuser.pneumo_july4a;

  title 'Model 3 Fatal: 28 day outcome; p<0.05 excluding riskbug';

    model mortal=fatalmccabe surg ICU service pretreatdays/
          selection=forward
          ctable pprob = (0 to 1 by 0.1)
          lackfit
          risklimits;

run;

* to run regression analysis: predictors of 28 day outcome;

proc logistic data=sasuser.pneumo_july4a;

  title 'Model 4 Fatal: 28 day outcome; p<0.05 including riskbug';

    model mortal=fatalmccabe surg ICU service pretreatdays riskbug/
* to run regression analysis: predictors of 28 day outcome;

```sas
proc logistic data=sasuser.pneumo_july4a;
  title 'Model 5 Fatal: 28 day outcome; p<0.10 include riskbug/exclude BSI';
  model mortal=age sex apache pretreatdays fatalmccabe surg ICU spec service riskbug/
    selection=forward
    ctable pprob = (0 to 1 by 0.1)
    lackfit
    risklimits;
  run;
```

* to run regression analysis: predictors of 28 day outcome;

```sas
proc logistic data=sasuser.pneumo_july4a;
  title 'Model 6 Fatal: 28 day outcome; p<0.10 include riskbug/exclude BSI,service';
  model mortal=age sex apache pretreatdays fatalmccabe surg ICU spec riskbug/
    selection=forward
    ctable pprob = (0 to 1 by 0.1)
    lackfit
    risklimits;
  run;
```
lackfit

risklimits;

run;

* to run regression analysis: predictors of 28 day outcome;

proc logistic data=sasuser.pneumo_july4a;

title'Model 7 Fatal:28 day outcome; p<0.10 excluding riskbug and BSI';

model mortal=age sex apache pretreatdays fatalmccabe surg ICU spec service/

selection=forward

ctable pprob = (0 to 1 by 0.1)

lackfit

risklimits;

run;

* to run regression analysis: predictors of 28 day outcome;

proc logistic data=sasuser.pneumo_july4a;

title'Model 8 Fatal:28 day outcome; with potential interactions';

model mortal=age sex apache pretreatdays fatalmccabe surg ICU spec riskbug age*pretreatdays apache*pretreatdays spec*pretreatdays riskbug*pretreatdays/

selection=forward

ctable pprob = (0 to 1 by 0.1)

lackfit

risklimits;
run;

* to run regression analysis: predictors of 28 day outcome;

proc logistic data=sasuser.pneumo_july4a;
  title 'Model 9 McCabe: 28 day outcome; all factors < 0.05 except service';
  model mortal=pretreatdays mcabe surg ICU riskbug/
    selection=forward
    ctable pprob = (0 to 1 by 0.1)
    lackfit
    risklimits;
run;

* to run regression analysis: predictors of 28 day outcome;

proc logistic data=sasuser.pneumo_july4a;
  title 'Model 9 Rapid1: 28 day outcome; all factors < 0.05 except service';
  model mortal=pretreatdays rapidmccabe1 surg ICU riskbug/
    selection=forward
    ctable pprob = (0 to 1 by 0.1)
    lackfit
    risklimits;
run;

* to run regression analysis: predictors of 28 day outcome;

proc logistic data=sasuser.pneumo_july4a;
  title 'Model 9 Fatal: 28 day outcome; all factors < 0.05 except service';
  model mortal=pretreatdays fatalmccabe surg ICU riskbug/
    selection=forward
    ctable pprob = (0 to 1 by 0.1)
    lackfit
    risklimits;
run;
* to run regression analysis: predictors of 28 day outcome;

**proc logistic data=sasuser.pneumo_july4a;**

**title'**Model 10 Rapid1: 28 day outcome; p<0.10 excluding service, risk bug, and BSI'**;

**model mortal=rapidMccabe1 age sex apache pretreatdays surg ICU spec/**

**selection=forward**

**ctable pprob = (0 to 1 by 0.1)**

**lackfit**

**risklimits;**

**run;**

* to run regression analysis: predictors of 28 day outcome;

**proc logistic data=sasuser.pneumo_july4a;**

**title'**Model 11 No McCabe: 28 day outcome; p<0.05 excluding McCabe'**;

**model mortal=pretreatdays surg ICU service riskbug/**

**selection=forward**

**ctable pprob = (0 to 1 by 0.1)**

**lackfit**

**risklimits;**

**run;**
risklimits;
run;

* to compare specimen collection between VAP and non-VAP patients;

proc freq data=sasuser.pneumo_july4a;
  tables test* VAP /chisq CMH;
run;

* to compare survival and McCabe scores between incident and prevalent NP;

proc freq data=sasuser.pneumo_july4a;
  tables incident*(status mortal mcape) /chisq CMH;
quit;