CENTRAL LINE-ASSOCIATED BLOOD-STREAM INFECTIONS AND VENTILATOR-ASSOCIATED PNEUMONIAS: CHANGING INFECTION RATE ACROSS DURATION OF HOSPITALIZATION AND WITH DIFFERENT DEFINITIONS OF TIME AT RISK

Mary Elizabeth Ritchey

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Dissertation Committee,
Michele L. Jonsson Funk, Chair
Danica Marinac-Dabic
Stephen W. Marshall
William A. Rutala
David J. Weber

ABSTRACT

Mary Elizabeth Ritchey

Central line-associated blood-stream infections and ventilator-associated pneumonias: changing infection rate across duration of hospitalization and with different definitions of time at risk

(Under the direction of Michele L. Jonsson Funk)

Background: Patients with mechanical ventilators (MV) and central lines (CL) have increased rates of infection during hospitalization compared with other patients. Our objectives were to 1) model changing infection rates varied over device duration adjusting for changes in risk factor distribution throughout that time and 2) to determine whether changing rate models were a more appropriate analysis than constant rate models.

Methods: Electronic healthcare records of inpatients at UNC Hospitals between January 1, 2002 and December 31, 2007 who used central line(s) or mechanical ventilator were collected. We modeled changing rates across duration of device placement via discrete-time hazards regression, adjusting for age, gender, race/ethnicity, comorbidities, patient location, and hospital service. We compared changing rate to constant rate models via differences in error and F-tests.

Results: MV-associated infection peaked around 7 days; CL-associated infection peaked around 14 days. Rates varied between 2 and 10 infections per 1000 device-days. MV infection rates were higher among patients with trauma, central venous catheters, or blood-stream infection. Infection rates were lower on the floor compared to ICU. After 11 days, medical and pediatric patients had decreased MV

infection rates compared with surgical patients. With CL, rate of infection was higher in Black individuals, and patients in intensive care units (ICUs) or on a surgical service. In the first week, males had increased infection risk compared to females. Changing rate models fit the observed rates better than constant rate models for surgical and ICU patients, and the UNC Hospitals overall population. Various definitions of device exposure indicated that changing rate models were better for at least some patient groups.

Conclusion: Variation in rates across duration of time at risk remained after adjusting for the changing population at risk. Awareness of patients at increased risk, monitoring throughout hospitalization and timing interventions and surveillance appropriately could reduce the incidence of MV and CL associated infections. Investigators should be aware that when comparing patient groups or different hospitals without accounting for the changing rate of infection across device duration estimates may not be meaningful.

To my sister, Amanda Jo Lerand, for always encouraging me on my path, consistently reminding me that it is the right one, and for choosing her own road with the same boldness and determination - for believing that even though there is light on this path of life, it doesn't mean that the road will look the same for each of us.

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LIST OF ABBREVIATIONS AND SYMBOLS

α	Alpha, intercept parameter
β	Beta, model parameter
BSI	Bloodstream infection
CDC	Centers for Disease Control and Prevention
CI	Confidence interval
CL	Central line
CLABSI	Central line-associated bloodstream infection
HAI	Hospital acquired infection
HR	Hazard ratio
ICU	Intensive care unit
IQR	Interquartile range
MV	Mechanical ventilator
NI	Nosocomial infection
OR	Odds ratio
SD	Standard deviation
UNC	University of North Carolina
VAP	Ventilator-associated pneumonia

I. INTRODUCTION

A. Device-associated nosocomial infections

In 2002, there were 1.7 million infections in hospitalized patients [1]. Nosocomial infections (NI) occur in up to 10% of all patients in the hospital [2]. Approximately 15% of all NI are pneumonia and another 14% are blood-stream infections (BSI) [1]. Thus, pneumonia and BSI represent a significant portion of the problem of NI and a large proportion of both are linked with specific medical devices [3]. Mechanical ventilation accounts for 83% of cases of nosocomial pneumonia. And, 87% of primary BSI are found in patients with central venous access or "central lines." [3]

Patients with device-associated pneumonia or BSI are at increased risk of death in the hospital [4-9]. In 2002, of the estimated 99,000 deaths associated with NI, 36,000 were from pneumonia and 31,000 from BSI [1]. These two medical devices are thus associated with two-thirds of NI-related mortality.

To provide perspective for these numbers, we examine the national mortality statistics. There were an estimated 2 million deaths in the United States in 2006. The top 10 causes of death are listed in Table 1, below [10]. While NI is not counted as a cause of death for national statistics and it would change the numbers in the table if it were included, we can see that 99,000 associated deaths could rank NI above diabetes as the sixth leading cause of death in the country. The 67,000 deaths from nosocomial pneumonia and BSI alone could rank as the eighth leading

cause of death. The 57,000 device-associated pneumonias BSIs could continue to rank eighth. Thus, the morbidity and mortality from these device-associated NI is substantial. With greater study and application in this field, there is the possibility of decreasing incidence and mortality, saving thousands of lives annually.

Table 1. Top 10 Causes of Death in the United States in 2006.

Rank	Cause of Death	Number of people	Percent of all deaths
1	Diseases of heart	631,636	26.0
2	Malignant neoplasms	559,888	23.1
3	Cerebrovascular diseases	137,119	5.7
4	Chronic lower respiratory diseases	124,583	5.1
5	Accidents (unintentional injuries)	121,599	5.0
6	Diabetes mellitus	72,449	3.0
7	Alzheimer's disease	72,432	3.0
8	Influenza and pneumonia	56,326	2.3
9	Nephritis, nephrotic syndrome and nephrosis	45,344	1.9
10	Septicemia	34,234	1.4

*Table from National Vital Statistics Report, 57(14), 2009.

The purpose of this study is to the elucidate timing of the rates device-associated infections during hospitalization. The goal is to model changing rates of mechanical ventilator and central line infections and to determine whether changing rate models provide a more accurate portrayal of the incidence of infections over time than constant rate models. We assess time-only models as well as models adjusting for patient characteristics, to determine whether variation in the rate of infection could be explained by changes in the patient population at risk across device duration. We also assess models with different measures of device exposure time, to determine whether changing rates are affected by method of exposure assessment.

B. Dissertation layout

In addition to this chapter, there are five primary sections in this dissertation. The next section contains Chapter II: a review of the literature. This section reviews

the current knowledge about risk factors for ventilator-associated pneumonia and central line-associated blood stream infection, the potential for measuring changing rates of nosocomial infection, and the measures of device exposure in nosocomial infection literature. Previous studies of nosocomial infection at UNC Hospitals are also included in this section.

The statement of aims is in Chapter III. It provides the scope of work along with specific aims and hypotheses to address the purpose of the research. Chapter IV provides the details of the methods used for this dissertation. An overview and description of the study population from UNC Hospitals begins the section. Analysis methods for each specific aim follow the overview.

The Results section consists of Chapters V-VIII. Chapter IX is the last substantive section of the dissertation. It provides the conclusions drawn based on this project and indicates future directions for continuation of the work.

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II. REVIEW OF THE LITERATURE

A. Background

Device specific healthcare-associated infection surveillance

National healthcare-associated infection (HAI) surveillance began in the 1970's and an annual report was generated using accumulated data from contributing hospitals [1-4]. The annual report included central line-associated bloodstream infection (CLABSI) and ventilator-associated pneumonia (VAP), as well as other intensive care unit (ICU) infection rates.

Beginning in 1991, each facility reported rates as the total number of infections divided by the total number of days patients had the device placed (device-days) for each type of ICU, and the national surveillance report then provided the 10th, 25th, 50th, 75th, and 90th percentile rates for each type of ICU across all reporting facilities. Prior to that time, the rate denominator was the total number of days patients were in the ICU (patient-days).

While stratifying by type of ICU (and teaching hospitals versus not for medical-surgical ICUs), no delineation was made for patient case-mix between the hospitals. This means that small, rural hospitals with less severe patients were compared to larger, tertiary care centers without adjustment. Also, only one rate was reported per unit, assuming that the rate of device-associated infection was constant throughout the patients' time in that ICU [2-4].

Beginning in 2005, the annual report also included rates for monitored devices on inpatient medical and medical/surgical wards and the percent of infections associated with specific categories of infection criteria [3,4]. Percentiles of utilization ratios, comparing days patients use devices to days patients are hospitalized were also included [4].

The information presented in these annual reports is appropriate for surveillance, but does not provide a full adjustment for patient case-mix. We do not know whether adjusting for risk factors for VAP or CLABSI would significantly change which hospitals fall into higher (or lower) infection rate percentiles. We also do not know the effect of adjusting for a changing rate of infection across the duration of device placement.

Other published literature compared with national surveillance

VAP and CLABSI rates presented in the published literature may use the device-days denominator required in national surveillance reports, or may use the patient-days denominator [1,5,6]. As neither device is removed when infection occurs, neither device-days nor patient-days specifically implies removal of the patient from the denominator for calculating rates. Authors may not adjust denominators for reported rates to reflect time when a patient already has an infection, and is thus unable to acquire an incident infection. Denominators not accounting for time with infection may be inflated, thus rates of device-associated infection may appear lower than actually occurring rates.

Published literature is also unclear in regards to whether multiple infections are captured per person. Without specification, hospitals reporting multiple

infections may appear to have higher device-associated infection rates than compared to those reporting only the first infection for patients.

B. Critical review of literature

Ventilator-associated pneumonia (VAP)

Patients with mechanical ventilators (MV) are typically found in ICUs. Between 2006 and 2007 [4], national surveillance indicated MV were used most frequently in trauma ICUs (pooled mean of 0.58 ventilator-days per patient-day) and least often in coronary ICUs (0.27 ventilator days per patient-day). The pooled mean of VAP across all hospitals included in the national surveillance ranged from 2.1 cases per 1000 vent-days in Pediatric Medical/Surgical ICUs to 10.7 per 1000 vent-days in Burn ICUs [4]. Reported VAP across all ICUs ranged from 0.0 to 16.7 per 1000 vent-days [4].

Other studies reported a 5-28% risk of VAP during hospitalization [7-26]. These studies found rates as low as 2.5 per 1000 vent-days and as high as 57.6 per 1000 vent-days.

Despite rates of pneumonia presented in these studies, there is some evidence that VAP does not occur at a constant rate across duration of MV. In one study, 3% of patients contracted VAP each day in the first week, 2% per day in the second week and 1% per day in subsequent weeks [27,28].

Time to onset of infection ranged from a mean of 3.3 days to 32.7 days post-MV insertion in adult ICUs [7-10,14,18,23,26]. Only two studies have reported time to onset of pneumonia in children: one with a mean of 8.9 days in the pediatric ICU and the other with a median of 37 days for preterm neonates in the neonatal ICU

[11,29].

Some risk factors have consistently been associated with increased VAP rate, including presence of a central venous catheter or primary blood-stream infection, reintubation, aspiration, location and change of location within the hospital, tracheostomy, and patient positioning [8,9,11,13,21,27,30-33]. Others, such as age, gender, race/ethnicity, hospital service, and comorbidities have been identified as risk factors in some, but not all studies [9,13,14,21,31,32].

Central line-associated blood stream infections (CLABSI)

Approximately 5 million central lines (CL) are inserted in the United States each year, with infections occurring in 3-8% of patients [34]. Between 2006-2007 [4], hospitals in the national surveillance reported that CL were used most often in surgical cardiothoracic ICUs (pooled mean 0.72 CL-days per patient-day) and least often in inpatient wards (range 0.09 CL-days per patient-day in rehabilitation ward to 0.26 CL-days per patient-day in adult step-down units). The mean of CLABSI in these hospitals ranged from 0.5 per 1000 CL-days in rehabilitation wards to 5.6 per 1000 CL-days in burn ICUs. Reported CLABSI ranged from 0.0 to 13.5 per 1000 CL-days in all ICUs [4].

Other studies reported rates of CLABSI ranging 0.7 to 18.5 per 1000 CL-days [15,23,25,35-38]. Four to 28% of all patients with CL developed BSI [22,36]. The average time to onset of infection was 20.4 days [39]. CLABSI was associated with a longer length of stay in the hospital, and, in some cases, increased mortality [22,23]. Studies to date did not look for or identify other risk factors.

No studies have been done looking at changes in the rate of CLABSI across

duration of CL placement. But, the longer mean time to infection implies that if a change in rate for CLABSI exists, it would occur over a longer duration of time compared with VAP.

Device-days versus Patient-days

In September 2007, the Division of Healthcare Quality Promotion at the CDC published a paper in *Infection Control and Hospital Epidemiology* [5]. The article discussed differences in CLABSI rate estimates using patient-days compared with CL-days). In the NNIS sample of ICUs, using patient-days rather than CL-days led to an average 7% change in the rank of rate estimates among the reporting hospitals. On average for all hospitals, patient-days accurately represented 76% of "high" infection rate hospitals as having high CLABSI rates when compared with the CL-days denominator. The authors noted that as the device use ratio (percent of patients in the ICU who had CL) increased, the percentile error when using patient-days as the denominator decreased.

In April 2006, the German equivalent to the Division of Healthcare Quality Promotion at the CDC found that rates of HAI were higher on the floors than in ICUs using device-days as denominators, but infection rates were much lower on floors when patient-days were the denominators [6]. The device use ratio is lower on the floors than in the ICUs; thus, the percentile error when using patient-days on the floors was expected to be large if device-days was considered the optimal measure.

Learning more about when device-associated HAI occur will enable us to tailor interventions to curtail these infections. By determining the changes in VAP and CLABSI rate across duration of device exposure, adjusted for known covariates

such as gender, age, patient location, and hospital service, infection control practitioners will be able to better utilize time and money in prevention and treatment of device-associated HAI. They will be able to determine how patient case-mix and severity contribute to their hospitals' rates of infections, thus making their own surveillance rates more applicable to improving patient care.

Changing rate across duration of exposure

Although most studies and the annual surveillance reports present constant rates of device-associated infections over time, there are a few small studies that indicate that the rate of device-associated infections may be changing throughout the duration of exposure [40,41].

Changing underlying hazard rates of VAP were reported in one study. Jaimes reported an increase over the first 10 days in an ICU and then a decrease and leveling-off for hazard rates at 20 days in the ICU [14]. These hazard rates were not adjusted for any potential confounders, and the rates of infection among different groups of patients at risk may vary across duration of MV.

Unfortunately, surveillance reports have been used to say that one hospital is 'better' than another hospital because it has fewer infections [41]. Since surveillance reports and much of the published literature do not adjust for age, gender, patient severity, case mix, or changing rate of infection across duration of exposure, it is difficult to determine whether the rates presented are appropriate for comparison of facilities. Analyzing the effect of changing rate across duration of device-exposure, and whether patient-days and device-days exhibit similar trends with changing rate and patient characteristics will help us to better understand the intricacies in

comparing device-associated HAI rates.

Device-associated Infection Rates at UNC Hospitals

In 2006, there were 164,728 device-days logged for patients at UNC Hospitals. The rate of VAP was 4.76 per 1000 ventilator-days (range: 0.91/1000 days in the pediatric ICU to 11.67/1000 days in the surgical ICU). The rate of CLABSI was 3.89 per 1000 CL-days (range: 0.27/1000 days in burn unit to 9.35/1000 days in the medical primary care unit) [unpublished data]. These rates are constant, calculated from the total number of days that all patients with a device had that device in place (including days after infection occurred and multiple infections in one person counting as multiple infections in the overall number) and fall below the 10th percentile in the latest national surveillance report [4].

In addition to the ICU infection rates, which could be compared with national surveillance reporting, the rates on the floors for CLABSI ranged from 1.11/1000 days to 7.52/1000 days. So, the low ICU infection rates at UNC Hospitals do not provide all of the information about infections associated with these devices.

Previous studies of infection at UNC Hospitals

A few studies of HAI have been conducted previously using UNC Hospitals data. Saviteer [42] discussed increased risk of HAI in elderly patients. The authors found that patients over age 60 had HAI rates 49% higher than patients under age 60. A total of 4,031 infections occurred in 2,662 admissions over four years (1980-84). All HAI were included in the study. Respiratory infection rates and bloodstream infection rates as well as overall HAI rates increased with increasing age (by decade). Duration of hospitalization (in three-day increments) was also assessed as

a risk factor for HAI. HAI rates increased from days 2-4 to days 14-16, then decreased to days 23+. No patient risk factors other than age were assessed in the study. No specific information was provided for device-associated infections.

In 1989, Brawley [40], reported findings from an analysis of multiple HAI also using UNC Hospitals data from 1980 to 1984. They found that HAI occurred in 2.6% of patients at a rate of 4.5 infections per 1000 patient-days. There was an average of 1.5 HAIs among those patients who had any infection. Twenty-nine percent of patients who developed HAI spent time in the ICU. Fifty-five percent of respiratory infections and 64% of BSI occurred in patients with more than one infection. Whites and females were more likely to have any HAI. Whites and males were more likely to have multiple HAI. Age and duration of hospitalization were not associated with infection rate. But, patients with more infections did have longer average hospital stays.

Weber [43] compared HAI found during surveillance in 1985-89 with HAI during 1980-84. Fewer HAI occurred in 1985-89 than in 1980-94. Aside from pathogen analysis, other risk factors were not assessed as part of this study. Again, no specific information was provided regarding device-associated infections.

In July 2007, Weber [44] compared VAP and other hospital acquired pneumonias at UNC Hospitals between 2000 and 2003. Over 90% of VAP occurred in ICU patients while 67% of other pneumonias were in ICU patients. Less than 15% of VAP occurred in the first four days of hospitalization compared with 21% of other hospital-acquired pneumonias. Increasing rates of VAP were noticed with increasing time since hospital admission.

Weber [45] also produced a study comparing the number of HAI using CDC-recommended ICU surveillance compared with comprehensive hospital-wide surveillance. Using the CDC targeted surveillance, only 21.4% of CLABSI and 37.9% of respiratory tract infections would have been found at UNC Hospitals during 2004-2005. The overall number of infections at UNC Hospitals was much larger than what would have been reported to the CDC for inclusion in the national surveillance report. Twenty-one percent of respiratory tract infections and 37% of BSI were associated with medical devices. Most of the ICU infections were associated with devices. Device-associated infection rates were higher in ICUs than on floors. Infection rates in step-down units were more similar to floors than ICUs. Patient risk factors were not assessed as part of this study.

C. Summary

Risk factors for VAP have been reported widely, but risk factors for CLABSI are less well known. Changing risks throughout patient hospitalizations have not been widely investigated, as much of the literature revolves around small outbreaks and the national surveillance reporting.

UNC Hospitals have low rates of VAP and CLABSI, compared to the hospitals providing information for national surveillance. UNC Hospitals are also monitoring infections throughout the entire facility, not just in ICUs. To decrease rates of infection, targeted interventions may be necessary.

Device-associated HAI risk may fluctuate throughout a patient's hospitalization. If this is the case, then targeting interventions to times of increased HAI risk would be an efficient way to decrease infections.

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III. STATEMENT OF SPECIFIC AIMS

We modeled infection rates while accounting for fluctuations in the rate of device-associated hospital infections across the duration of device exposure. We were interested in the rate of VAP and CLABSI over the time that patients were hospitalized. We accounted for the variation in these device-associated rates by describing the rate of infection in short time periods (1-7 days) from device-placement (or admission) to removal (or discharge) while accounting for age, gender, patient location, comorbidities (via ICD-9 codes) and hospital service (e.g. adult medical, adult surgical, pediatric). We also accounted for these variations using four measures of device exposure duration to determine whether there were differences in infection rates by type of denominator.

A. Specific aim 1

Aim: To clarify *whether* and *how* the rate of device-associated infections *varies* over duration of device exposure for patients who utilize MV or CL. Data for this analysis came from a cohort of patients at UNC Hospitals with MV or CL between 1 January, 2002 and 31 December, 2007. The denominator for this analysis was the number of days that the patient had the device without getting an infection.

Rationale: Mechanical ventilators and central venous catheters (central lines)

are among the top three devices associated with nosocomial infection. Many studies of HAI in the United States report a single, constant rate at each facility for each of these device-associated infection in each type intensive care unit. But, device-associated HAI rates are likely not constant throughout device exposure. Accounting for this changing of infection rate across duration of device exposure would allow us to more accurately determine when patients are at greatest risk for infection throughout hospitalization and to target interventions during that time.

Hypothesis: Our hypothesis was that the rate of VAP and CLABSI infections would fluctuate over the duration of utilization for MV and CL, respectively. We expected VAP and CLABSI to have different trajectories, but that the rates associated with each would increase over the first days of exposure then decrease to low, but constant rates of infection with subsequent use. We also expected the infection rates to differ based on patients' age, gender, comorbidities, hospital service (e.g. adult medical, adult surgical, pediatric), and patient location (ICU or floor/step-down unit).

B. Specific aim 2

Aim: To determine the *impact* of modeling the *changing rate* of VAP and CLABSI across duration of device exposure compared to constant infection rates and whether the variation remained with *different denominator* choices. Data for this analysis was from the same cohort of patients at UNC Hospitals who had MV or CL between 2002 and 2007.

Rationale: If the rate of device-associated hospital acquired infection varies across the duration of exposure, then changing rate models would provide a better

fit to the observed incidence and bias could be introduced when comparing groups of patients without accounting for the variation in rates over time. Because some hospitals use alternative measures of the duration of exposure, we also assessed these denominator choices to see if the potential for bias was indicated in all measures of device exposure.

Hypothesis: Our hypothesis was that the changing rate of VAP or CLABSI would provide more meaningful estimates of the observed incidence than a constant rate of infection throughout device exposure. A secondary, confirmatory hypothesis was that both constant and changing rates of infection would be higher when using device-days as a denominator compared with the patient-day denominator and that removing patients with infection from the population at risk would increase the estimated rates for both patient-days and device-days for all rate measures.

Because VAP and CLABSI were expected to differ based on patient characteristics and risk factors, we assessed various subpopulations of interest to determine whether the changing or constant rates provided meaningful estimates of the observed incidence in various target groups. Our hypothesis was that the changing rate models would provide more meaningful estimates when there was greater variation in a target group across the duration of device exposure.

Results layout

Chapters V and VI present the results from specific aim 1. Chapter V is the manuscript for central line-associated bloodstream infection results; Chapter VI is the manuscript for ventilator-associated pneumonia results. Chapters VII and VIII present the results from specific aim 2. The ventilator-associated pneumonia results

are in manuscript form in Chapter VII. And, Chapter VIII includes supplemental results for aim 2. The information covered in Chapter VIII is presented in tabular and graphical form with short descriptions and covers VAP results not included in the Chapter VII manuscript as well as all CLABSI results from aim 2.

IV. METHODS

A. Subject identification/sampling

Source population: University of North Carolina (UNC) Hospitals data

UNC Hospitals has been collecting aggregate level data on device-associated HAI since 2002. They have also been using an electronic medical record since the late 1970's. Since the electronic version is the medical record at UNC Hospitals, missing data is minimal. Individual data is available to assess patient factors that influence HAI rates such as gender, age, race/ethnicity, comorbidities, patient location and hospital service (e.g. surgical or medical).

Study setting and design

The source population for this study was all patients hospitalized at UNC Hospitals between 1 January, 2002 and 31 December, 2007 for at least 24 hours. The study population consisted of a retrospective cohort of all patients in the source population who utilized a CL or MV during their hospital stay. There was no interaction between investigators and subjects and no new information was collected as part of the study.

Data from the source population was collected as part of usual care at UNC Hospitals (see Table 2). Device utilization was collected by nursing staff as a routine part of daily assessment of patient acuity ("QUADRAMED," nursing quality indicators data). Because it was collected as part of the routine assessment and was used to

determine nurse staffing, there was incentive for accurate assessment and the information provided by the nurses was expected to reflect actual patient conditions. Prior to this project, the Department of Hospital Epidemiology at UNC Hospitals used the nursing assessment data to determine device-day denominators for their quarterly reported device-associated HAI infection rates.

Table 2. Source data for variables.

Variable	Description	Source dataset
Admission Date	date patient admitted to hospital	Hospital Infection Database, Physician Billing Data
Ventilator Use Dates	date ventilator in use	Nursing Assesment
Central Line Use Dates	date central line in use	Nursing Assessment
Discharge Date	date patient discharged from hospital	Hospital Infection Database
Infection Date	date of infection	Hospital Infection Database
Infection Type	type of infection (VAP, CLABSI)	Hospital Infection Database
Age	age of patient at admission	Hospital Infection Database, Physician Billing Data
Sex	gender of patient	Physician Billing Data
Race	race of patient	Physician Billing Data
Ethnicity	ethnicity of patient	Physician Billing Data
Service	hospital service attending patient	Physician Billing Data
location	location of patient (which ICU, which floor)	Hospital Infection Database, Nursing Assessment, Physician Billing Data
ICD-9 codes	ICD-9 codes associated with patient at time of discharge	Physician Billing Data

Identification of infection

The UNC Hospitals Infection database was established in 1977 in the Department of Hospital Epidemiology. It included all HAI at UNC Hospitals. Infection control practitioners and nurses used criteria developed by the CDC to conduct infection control surveillance throughout the hospital. Prior to inclusion of an infection in the database, it was reviewed by a nurse supervisor and a physician who specialized in infectious disease and critical care medicine. Definitions for VAP and

CLABSI between 2002 and 2007 are below.

Ventilator Associated Pneumonia (VAP)

The CDC definition for VAP stated that a physician diagnosis for pneumonia alone was not sufficient for nosocomial pneumonia. Signs and symptoms, radiology findings, and laboratory confirmation must also be presented. In the case of VAP, the patient had to meet criteria for pneumonia and have had the device in place to assist or control respiration continuously over the 48 hours prior to the onset of infection [1]. Thus, the patient must have a MV for at least 2 days to be considered at risk for VAP.

Central line-Associated Blood-stream Infection (CLABSI)

The CDC definition for CLABSI stated that BSIs must either be laboratory confirmed or constitute clinical sepsis. Laboratory-confirmed BSIs needed to have a recognized pathogen not linked to another infection site or signs of infection with a common skin contaminant culture [1]. At least one CL had to be present for at least 24 hours (1 day) before the patient could have CLABSI.

Since multiple VAP and CLABSI could occur within one patient, one hospitalization, or even one device placement period, there could be multiple infections recorded per patient in the infection database.

Selection Criteria

All patients at UNC Hospitals between 2002 and 2007 with documented use of a CL for at least one day or MV for at least two days while in the hospital were included in this study. Patients admitted with or acquiring infection within 24 hours of hospitalization for CL or 48 hours for MV were not considered to have a nosocomial

infection and were not included in analyses. All other patients with these devices were included for analysis. These criteria were congruent with CDC guidelines and UNC Hospitals HAI surveillance [1,2].

The advantage of including all patients with one of these medical devices was that it provided information for ICU and floor patients and both adult and pediatric patients. Many published studies are limited to ICU patients or report solely adult or pediatric infection rates. Because we included all patients, we were able to provide a comparison across patient locations and ages. We were also able to assess these as risk factors for device-associated infection.

We assessed a larger number of people who have devices placed over a longer calendar period than has previously been reported in the published literature. Thus, the number of infections seen was large and we were assured that we were analyzing trends in duration of device placement prior to infection rather than only monitoring an outbreak. With this large amount of data, increases in infection rate were likely an actual increase, not a measure of statistical chance.

B. Methods for proposed study

Time at risk for VAP or CLABSI

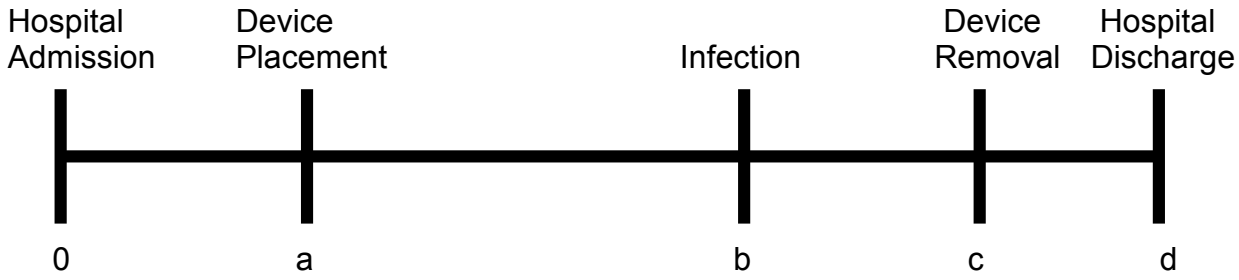
The aims of this proposal focused on whether each patient's duration of hospitalization or device duration should be incorporated into calculations of device-associated HAI rates. For this reason, time-at-risk was considered the "exposure." We calculated multiple time-at risk variables for the analyses.

Dates of admission, device placement, discharge, and device removal were used to determine time-at-risk variables. Date of infection was used in calculations

among patients who developed VAP or CLABSI.

Four calculations of exposure time were used as denominators in this study. “Patient-days” was the time from hospital admission to hospital discharge for all patients. In Figure 2., patient-days was the time between ‘0’ and ‘d.’ “Device-days” was the time between device placement (‘a’ in Figure 2.) and device removal (‘c’). Acquiring infection did not necessitate removal of the device, and multiple infections per device placement were possible, so the CDC definitions did not make recommendations concerning excluding time with the device after infection occurred. Thus, “device-days” was the presumptive denominator in national surveillance of HAI infection rate calculations. And, studies which utilized “patient-days” presumptively used the definition above as well.

Figure 1. Calculating time at risk



The other two exposure measures were truly for time-at-risk. “Patient-days-at-risk” was the duration of time between hospital admission (‘0’) and infection (‘b’) for patients developing infection and the time between hospital admission and hospital discharge (‘d’) for patients not developing infection. “Device-days-at risk” was the duration of time between device placement (‘a’) and infection for patients developing infection and the time between device placement and removal (‘c’) for those not developing infection.

Table 3. Description of exposed time variables

Exposure time	Description	Calculation from Figure 2.
Patient-days	Time from admission to discharge	Time d – Time 0
Device-days	Time from device placement to removal	Time c – Time a
Patient-days-at-risk	Time from admission to infection among infected and from admission to discharge among uninfected	Time b – Time 0, if infected Time d – Time 0, if uninfected
Device-days-at-risk	Time from device placement to infection among infected and from placement to removal among uninfected	Time b – Time a, if infected Time c – Time a, if uninfected

Exposure period

Dates of admission and discharge were obtained from physician billing data. Date(s) of infection diagnosis were documented in UNC Hospitals Infection Database after confirmation by an infection control nurse and doctor. Dates of device placement and removal were determined based on dates nurses reported assessment of the devices as part of their daily routine care. CL and MV placement were assumed to occur on the date of admission when the nursing assessment indicated presence of a CL or MV on that day. When a CL or MV was first noted after the date of admission, we assumed it was placed one day prior to the nurse indicating device presence and counted the first date of assessment as the day after placement. A one-day gap in CL use or two-day gap in MV use in the nursing assessment was considered to represent continuous use. A gap of more than one day for CL or two days for MV was assumed to reflect removal and replacement of the devices. We did this because not all nurses record quality indicators for every shift and because the one and two day periods were consistent with the CDC and UNC Hospitals time-line for device-associated infection surveillance definitions.

Measurement characteristics

A patient could have both a MV and CLs placed during a hospitalization.

Each device could be placed on a different day and be used for a different amount of time. Each device could be associated with a separate infection event. We analyzed VAP and CLABSI models separately. A patient could have multiple VAP or CLABSI associated with a single device duration throughout hospitalization. The main analyses assessed the first infection associated with each device. Sensitivity analyses for both specific aims assessed similar models with multiple infections per device placement.

A patient could also have multiple CL placed at the same time during a hospitalization. In our models, multiple CLs only contributed one device-day for each calendar-day. We were unable to assess the effect of multiple lines versus a single CL or of different types of CL (e.g. single or triple lumen).

By definition, patients could not have a device-associated infection during the first 1-2 days of hospitalization or device placement. Thus, we did not include this time in any of the models.

Covariates - gender, race, ethnicity, and age

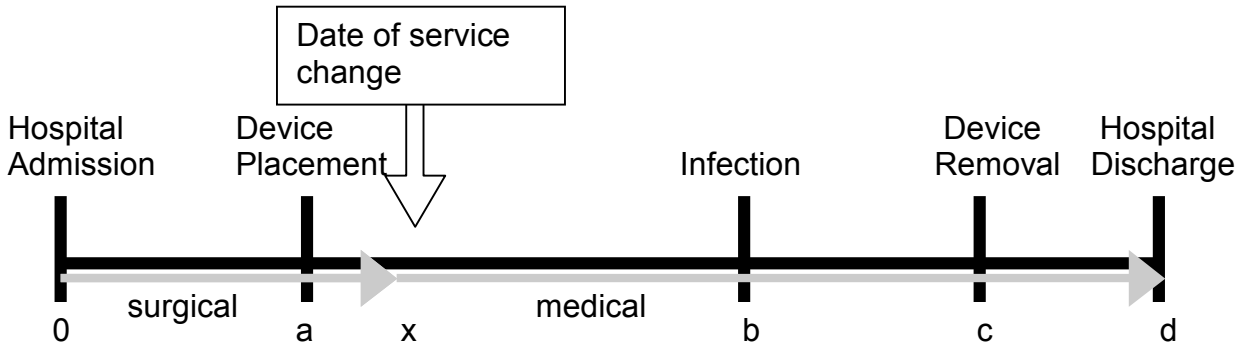
Gender, race/ethnicity, and age were obtained from the physician billing data for each patient. Gender was recorded as a dichotomous variable. Race/ethnicity was categorized based on the information in the billing data and treated as an indicator variable in models. Age on date of admission was recorded in years and included in models as a continuous covariate [3].

Covariates - location

Location of patient in the hospital was considered a time-dependent variable in this study. Patient location was collected from the nursing assessment data for

each day of device placement and from the physician billing data for the remainder of the hospitalization. A dichotomous ICU versus floor/step-down unit covariate was used for study analyses.

Figure 2. Changing service over time in hospital.



Covariates - hospital service

The hospital service providing care to the patient was a time-dependent variable. Starting hospital service was collected on date of admission from the physician billing data. Dates for any change in services were also collected from the physician billing data. Change in service was converted from the date of change to the number of days since admission or device placement (depending on the exposure variable used). Thus, in Figure 2, time between 0 and x was assigned to the surgical service and time between x and d was assigned to the medical service.

Covariates - comorbidities

Up to three ICD-9 codes for each hospitalization were recorded in the physician billing data. They were used to adjust for comorbid conditions. Indicator variables were included for the following comorbidities: diabetes, cardiovascular complications, trauma, pulmonary complications (i.e. chronic obstructive pulmonary disease, asthma), acute respiratory distress syndrome (ARDS), sepsis, acute renal

failure, and immune suppression (i.e. cancer, HIV, transplant) as indicated in previous literature [4-10].

Data analysis

Specific Aim 1. Measuring changing rates of infection across duration of device placement

The first specific aim of this proposal was to describe and model how the rates of CLABSI varied across duration of time with CL and MV, respectively. The analysis for this aim consisted of three overarching steps. Each step was conducted separately for each device and two separate manuscripts were developed for CLABSI and VAP. An overview of the steps included in this analysis is in Table 4.

Table 4. Steps involved in analysis of Specific Aim 1.

Step number	Short Description	Accomplished by:
1.1	Clarify and describe changing rates*	• Rates of infection conditional on continuing device duration and not having previous infection • Graphs • Life tables
1.2	Model changing rates	• Test for relationship between covariates and time to infection • Test for confounding • Test for time interactions • Discrete-time hazards regression
1.3	Deterministic Sensitivity analyses	• Multiple infections per device placement • Gap analysis • For CL, assess only placements not including date of admission

* All rates for aim 1 used the device-days-at-risk time variable.

Aim 1.1 Clarify and describe changing rates

Knowing the patterns of infection over time with the device and plotting the change in daily rate over time allows us to have a better understanding of when hospitalized patients get device-associated infections. Thus, the first step of aim 1 was to clarify and describe the infection rate for each day with each device.

An overall rate for VAP was determined by dividing the number of first VAP infections by the total number of ventilator-days prior to infection among all patients. An infection rate for each day with the device was then calculated by dividing the number of VAPs on that day (date of device placement was day 0) by the people with a ventilator on that day and without prior infection. The overall and changing rates of infection were plotted. Similar rates were calculated for CLABSI.

Life tables including the number of people with continuing device use and without prior infection, number of people with incident infection each day, rate of infection conditional on continuous device use, and rate of survival from device placement to each day were constructed. Conditional infection rates and survival curves were graphed.

These initial graphs were difficult to interpret due to noise in the day-to-day infection rates across device duration. Short time intervals were defined for subsequent analysis. For CL, we estimated hazard and survival rates across 3-day periods throughout the first 21 days of insertion, weekly hazard rates were determined between days 22 and 56, and a single CLA-BSI rate was determined for subsequent duration. For MV, we estimated hazard and survival rate across three-day periods for the first 21 days, weekly hazard rate between 22 and 35 days, and a single VAP rate for all person-time greater than 36 days. Rate of CLA-BSI across duration with CL and rate of VAP across duration with MV were estimated using lifetable methods and plotted with 95% confidence intervals.

Aim 1.2 Model changing rates

Discrete-time hazards regression [11] was used for modeling because it

explicitly modeled the changing rates of CLABSI and VAP across duration of device placement and it allowed multiple time-dependent variables. It also allowed the hazard function to have a previously unspecified shape [12]. We began with a model including only duration of device placement as the predictor of infection. We then determined the extent of change in the rates of device-associated HAI while accounting for risk factors. The covariates examined were: age, gender, race/ethnicity, comorbidities (as captured via ICD-9 codes), patient location, and hospital service.

A model containing all potential confounders was used to determine whether there were any time interactions. All covariates were tested for interaction with time by multiplying the indicator variables for the covariate by the indicator variables for exposure time and including that in a new model. An a priori $\alpha=0.05$ for the interaction term or the likelihood ratio test between the two models was used to determine statistical significance for these interactions. If hazard plots visually indicated a categorical interaction between a covariate and time, this categorical interaction was also assessed using an a priori $\alpha=0.05$.

All covariates not interacting with time were included in the model as risk factors. This process of model building allowed us to account for differences in the rate of infection across duration of device placement that were attributable to risk factors. It also allowed us to model time as the "exposure." And, it allowed us to assess whether any variation in the rate of infection could be explained by changes in the patient population at risk across duration of device placement.

Aim 1.3 Deterministic sensitivity analyses

Two possible sources of bias warranted special consideration. The first was our method of determining duration of device placement. Since we used nursing assessment data to get information on patients with devices, we assumed for the main analysis that a 1-2 day gap in device placement represented continuous use. In order to determine whether this assumption dramatically influenced our results, we assessed gaps of 1, 2, 5, and 7 days as continuous device placement.

The second source of bias was that CL use could occur outside the hospital. Thus, patients with CL assessment on the date of hospital admission may have had the CL for an unknown duration rather than starting an initial placement. Thus, we also assessed the rate of CLABSI among only those patients without a CL assessment noted on the date of admission.

While device-days-at-risk was the denominator of interest, we also knew that multiple device-associated infections could occur within a single device placement. Thus, we conducted a sensitivity analysis to determine whether changes in infection rates across device duration were still present when multiple infections per placement were included in the analysis.

Note about missing data

Missing data was minimal. Missingness was no greater than 5% for any variable and no formal analysis plan for missing data was included in the study. The number of placements in each model was kept as high as possible, thus the number of placements analyzed varies between models.

Specific Aim 2. Impact of denominator

The second aim of this proposal was to determine the impact of changing versus constant device exposure assessments for VAP and CLABSI infection rates among hospitalized patients and to determine whether the variation in rates remained important with different measures of exposed time (i.e. different denominator choices). The analysis for this aim consisted of five steps. Each step was conducted separately for each device type, and a single manuscript was developed to present the results for VAP. The results for CLABSI were similar and are presented in an abbreviated format. An overview of the steps is presented in Table 5 (next page).

Aim 2.1 Rates associated with devices

The second aim of this proposal focused more specifically on whether each patient's exposure should be incorporated into calculations of rates of infection and to what extent measuring changing rates of infection over time provides new, meaningful information. As a first step, we calculated the rates of infection at UNC Hospitals using the actual number of infections on each day and the number of exposed patients each day indicated by device exposure. These 'actual' rates of infection were compared to constant rate and changing rate models. Observed rates were calculated using each of the four denominators of exposure time. Short definitions for these denominators are provided in Table 6.

Table 5. Steps involve in analysis for Specific Aim 2

Step number	Short Description	Accomplished by
2.1	Determine daily rate of infection based on each of four options for exposed time	• Calculate number of people contributing patient-time each day • Calculate daily rate of infection by dividing number of infections by patient-time for each time variable
2.2	Determine unadjusted, constant rates of infection (for each denominator)	• Divide total number of infections by total number of days patients exposed
2.3	Model unadjusted changing rate over time (for each denominator)	• Discrete-time hazards models
2.4	Create tables and graphs comparing observed and model-based rates of infection	• Develop one table for each denominator • Each table should include: o observed number of people contributing patient-time each day; o observed infection rate each day; o discrete-time hazards model expected infection rate for each day; o error between model and observed daily infection rate; o difference between expected and observed number of infections; o error between constant rate and observed rate for each day; o difference between expected number of people from constant rate compared to observed rate of infection each day • Graph information from tables
2.5	Develop constant rate and changing rate models adjusted for risk factors indicated in aim 1.	• Poisson models for constant rate of infection adjusted for covariates indicated in aim 1 • Discrete-time hazards models for changing rates of infection, adjusting for covariates indicated in aim 1 • Develop tables for comparing these models to the observed rates of infection like those in aim 2.4

Table 6. Four exposure time calculations for rate denominators.

Denominator for rate	**Exposure time calculation among infected**	**Exposure time calculation among uninfected**
Patient-days	time from admission to discharge	time from admission to discharge
Patient-days-at-risk	time from admission to infection	time from admission to discharge
Device-days	time from device placement to removal	time from device placement to removal
Device-days-at-risk	time from device placement to infection	time from device placement to removal

Aim 2.2 Unadjusted, constant infection rates

Unadjusted, constant rates of infection will be determined using a Poisson regression model including only the intercept. This was equivalent to dividing the total number of infections associated with a device by the total number of exposed days for all patients. Ninety-five percent confidence intervals were determined using the intercept parameter estimate and standard deviation from the model.

$$rate = e^{\alpha}$$

The first 1-2 days (for CLABSI and VAP models, respectively) of hospitalization or device placement were not included in each persons total patient-days or device-days calculations. Thus, the time when patients were not yet at risk for the infections was not included in the total number of days at risk.

Aim 2.3 Unadjusted, changing rates over time

We also modeled the data allowing the rate of infection to change across the duration of exposure using discrete-time hazards analysis. Models for each denominator including only the duration of exposure provided information about the expected rate of infection for each day. This set of models allowed us to determine the differences between a changing rate of infection across duration exposed time compared to the constant rate models.

We conducted two discrete-time hazards analyses for each denominator. The first had time periods of longer length to allow for smoothing and visualization of underlying trends. The second used shorter time periods, lengthening later time periods due to sparse data with longer duration of exposure.

Hazard rates were calculated for each time interval using the associated, period-specific intercept (α_n).

$$hazard_n = \frac{1}{1 + e^{(\alpha_n)}}$$

Typically, the hazard for a discrete time period is the conditional probability of an event that can only occur once per patient. In our patient population, infection could occur multiple times in one person, one admission, or even during one device placement. We used generalized estimating equations [13] to account for multiple admissions or device placements in one person and multiple infections per placement. Because only a few device placements and admissions had more than one associated infection, we used an exchangeable correlation matrix, requiring only one parameter, but allowing for non-zero correlation between multiple device placements and infections in one person.

Aim 2.4 Comparing actual and modeled rates

A table was created for each denominator option for comparison of the actual rate each day to the constant rate model and changing rate models of infection. Each table included information about the number of people with exposed time on that day (i.e. denominator) as well as the actual number and rate of infections on that day.

The rate from each of the models was multiplied by the number of patients continuing to contribute to the duration of device placement in order to calculate an expected number of infections for each day. The modeled rates of infection were subtracted from the actual daily rate of infection for each day of exposure duration. The difference between the modeled and actual rate was squared and summed

across the duration of exposure to calculate the sum of squared error term for the model. The standard deviation of the rate of infection was used to determine 95% confidence intervals. Graphs comparing the numbers of expected and observed infections and infection rates were utilized to visually compare the calculation techniques. Differences between the model-predicted and observed infection rates each day were plotted across the duration of exposure. F-tests comparing the constant rate model to both the longer time interval discrete-time hazards model and the shorter time interval discrete-time hazards models and a F-test comparing the discrete-time hazards models were also used to determine whether models with fewer parameters had comparable fit to the observed incidence [14,15] with an a priori α=0.05 chosen to identify statistical significance.

Aim 2.5 Adjusted model rates

Adjusted constant and changing rate models were also fit to the data for each of the four denominator choices using all covariates from Specific Aim 1. These adjusted models allowed us to determine the extent to which the modeled constant and changing rates of infection could be explained by changes in the patient population at risk across duration exposure.

We also assessed constant and changing rate models for specific subpopulations of interest. Rates of pneumonia may vary across these different groups of patients as well as throughout the duration of device exposure. Inclusion of these risk factors allowed us to assess whether the rate of infection across the duration of ventilation was independent of changes in risk factor distribution throughout time.

Target populations were chosen to determine whether models performed differently for different groups of interest. These five target groups were: patients over age 65, patients under age 18, patients in an intensive care unit (ICU), patients on a surgical service, and patients on an surgical service with a trauma diagnosis.

The constant rate models for each subpopulation were determined using the linear vector, including the intercept, from univariate regression of a Poisson model of the entire study population, to model the natural log of the constant rate among the target population. Discrete-hazard models for the entire population were constructed with the addition of a dichotomous covariate for inclusion in the target population. The conditional rate for each time interval for the target population was then calculated and compared to the actual daily rate of infection for that group.

Tables and graphs similar to those described in aim 2.4 were created for these target subgroups using the adjusted models. Graphs and F-tests were used to compare the models in each subgroup.

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V. RESULTS: CHANGING RATE OF BLOOD-STREAM INFECTION ACROSS DURATION OF CENTRAL VENOUS ACCESS

A. Introduction

About 5 million central venous catheters or “central lines” are inserted every year in the United States [1]. Patients with central lines (CL) represent 87% of all primary blood-stream infections [1]. Reported CLABSI rates range 0.7 to 18.5 per 1000 CL-days [1,3-9]. Patients with CL-associated bloodstream infections (CLABSI) are at increased risk of dying in hospitals with nearly 27,000 attributable annual deaths [2].

While rates of CLABSI are widely reported in the literature, most studies assume a constant infection rate throughout duration of CL use. Changes in the rate of CLABSI throughout CL duration have not been well documented. Further, few previous studies have used multivariate analysis to adjust for covariates.

The primary objective of this study was to determine whether and how the rate of CLABSI changed throughout the duration of CL use. A secondary objective was to identify risk factors for CLABSI and to assess whether any variation in the rate of infection could be explained by changes in the patient population at risk across duration of CL placement.

B. Methods

Participants

This study includes 27,397 individuals who were hospitalized at UNC Hospitals between 1 January, 2002 and 31 December, 2007 and had at least one CL inserted for one or more days during their hospitalization.

Data were collected as part of usual hospital care in UNC Hospitals. Information about whether patients had a CL and hospital location was collected by the nursing staff as a routine part of their daily assessment. Demographic, hospital service, and diagnosis data were extracted from administrative physician billing records. Infection data were retrieved from the standardized surveillance records of the Department of Hospital Epidemiology. Data from the three sources were combined using medical record numbers, dates of admission and CL use.

Outcome

Infection control surveillance was conducted by five infection control professionals supervised by two full-time faculty. Comprehensive hospital-wide surveillance was performed using definitions developed by the Centers for Disease Control and Prevention [10]. CLABSI was defined as any bloodstream infection occurring at least one day after CL placement through the first day after CL removal with no other explanation for the infection.

Time at risk

CL placement was assumed to occur on the date of admission if the nursing assessment indicated presence of a CL on that day. When a CL was first noted after the date of admission, we assumed it was placed one day prior to the nurse

indicating its presence and counted the first date of assessment as the day after placement. A one-day gap in CL use from the nursing assessment was considered to represent continuous use. A gap of more than one day was assumed to reflect removal of all CLs and subsequent insertion of one or more new lines.

Covariates

Variables collected for this study included: dates of admission(s) and discharge(s), dates when the patient had at least one CL, date of onset of CLABSI(s), gender, race, location of patient within hospital, service to which patient was assigned, and up to three ICD-9 diagnosis codes for each patient. Race was defined as White, Black, Hispanic, and other or non-specified race. Age was determined at time of admission and centered at 50 years for analysis. Patient location was defined as in an intensive care unit (ICU) versus on a floor or step-down unit. Hospital service was collapsed into broad categories of adult medical, adult surgical, pediatric, or other service (including rehabilitation, obstetrics/gynecology, etc.).

Because a patient may move or change service during the course of one CL placement, we represented patient location and hospital service as time dependent variables across CL duration. When a patient changed location or service, the first location or service continued to contribute time toward CLABSI for one day after the move.

Up to three ICD-9 diagnosis codes were used to determine patient comorbidities during each admission. We focused on the eight comorbidities that have previously been associated with device-associated nosocomial infection [11-

17]: diabetes, cardiovascular complications, trauma, pulmonary complications (COPD and asthma), acute respiratory distress syndrome, sepsis, acute renal failure, and immune suppression (cancer, HIV, and transplant patients).

Statistical analysis

The data were analyzed using survival (time-to-event) methods. The number of patients at risk decreased with increasing CL duration, with relatively few patients having line(s) continuously inserted for more than two months. Thus later time periods had more imprecision, and accordingly we estimated hazard and survival rates across 3-day periods throughout the first 21 days of insertion, weekly hazard rates were determined between days 22 and 56, and a single CLABSI rate was determined for subsequent duration. Rate of CLABSI across duration with CL was estimated using lifetable methods and plotted with 95% confidence intervals.

We used discrete-time hazards analysis [18] to model rate of CLABSI across duration of CL placement and to identify risk factors. We accounted for the fact that a single patient may have multiple CL placements using generalized estimating equations [19]. Time intervals in this analysis were the same as those in the life table analysis and models were censored after 56 days of CL placement. Rates of CLABSI were calculated from the models using the following formula: $h_t = \frac{1}{1+e^{-\alpha}}$ where α represents the log odds of the hazard rate for a given time interval in the model.

Gender, race/ethnicity, age, comorbidities, hospital service, and patient location were each individually added to the life tables and discrete-time hazard models to assess their potential as risk factors. Visual inspection of lifetable plots

was used to assess potential interactions with time. Time interactions were deemed significant if a Wald or likelihood ratio test p-value was less than 0.05 when comparing models with and without the interaction term(s).

A discrete-hazards model including all covariates and any significant time interactions was used to determine adjusted hazard rates and 95% confidence intervals for each time interval. Mutually adjusted odds ratios and 95% confidence intervals for potential risk factors were also calculated from this model.

Lifetable and discrete-time hazards analyses were repeated for rate of all CLABSI including multiple (repeated) infections across CL placement, again adjusting for multiple durations of CL use within patients and potential risk factors.

C. Results

Demographics

During the study period, January 1, 2002 to December 31, 2007, there were 125,594 patients admitted to UNC Hospitals. Of those patients, 27,397 (21.8%) had at least one CL for at least one day. Forty-eight percent were female, 60.0% were White, and 29.6% were Black (Table 7). The average age on the date of admission was 43 (standard deviation (sd) 25) years. Overall, 21.2% of admissions were individuals under 18 years of age.

Among these 27,397 people, 39% had more than one period of CL use for a total of 57,687 placements (Table 8). The average number of CL durations per person was 2.1 (sd 2.6). The median CL duration was 7 days (interquartile range (IQR) 2-8 days).

Table 7. Characteristics of patients with central lines at UNC Hospitals in 2002-2007.

	Number of people	%	Number with CLABSI*	%	Risk of CLABSI per 100 people (95% CI)
Total	27397		1231		4.5 (4.2, 4.7)
Gender					
Male	14167	51.7	540	43.9	3.8 (3.5, 4.1)
Female	13230	48.3	691	56.1	5.2 (4.8, 5.6)
Race					
White	16425	60.0	631	51.3	3.8 (3.5, 4.1)
Black	8115	29.6	452	36.7	5.6 (5.1, 6.1)
Hispanic	1101	4.0	52	4.2	4.7 (3.5, 6.0)
Other race	1752	6.4	96	7.8	5.5 (4.4, 6.5)
People with central lines by year					
2002	4656	17.0	223	18.1	4.8 (4.2, 5.4)
2003	5058	18.5	250	20.3	4.9 (4.3, 5.5)
2004	5482	20.0	221	18.0	4.0 (3.5, 4.6)
2005	5714	20.9	211	17.1	3.7 (3.2, 4.2)
2006	5978	21.8	190	15.4	3.2 (2.7, 3.6)
2007	6197	22.6	173	14.1	2.8 (2.4, 3.2)
Admissions per person (sd*)	1.7 (2.1)		3.0 (4.5)		
Central line placements per person (sd)	2.1 (2.6)		4.5 (5.4)		
Combined duration with central line per person (sd)	15 (27)		63 (67)		

*CLABSI: central line-associated blood-stream infection; sd: standard deviation.

Thirty-eight percent of CL placements were in patients with at least one comorbidity. The most frequent recorded comorbidities were immunodeficiency (14.5%), acute respiratory distress syndrome (10.6%) and cardiovascular complications (6.4%). Thirty percent of CL placements began in the ICU. Thirty percent of CL placements began on an adult surgical service, 42% began on an adult medical service, and 17% began on a pediatric service. Only 3% had service changes and less than 1% had location changes between the ICU and floor/step-down unit while maintaining CL placement.

Table 8. Characteristics of patients by total number of central line placements at UNC Hospitals in 2002-2007.

	Number of CL* placements	% of placements	Days with CL	Number of CLABSI*
Total	57,687		414,887	1355
Gender				
Male	29,719	51.5	219,662	769
Female	27,966	48.5	195,204	586
Race				
White	33,420	57.9	238,263	676
Black	18,639	32.3	131,293	503
Hispanic	1,819	3.2	14,463	61
Other race	3,809	6.6	30,868	115
Age (sd)	43 (25)			37 (27)
Comorbidities				
Average number (sd)	0.41 (0.56)			0.47 (0.60)
Diabetes	547	0.9	2,735	4
Cardiovascular Complications	3,667	6.4	21,250	47
Trauma	2,455	4.3	21,903	80
Pulmonary Complications	873	1.5	4,966	10
Acute Respiratory Distress Syndrome	6,099	10.6	71,918	316
Sepsis	122	0.2	1,054	1
Acute Renal Failure	1,651	2.9	3,284	56
Immunodeficiency	8,369	14.5	49,986	123
Total number comorbidities				
0	35,977	62.4	249,505	792
1	19,681	34.1	144,301	492
2	1,985	3.4	20,448	68
3	44	0.1	633	3
Beginning location				
ICU	17,041	29.5	161,787	660
Floor or step-down unit	40,640	70.4	253,037	695
Number CL placements with at least one change	4	0.0	40	0
Beginning Hospital Service				
Medicine	24,309	42.1	154,153	618
Surgery	17,490	30.3	128,079	648
Pediatric	9,825	17.0	97,119	23
Other	3,671	6.4	17,042	66
Number CL placements with at least one change	1,619	2.8	27,860	101
Median duration of CL placement (IQR)	7 (2, 8)			30 (12, 37)

*CL: central line; CLABSI: central line-associated blood-stream infection; CI: confidence interval; sd: standard deviation; IQR: interquartile range.

Infection rate

A total of 1,469 infections occurred in 4.5% of all patients and in 2.3% of all CL placements resulting in 5.36 CLABSI (95% Confidence interval (CI) (5.10, 5.63)) per 100 patients admitted and 3.27 CLABSI per 1000 CL-days (95% CI 3.09, 3.44 per 1000 CL-days) (Table 9). Among the 1,355 CL placements resulting in at least one CLABSI, 43% were in females, 50% in Whites, and 37% in Blacks (Table 8). Comorbidities were listed among ICD-9 codes in 42% of CL placements; the most frequent of which were acute respiratory distress syndrome, immunodeficiency, and trauma. Forty-nine percent were admitted to an ICU and 48% to adult surgical service. The median number of days before infection was 9 (IQR 5-17) and the median total time with CL placement resulting in at least one infection was 21 (IQR: 12-37) days.

Time-to-infection analysis

Unadjusted life table estimates for time to CLABSI are shown in Table 10. The rate of infection rose steadily through the first two weeks following placement, declined steadily over weeks three and four, and then increased slowly with additional time.

The number of first infections peaked during days 4-6 for a total of 270 CLABSI. Second infections began occurring at the end of the first week. Nearly 50% of first CLABSI occurred by the end of day 9, and over 75% of first infections by day 18. Accounting for multiple infections, 50% occurred by the twelfth day and 75% by day 21.

Table 9. Risk and rate of CLABSI by total number of central line placements at UNC Hospitals in 2002-2007.

	CLABSI* risk per 100 placements (95%CI*)	CLABSI rate per 1000 CL-days (95%CI)
Total	2.3 (2.2, 2.5)	3.27 (3.09, 3.44)
Gender		
Male	2.6 (2.4, 2.8)	3.50 (3.25, 3.75)
Female	2.1 (1.9, 2.3)	3.00 (2.76, 3.24)
Race		
White	2.0 (1.9, 2.2)	2.84 (2.62, 3.05)
Black	2.7 (2.5, 2.9)	3.83 (3.50, 4.17)
Hispanic	3.4 (2.5, 4.2)	4.22 (3.16, 5.27)
Other race	3.0 (2.5, 3.6)	3.73 (3.05, 4.41)
Comorbidities		
Diabetes	0.7 (0.0, 1.4)	1.46 (0.03, 2.89)
Cardiovascular Complications	1.3 (0.9, 1.6)	2.21 (1.58, 2.84)
Trauma	3.3 (2.6, 4.0)	3.65 (2.85, 4.45)
Pulmonary Complications	1.1 (0.4, 1.9)	2.01 (0.77, 3.26)
Acute Respiratory Distress Syndrome	5.2 (4.6, 5.7)	4.39 (3.91, 4.88)
Sepsis	0.8 (0.0, 2.4)	0.95 (0.00, 2.81)
Acute Renal Failure	3.4 (2.5, 4.3)	17.05 (12.62, 21.48)
Immunodeficiency	1.5 (1.2, 1.7)	2.46 (2.03, 2.90)
Total number comorbidities		
0	2.2 (2.0, 2.4)	3.17 (2.95, 3.40)
1	2.5 (2.3, 2.7)	3.41 (3.11, 3.71)
2	3.4 (2.6, 4.2)	3.33 (2.54, 4.11)
3	6.8 (0.0, 14.3)	4.74 (0.00, 10.09)
Beginning location		
ICU	3.9 (3.6, 4.2)	4.08 (3.77, 4.39)
Floor or step-down unit	1.7 (1.6, 1.8)	2.75 (2.54, 2.95)
Beginning Hospital Service		
Medicine	2.5 (2.3, 2.7)	4.01 (3.69, 4.32)
Surgery	3.7 (3.4, 4.0)	5.06 (4.67, 5.45)
Pediatric	0.2 (0.1, 0.3)	0.24 (0.14, 0.33)
Other	1.8 (1.4, 2.2)	3.87 (2.94, 4.81)
CL placements with at least one change in location	6.2 (5.1, 7.4)	3.63 (2.92, 4.33)

*CLABSI: central line-associated blood-stream infection; CI: confidence interval; CL: central line.

Modeling

Discrete-time hazards models were limited to the first 2 months (56 days) of CL placement. Results from the unadjusted discrete-time hazards model yielded the

same trends as found in life table analysis and indicate that the rate of CLABSI varies across CL duration (Figure 3). There was a general trend of increasing rate across time with CL, but rates were lower at the end of the third week and during the fourth week than in periods before and after.

Table 10. Life table for CLABSI* at UNC Hospitals during 2002-2007.

Cumulative duration of CL* placement (days)	Number of placements without CLABSI at beginning of interval	CLABSI during interval	Proportion (per 1000) with CLABSI during interval	95% Confidence Interval	Proportion without CLABSI at end of interval	Standard Error
1-3	57687	236	1.60	(1.39, 1.80)	1.00	
4-6	30635	270	3.54	(3.12, 3.97)	0.99	0.001
7-9	17288	193	4.29	(3.69, 4.89)	0.98	0.001
10-12	11350	150	4.92	(4.14, 5.71)	0.96	0.001
13-15	8109	111	5.04	(4.10, 5.97)	0.95	0.002
16-18	5974	83	5.07	(3.99, 6.16)	0.94	0.002
19-21	4528	52	4.19	(3.05, 5.32)	0.93	0.003
22-28	3427	78	4.12	(3.21, 5.03)	0.90	0.004
29-35	1910	51	4.76	(3.46, 6.06)	0.88	0.005
36-42	1124	35	5.32	(3.56, 7.08)	0.85	0.007
43-49	725	24	5.58	(3.35, 7.81)	0.83	0.009
50-56	472	13	4.62	(2.12, 7.13)	0.80	0.010
57+	332	59	7.57	(5.64, 9.49)	0.66	0.020

*CLABSI: central line-associated blood-stream infection; CL: central line.

Thus, the constant rate was an overestimate early on and an underestimate with longer duration (Figure 4). Peak modeled infection rate (5.07 CLABSI (95% CI 4.09, 6.28) per 1000 CL-days) occurred 16-18 days post-CL placement with another spike during the seventh week (5.57 per 1000 CL-days (95% CI 3.73, 8.30)). Adjusting for year of CL placement did not alter the trends seen with duration of CL placement.

Figure 3. Changing and constant rate of central line associated blood-stream infections over duration of central line placement (with 95% confidence intervals for changing rate).

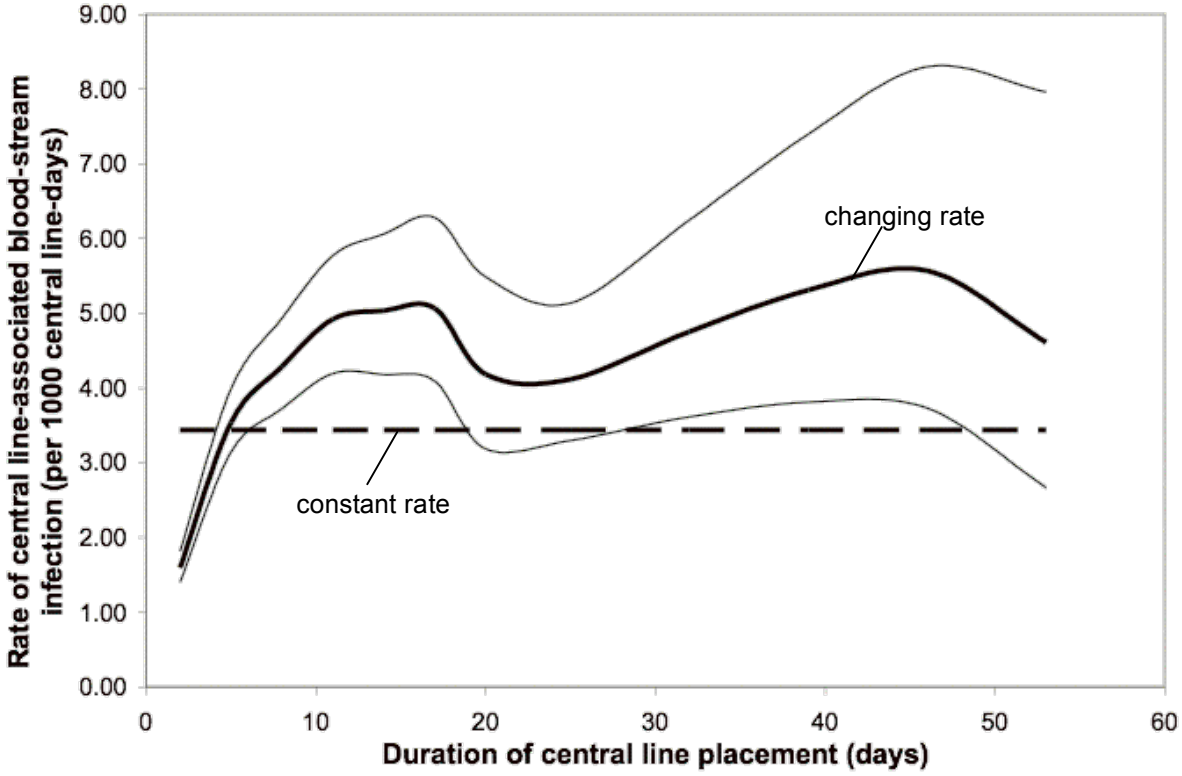
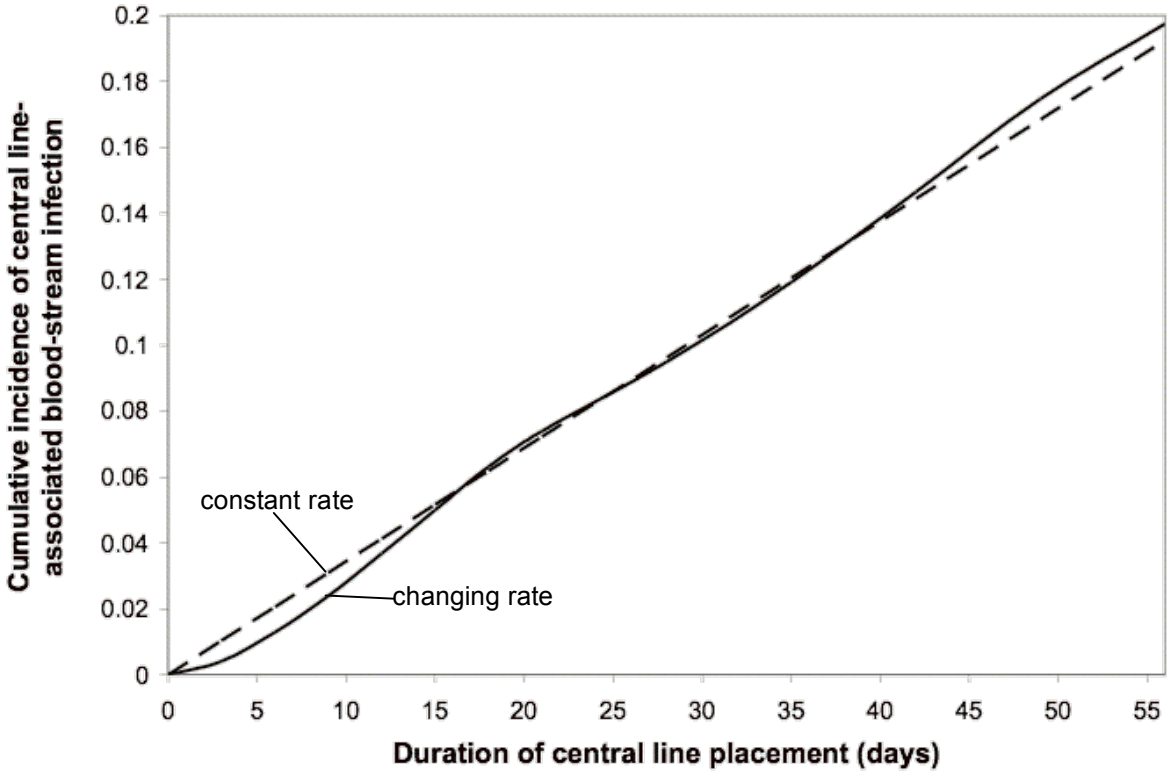


Figure 4. Cumulative incidence of central line-associated blood-stream infection across duration of central line placement.



Unadjusted risk factor assessment

Initially, we conducted univariate analyses in which potential risk factors were added to discrete-time hazard models individually to assess the effect on rate of CLABSI throughout CL placement (Table 11). Compared to White patients, Blacks (OR 1.39, 95% CI 1.23, 1.56), Hispanics (OR 1.31, 95% CI 1.04, 1.65), and other races (OR 1.38, 95% CI 1.10, 1.73) had increased rate of CLABSI. Patients located in the ICU (OR 1.41, 95% CI 1.27, 1.58) or on a surgical (OR 1.20, 95% CI 1.05, 1.37) or pediatric service (OR 1.10 (95% CI 0.95, 1.26) also had increased CLABSI rates compared with patients on the floor/step-down unit or on a medical service. Increasing age was not associated with increased CLABSI (OR per 10 year increase 0.99, 95% CI 0.97, 1.01). Cardiovascular complications (OR 0.72, 95% CI 0.53,

0.97) and immunodeficiency (OR 0.74, 95% CI 0.61, 0.89) were associated with decreased rate of CLABSI while acute respiratory distress syndrome (OR 1.35, 95% CI 1.18, 1.54) and acute renal failure (OR 1.32, 95% CI 1.01, 1.74) increased CLABSI rate. There were too few CLABSI among patients with diabetes, pulmonary complications, and sepsis to assess these as potential risk factors in discrete-time hazard models.

Table 11. Odds ratios for risk factors for CLABSI*.

	Univariate OR* (95% CI)	Fully adjusted OR (95% CI)
Gender		
Female	Ref*	ref
Male ≤ 7 days	1.36 (1.16, 1.58)	1.32 (1.13, 1.55)
Male > 7 days	1.03 (0.89, 1.19)	0.99 (0.85, 1.15)
Race		
White	ref	ref
Black	1.39 (1.23, 1.56)	1.36 (1.21, 1.54)
Hispanic	1.31 (1.04, 1.65)	1.07 (0.83, 1.40)
Other race	1.38 (1.10, 1.73)	1.31 (1.03, 1.67)
Age		
50 years old	ref	ref
per 10 year increase	0.99 (0.97, 1.01)	1.00 (0.96, 1.04)
Initial patient location		
Floor or step-down unit	ref	ref
ICU	1.41 (1.27, 1.58)	1.34 (1.19, 1.52)
Initial hospital service		
Medicine	ref	ref
Surgery	1.20 (1.05, 1.37)	1.15 (1.00, 1.33)
Pediatrics	1.10 (0.95, 1.26)	0.94 (0.75, 1.18)
Other	0.44 (0.28, 0.67)	0.49 (0.31, 0.75)
Comorbidities^		
Cardiovascular complications	0.72 (0.53, 0.97)	0.64 (0.47, 0.88)
Trauma	1.17 (0.92, 1.48)	1.01 (0.78, 1.31)
Acute respiratory distress syndrome	1.35 (1.18, 1.54)	1.12 (0.97, 1.30)
Acute renal failure	1.32 (1.01, 1.74)	1.27 (0.96, 1.68)
Immunodeficiency	0.74 (0.61, 0.89)	0.84 (0.69, 1.03)

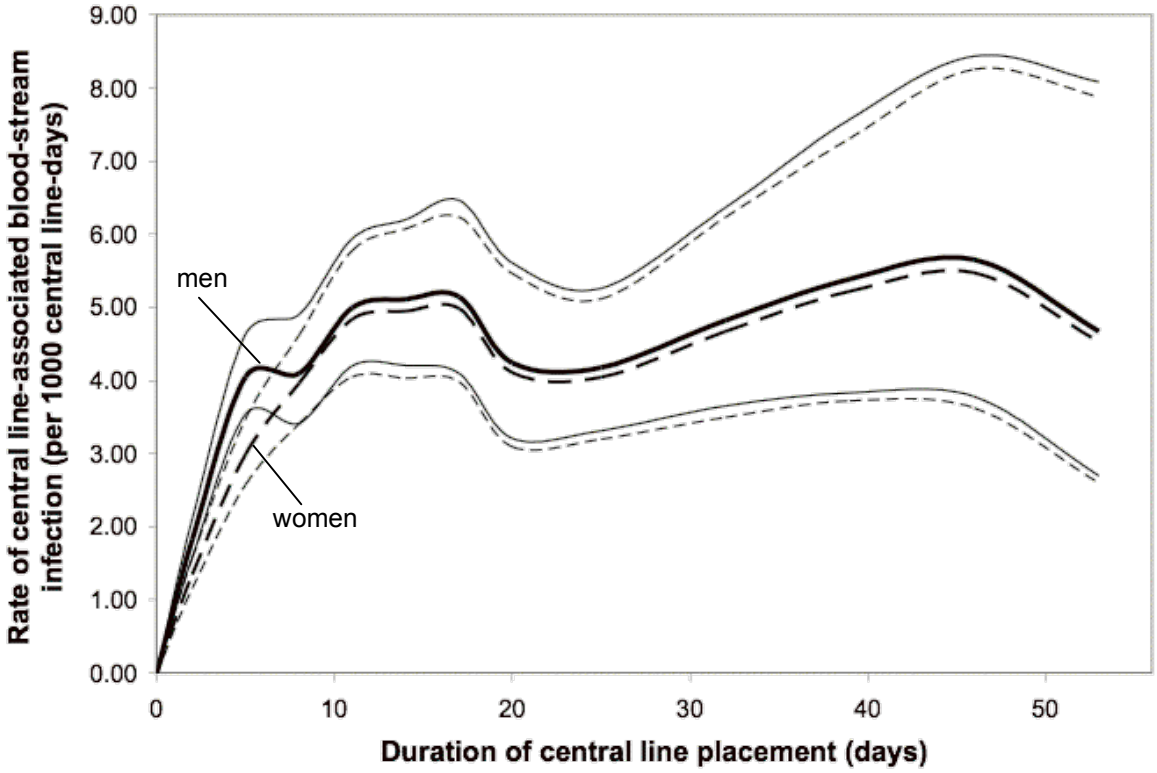
*CLABSI: central line-associated blood-stream infection; OR: odds ratio; CI: confidence interval; ref: reference group.

^Referent for each comorbidity is all patients without that comorbidity.

Averaged across all time intervals, males had 17% higher odds of CLABSI compared to females (95% CI 1.04, 1.31). But, the effect of gender differed across

time (Figure 5), with males having 36% greater CLABSI rate in the first week of CL placement (OR 1.36, 95% CI 1.16, 1.58) but similar to females thereafter (OR 1.03, 95% CI 0.89, 1.19). Adjusted models included separate terms for the effect of gender through the seventh day and after seven days with a CL.

Figure 5. Rate of central line associated blood-stream infections over time for men and women (with 95% confidence intervals).



Full model adjusted for all covariates

Effect of time

The overall trends across CL duration remained similar to the unadjusted model (Figure 5). Rate of CLABSI increased across the first 2 weeks, decreased over the third and fourth weeks, and increased slightly with subsequent CL duration. The rate of CLABSI among 50 year-old white women located on a floor, medical service, and with no noted comorbidities (i.e, the baseline group, with all covariates

at the reference level) increased over the first week to 2.39 (95% CI 1.76, 3.25) per 1000 CL-days and in the second week to 3.07 CLABSI per 1000 CL-days. CLABSI decreased in the third and fourth weeks to a minimum of 1.56 (95% CI 0.72, 3.37) on day 24, and increased with additional duration. Rate of CLABSI in other groups followed similar patterns of increasing and decreasing over time, but were higher or lower based on the odds of the covariate patterns. For instance, the rate of CLABSI on the sixth day after placement among 50 year-old Black men in the ICU, surgical service, and who had a trauma diagnosis was 7.99 (95% CI 5.25, 10.74) per 1000 CL-days. The low-point on day 24 was 3.75 (95% CI 1.69, 8.30) per 1000 CL-days.

Adjusted risk factor assessment

Adjusting for all other covariates and the effects of time, the rate of CLABSI among Black patients was 36% higher than among white patients (OR 1.36, 95% CI 1.21, 1.54) (Table 11). Hispanic patients had similar CLABSI rate across CL placement compared to whites (OR: 1.07, 95% CI 0.83, 1.40). Patients in ICU had 28% higher CLABSI rate (OR 1.34, 95% CI 1.19, 1.52) compared to patients located on a floor or step-down unit. CLABSI did not increase with increasing age (OR per decade 1.00, 95% CI 0.96, 1.04). Surgical patients had increased CLABSI across duration of CL placement (OR 1.15, 95% CI 1.00, 1.33) while pediatric patients were similar to medical patients (OR 0.94, 95% CI 0.75, 1.18). Cardiovascular complications were associated with lower CLABSI rate (OR 0.64, 95% CI 0.47, 0.88), and other comorbidities were associated with no change or slightly increased CLABSI rate.

D. Discussion

The rate of CLABSI was higher during the second week and early in the third week after initial CL placement. The overall peak in the rate of CLABSI was on days 16-18. The increase in CLABSI over the first two weeks, then decrease after 18 days to a lower infection rate on days 22-28 mimics the change in the rate of all nosocomial infections over duration of hospitalization found by Saviteer, et al. [20]. In addition, our study provides information that the rate of CLABSI across duration with CL continues to fluctuate when adjusting for risk factors.

Identified risk factors for CLABSI include severity and type of underlying illness [10]. Gender, race, age, patient location (ICU vs floor), and hospital service have not been well studied as potential confounders in CLABSI, but have been identified as risk factors in ventilator-associated pneumonia, another device-associated infection [11, 15, 17, 21-28]. Between 2002 and 2007, we found that the rate of CLABSI at UNC Hospitals changed throughout patients' duration of CL use and varied by gender, race, comorbidities, location within hospital, and hospital service.

The changing CLABSI rate across time was lower than the constant rate over the first three days and higher after days 4-6. Since 50% of CL placements last fewer than 6 days, lower rates during this time period decrease the overall constant rate. We do not know whether these patients who had at least one CL for less than 6 days without getting an infection were more or less healthy than those who continued use of CL(s) for more than 6 days. Patients who were more healthy may have needed a CL for a shorter period of time, and because they were healthier

would have been less likely to have an infection during their time with a CL. Patients who were less healthy were at greater risk for other, more severe competing risks, such as death. One difficulty in interpreting our results is that patients who were more likely to die than to get CLABSI may look similar in our data to patients who were healthier and thus more likely to have the CL removed quickly. Research including information on mortality and other competing risks would help parse out the differences concerning the amount of time healthier and sicker patients use CLs.

We only included one hospital in this analysis. We were also unable to assess type of line (i.e. single or triple lumen), body location of the line (i.e. jugular or subclavian), adherence to aseptic technique, and whether antimicrobial impregnated lines were used. All of these factors may influence CLABSI rate; but practices are standardized across this hospital and would not play a role in infections across CL duration or by service. Thus, we expect that the variation in CLABSI throughout CL duration would be seen at other facilities as well.

An assumption of our data was considering a gap of more than one day to represent removal and placing new CL(s), so we conducted a separate analysis repeating the life table and discrete-time hazard modeling with a two-day gap in CL data representing the same CL. This analysis yielded similar results, with an increase in CLABSI over the first week, relatively stable estimate in the second week, peak in infection rate early then decreasing throughout the third week, and a slow increase throughout remaining time with a CL.

Another concern with our data was that we were unable to determine whether patients who had CL at the time of admission (i.e. day zero) came to the hospital

with CL or had one (or more) inserted on that day. We conducted a subset analysis including only patients without CL at admission and found the same trend of increasing CLABSI to the beginning of the third week then a drop in the rate through the fourth week and slight increase with subsequent CL duration.

E. Conclusions

Central line-associated blood-stream infections (CLABSI) are an important cause of morbidity and mortality in hospitalized treatments, accounting for 14% of all healthcare-associated infections and over 30% of nosocomial infection-related mortality in the United States [2]. Duration of CL placement does appear to influence the risk of CLABSI for a patient. Gender, race, age, patient location, hospital service, and comorbidities change the risk of infection. Being aware of who is at increased risk of infection, monitoring patients closely throughout hospitalization and timing interventions and surveillance appropriately could decrease the rate of CLABSI among patients with CLs.

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VI. RESULTS: CHANGING RATE OF VENTILATOR-ASSOCIATED PNEUMONIA THROUGHOUT DURATION OF MECHANICAL VENTILATION

A. Introduction

Over 200,000 cases of ventilator-associated pneumonia (VAP) occur annually in the United States [1-2]. The risk of VAP during hospitalization is 5-28%. Reported rates of VAP in hospitalized patients range from zero to 57.6 per 1000 ventilator-days [1, 3-21]. Hospitals reporting to the Centers for Disease Control and Prevention's National Healthcare Safety Network have pooled mean rates from 2.1 per 1000 ventilator-days among pediatric intensive care patients to 10.7 per 1000 ventilator-days among burn unit patients [22].

There is some evidence that the risk of VAP varies across the duration of ventilation. In a study of all nosocomial infections at University of North Carolina (UNC) Hospitals, rates of infection, measured in three-day increments, increased from days 2-4 to days 14-16, then decreased to day 23 of hospitalization [23]. In one study of VAP, 3% of patients contracted pneumonia each day in the first week, 2% per day in the second week and 1% per day in subsequent weeks [24-25]. Another study reported an increase in VAP over the first 10 days in an intensive care unit (ICU) and then a decrease and plateau after 20 days in the ICU [10]. However, these studies present data from Canada, Turkey, and before 1985 in the United States, and were of small size.

Risk factors for VAP have been identified [4-5,7,9-10,17,24,26-29], but

infection rates in previous studies were not adjusted for the presence of these risk factors. Rates of pneumonia likely vary across these different groups of patients as well as throughout the duration of mechanical ventilation. Adjusting for risk factors allows us to determine whether the rate VAP differs across the duration of ventilation independent of changes in risk factor distribution over that time period.

Our objective was to determine if the rate of VAP changes across duration of mechanical ventilator use and if variation in the rate is explained by changes in the patient population at risk of infection throughout that time. A secondary objective was to provide further evidence to clarify risk factors for VAP.

B. Methods

Participants

This study included 11,041 patients at UNC Hospitals between 1 January, 2002 and 31 December, 2007 who had a mechanical ventilator (including both patients with endotracheal tubes and/or tracheostomy) for at least two days.

Data were collected as part of usual care at UNC Hospitals. Information about ventilator use, central venous catheter use, and location was collected via the nursing staff as part of a daily assessment of patient severity. Data regarding patient demographics, hospital service, and comorbid diagnoses were obtained via administrative physician billing records. Infection data were retrieved from nosocomial infection surveillance records of the Department of Hospital Epidemiology. Data from the three sources were combined using medical record numbers, and dates of admission, ventilator use, and discharge.

Time at risk

If the nursing assessment indicated presence of a ventilator on the date of admission, we assumed ventilator placement occurred on that date. Otherwise, if ventilation was first noted after the date of admission, we assumed that the ventilator was placed on the day prior to the nurse indicating its presence during his or her assessment. Per UNC Hospitals operational definition, we did not classify pneumonia in the first two days as VAP and considered patients at risk of VAP for two days after ventilator removal. We also assumed continuous use of ventilation for gaps of up to two days in the nursing assessment. Gaps of more than two days were considered to represent removal and reinsertion of the ventilator.

Outcome assessment

Infection control surveillance was conducted by five infection control professionals supervised by two full-time faculty. Comprehensive hospital-wide surveillance was performed using definitions developed by the Centers for Disease Control and Prevention [30-31].

Covariates

Variables collected for this study included: dates of admission(s) and discharge(s), dates of mechanical ventilation, dates of concurrent central venous catheterization, date of onset of infection(s), gender, race/ethnicity, patient location, hospital service, and up to three ICD-9 diagnosis codes for each patient. Race/ethnicity was defined as White, Black, Hispanic, and other or non-specified race. Age was determined at time of admission and centered at 50 years for analysis.

Patient location was defined as in an intensive care unit (ICU) versus on a step-down unit or floor. Hospital service was collapsed into broad categories of medical, surgical, or pediatric service. Patients not on a medical, surgical, or pediatric service (e.g. psychiatric services) were not included in the analysis. Because a patient may move or change service during the course of one ventilator use, patient location and hospital service were represented as time dependent variables. If a patient changed location or service during an admission, VAP was attributed to the original location or service for two days after the move.

Up to three ICD-9 diagnosis codes were used to identify patient comorbidities during each admission. We focused on those that have previously been associated with device-associated nosocomial infection [4, 7, 9, 26-29]: diabetes, cardiovascular complications, trauma, pulmonary complications (COPD and asthma), acute respiratory distress syndrome, sepsis, acute renal failure, and immune suppression (cancer, HIV, and transplant patients).

Statistical analysis

The data were analyzed using survival (time-to-event) methods. The number of patients at risk decreased with increasing ventilator duration, with relatively few patients ventilated continuously for more than 35 days. Thus, since later time periods had fewer events and greater imprecision, we estimated hazard and survival rate across three-day periods for the first 21 days, weekly hazard rate between 22 and 35 days, and a single VAP rate for all person-time greater than 36 days. Rates of VAP across duration of ventilation and associated 95% confidence intervals were estimated using life table methods.

We used discrete-time hazards analysis [32] to model rate of first VAP across duration of ventilation and to identify risk factors. We accounted for the fact that a single patient might have multiple ventilator placements using generalized estimating equations [33]. Time intervals in the discrete-time hazards analysis were the same as those in the life table analysis and models were censored after 35 days of ventilation.

Gender, race/ethnicity, age, comorbidities, hospital service, and patient location were each individually added to the life tables and discrete-time hazard models to assess their potential as risk factors. Visual inspection of life table plots was used to assess potential interactions with time. Time interactions were deemed significant if a Wald or likelihood ratio test p-value was less than 0.05 when comparing models with and without the interaction term(s).

A discrete-hazards model including all covariates and any significant time interactions was used to determine adjusted hazard rates and 95% confidence intervals for each time interval. Mutually adjusted odds ratios and 95% confidence intervals for potential risk factors were also calculated from this model.

C. Results

Study Demographics

During the study period (1 January, 2002 to 31 December, 2007) there were 125,594 patients admitted to UNC Hospitals. Among them, 11,041 (8.8%) people had mechanical ventilation. Of those, 9,347 were on ventilation for at least two days on a medical, surgical, or pediatric service. Forty-two percent were female, 57% were white, and 30% were Black (Table 12). The average age at admission was 38

years (standard deviation (sd) 29). There were an average of 1.5 (sd 1.3) ventilator placements per person for a total of 12,301 ventilator placements of at least two days duration. The median duration of ventilation per placement was 4 days (interquartile range (IQR) 2-8) with an average duration of ventilation per person of 12 days (sd 26).

Table 12. Characteristics of patients with ventilators at UNC Hospitals during 2002-2007.

	Number of people	%	Number people with VAP*	Risk of VAP per 100 people (95%CI*)
Total	9347		416	4.45 (4.45, 4.46)
Gender				
Male	5465	58.5	238	4.35 (4.35, 4.36)
Female	3882	41.5	178	4.59 (4.57, 4.60)
Race				
White	5356	57.3	241	4.50 (4.49, 4.51)
Black	2842	30.4	130	4.57 (4.56, 4.59)
Hispanic	562	6.0	28	4.98 (4.90, 5.06)
Other races	587	6.3	17	2.90 (2.84, 2.95)
People with ventilators by year				
2002	1225	13.1	50	4.08 (4.05, 4.11)
2003	1496	16.0	68	4.55 (4.52, 4.57)
2004	1710	18.3	80	4.68 (4.65, 4.70)
2005	1782	19.1	88	4.94 (4.91, 4.96)
2006	1880	20.1	70	3.72 (3.70, 3.74)
2007	1851	19.8	60	3.24 (3.22, 3.26)
Admissions per person (sd*)	1.09 (0.31)		1.06 (0.46)	
Ventilator placements per person (sd)	1.49 (1.28)		1.60 (1.50)	
Combined duration of ventilation per person, in days (sd)	12 (26)		19 (37)	

*VAP: ventilator-associated pneumonia; CI: confidence interval; sd: standard deviation.

Fifty-one percent of ventilator placements were in patients with at least one comorbidity (Table 13). The most common comorbidities were acute respiratory distress syndrome (ARDS, 32.9%), trauma (9.6%), and cardiovascular complications (7.5%). Most ventilator placements were initially located in the ICU (91.1%) and started on a surgical service (43.3%). Few patients changed location (0.2%) or service (1.7%) while using a ventilator.

Table 13. Characteristics by ventilator placement for patients with ventilation at UNC Hospitals during 2002-2007.

	Number of ventilator placements	% of placements	Number of days with ventilation	Number of VAP*
Total	12301		86130	456
Gender				
Male	7195	58.5	50340	240
Female	5106	41.5	35790	179
Race				
White	7011	57.0	46835	243
Black	3816	31.0	28624	130
Hispanic	752	6.1	5155	29
Other race	722	5.9	5516	17
Age (sd)	38 (29)			39 (27)
Comorbidities				
Average number (sd)	0.60 (0.65)			0.74 (0.71)
Cardiovascular Complications	927	7.5	4555	20
Trauma	1178	9.6	10174	71
Acute Respiratory Distress Syndrome	4052	32.9	36289	169
Acute Renal Failure	360	2.9	3212	13
Immunodeficiency	596	4.8	3303	18
Total number comorbidities				
0	5977	48.6	37045	179
1	5277	42.9	39258	185
2	1019	8.3	9512	54
3	28	0.2	315	1
Patient Location				
ICU	11208	91.1	74818	385
Floor or step-down unit	1092	8.9	11303	34
Number ventilator placements with at least one change	29	0.2		1
Hospital Service				
Medicine	2978	24.2	19065	48
Surgery	5325	43.3	38156	264
Pediatric	3643	29.6	26848	96
Number ventilator placements with at least one change	215	1.7		13
Median duration with concurrent central venous access (IQR)	2 (1, 7)			6 (3, 12)
Median duration with concurrent central venous catheter-associated blood-stream infection (IQR)	0 (0, 0)			0 (0, 0)
Median duration of ventilation (IQR)	4 (2, 8)			7 (5, 14)

*VAP: ventilator-associated pneumonia; sd: standard deviation; IQR: interquartile range.

Infection Rate

Among the 12,301 ventilator placements, there were 456 initial VAP cases. Overall, 4.5% of patients and 3.7% of all ventilator placements sustained an infection, resulting in an unadjusted, constant rate of 5.29 (95%CI 4.81, 5.78) VAP per 1000 ventilator-days (Table 14). The median ventilation duration prior to VAP among patients developing pneumonia was 7 days (IQR 5-14).

Table 14. Characteristics by ventilator placement for patients with ventilation at UNC Hospitals during 2002-2007.

	VAP risk per 100 placements (95%CI)	VAP rate per 1000 ventilator-days (95%CI)
Total	3.71 (3.37, 3.88)	5.29 (4.81 5.78)
Gender		
Male	3.34 (2.92, 3.55)	4.77 (4.71, 4.83)
Female	3.51 (3.00, 3.76)	5.00 (4.93, 5.07)
Race		
White	3.47 (3.04, 3.68)	5.19 (5.12, 5.25)
Black	3.41 (2.83, 3.70)	4.54 (4.46, 4.62)
Hispanic	3.86 (2.48, 4.56)	5.63 (5.42, 5.83)
Other race	3.73 (2.62, 4.29)	3.08 (2.94, 3.23)
Comorbidities		
Cardiovascular Complications	2.16 (1.22, 2.63)	4.39 (4.20, 4.58)
Trauma	6.03 (4.67, 6.72)	6.98 (6.82, 7.14)
Acute Respiratory Distress Syndrome	4.17 (3.56, 4.48)	4.66 (4.59, 4.73)
Acute Renal Failure	3.61 (1.68, 4.59)	4.05 (3.83, 4.27)
Immunodeficiency	3.02 (1.65, 3.72)	5.45 (5.20, 5.70)
Total number comorbidities		
0	2.99 (2.56, 3.22)	4.83 (4.76, 4.90)
1	3.51 (3.01, 3.76)	4.71 (4.64, 4.78)
2	5.30 (3.92, 6.00)	5.68 (5.53, 5.83)
3	3.57 (0.00, 7.08)	3.17 (2.55, 3.80)
Patient Location		
ICU	3.44 (3.10, 3.61)	5.15 (5.09, 5.20)
Floor or step-down unit	3.11 (2.08, 3.64)	3.01 (2.91, 3.11)
Hospital Service		
Medicine	1.61 (1.16, 1.84)	2.52 (2.45, 2.59)
Surgery	4.96 (4.37, 5.26)	6.92 (6.84, 7.00)
Pediatric	2.64 (2.12, 2.90)	3.58 (3.50, 3.65)

*VAP: ventilator-associated pneumonia; sd: standard deviation; IQR: interquartile range.

Time-to-infection Analysis

Unadjusted life table estimates for time to VAP are shown in Table 15. The rate of VAP rose steadily over the first week following placement, declined over the second week, rose to a second peak over the third week and leveled off with subsequent ventilator duration.

Table 15. Life table for ventilator-associated pneumonia (VAP) at UNC Hospitals during 2002-2007.

Cumulative duration of ventilator placement (days)	Number of placements without VAP at beginning of interval	VAP during interval	Proportion (per 1000 ventilator-days) with VAP during interval	95% Confidence Interval	Proportion of ventilator placements without VAP at end of interval	Standard Error
2-3	12301	67	3.27	(2.49, 4.05)	0.99	
4-6	6509	129	7.85	(6.50, 9.20)	0.97	0.002
7-9	3899	87	8.43	(6.66, 10.19)	0.95	0.003
10-12	2670	38	5.30	(3.62, 6.98)	0.94	0.004
13-15	1904	19	3.64	(2.01, 5.28)	0.93	0.004
16-18	1450	20	4.98	(2.80, 7.16)	0.92	0.005
19-21	1143	24	7.54	(4.54, 10.55)	0.90	0.006
22-28	911	18	3.39	(1.83, 4.96)	0.88	0.007
29-35	586	17	4.89	(2.57, 7.22)	0.85	0.009
36+	384	34	3.93	(2.61, 5.25)	0.78	0.015

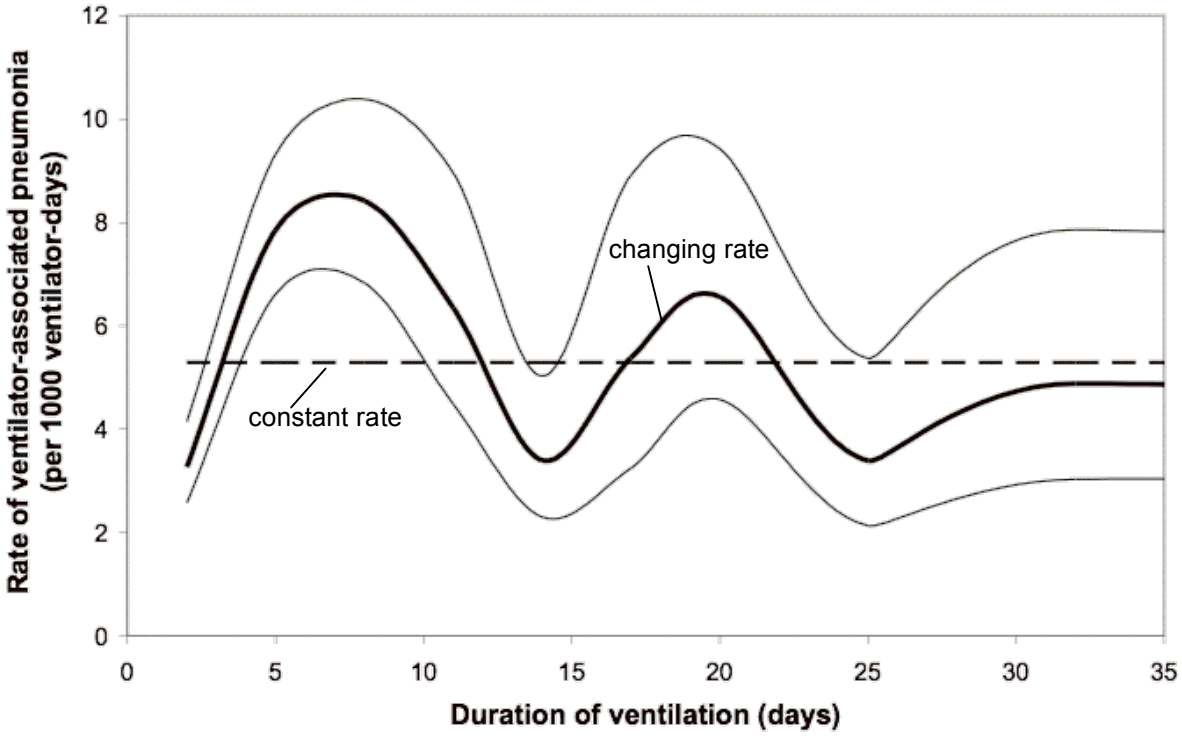
Over half of ventilation durations were less than 6 days. Less than 10% of ventilators were used for more than three weeks. The number of incident VAP cases peaked on days 4-6 for a total of 129 VAP cases. Over half of all VAP cases occurred by the ninth consecutive day of ventilation and nearly 75% occurred by day 15.

Modeling

Discrete-time hazards models were limited to the first five weeks (35 days) of ventilator duration. Results from the unadjusted model yielded the same trends as those found with the life tables (Figure 6). The rate of VAP initially rose to a peak on days 7-9 (rate: 8.42 per 1000 ventilator-days, 95%CI 6.83, 10.38), and then dipped

to a low on days 13-15 (rate 3.40 per 1000 ventilator-days, 95%CI 2.30, 5.03). Rates of VAP increased over the third week to a second peak on days 19-21 (rate: 6.57 per 1000, 95%CI 4.57, 9.43). Subsequent rates ranged 3.4 to 4.9 per 1000 ventilator-days. Thus, the constant rate underestimated the cumulative incidence for most of the first three weeks of ventilation and was an overestimate with longer duration (Figure 7). Adjusting for year of ventilator placement did not alter the trends in VAP by duration of ventilation.

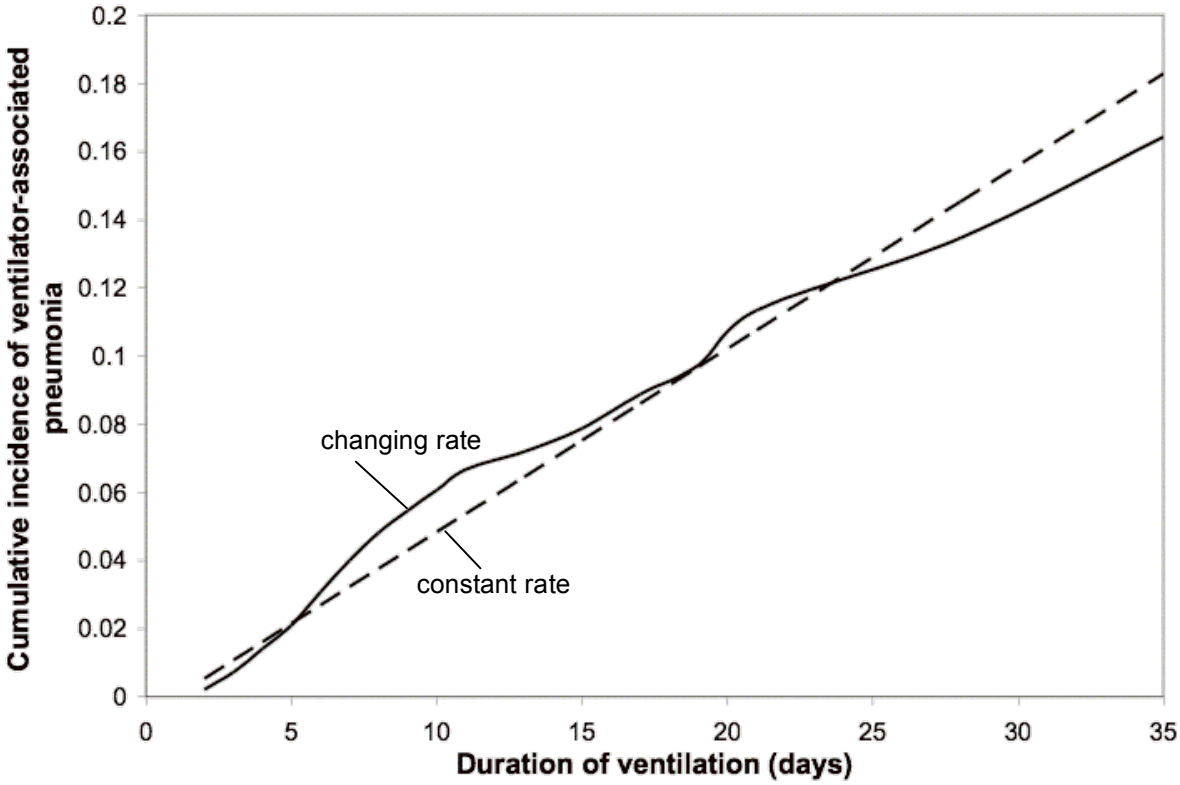
Figure 6. Rate (with 95%CI) of ventilator-associated pneumonia across duration of ventilation from unadjusted models.



Unadjusted risk factor assessment

Initially, we conducted univariate analyses in which potential risk factors were added to the discrete-time hazards models individually to assess the effect on the rate of VAP throughout ventilator duration (Table 16). Compared to white patients,

Figure 7. Cumulative incidence of ventilator-associated pneumonia across duration of ventilation from unadjusted models.



odds of VAP for Hispanic patients were similar (odds ratio (OR): 1.06, 95%CI 0.73, 1.56) while those for Black patients (OR 0.86, 95%CI 0.70, 1.06) and patients of other races (OR 0.58, 95%CI 0.35, 0.96) were lower. Odds of VAP were lower for patients on a floor or step-down unit compared to patients in the ICU (OR 0.56, 95%CI 0.39, 0.80). Older patients were more likely to contract VAP (OR per 10 year increase 1.03, 95%CI 1.00, 1.07). There were too few ventilator placements among patients with diabetes, pulmonary complications, and sepsis to assess their potential as risk factors. Patients with trauma (OR 1.50, 95%CI 1.15, 1.95) were more likely to have VAP than patients without trauma. Patients with ARDS were less likely to have VAP than patients without ARDS (OR 0.86, 95%CI 0.70 1.04). Other

comorbidities did not indicate an association with VAP over time. Concurrent central venous catheter and ventilator use increased risk of VAP by 46% (OR 1.46 95%CI 0.99, 2.16) and having a central venous catheter-associated blood-stream infection increased risk of VAP by 114% (OR 2.14 95%CI 1.58, 2.88).

Table 16. Odds ratios for risk factors of ventilator associated pneumonia.

	Univariate OR * (95%CI*)	Fully adjusted OR (95%CI)
Gender		
Female	ref*	ref
Male	0.95 (0.78, 1.15)	0.89 (0.72, 1.08)
Race		
White	ref	ref
Black	0.86 (0.70, 1.06)	0.93 (0.75, 1.16)
Hispanic	1.06 (0.73, 1.56)	1.11 (0.73, 1.67)
Other race	0.58 (0.35, 0.96)	0.61 (0.36, 1.02)
Age		
50 years old	ref	ref
Per 10 year increase	1.03 (1.00, 1.07)	0.94 (0.88, 1.01)
Patient location		
ICU*	ref	ref
Floor or step-down unit	0.56 (0.39, 0.80)	0.33 (0.22, 0.50)
Hospital service		
Surgery	ref	ref
First 11 days - Medicine	0.73 (0.40, 1.34)	0.61 (0.33, 1.13)
First 11 days - Pediatrics	1.10 (0.72, 1.68)	0.67 (0.38, 1.18)
After 11 days - Medicine	0.30 (0.21, 0.43)	0.30 (0.21, 0.43)
After 11 days - Pediatrics	0.38 (0.28, 0.50)	0.27 (0.17, 0.42)
Comorbidities‡		
Cardiovascular complications	1.01 (0.64, 1.58)	0.95 (0.59, 1.52)
Trauma	1.50 (1.15, 1.95)	1.60 (1.18, 2.17)
Acute respiratory distress syndrome	0.86 (0.70, 1.04)	0.99 (0.79, 1.23)
Acute renal failure	0.78 (0.46, 1.34)	0.86 (0.49, 1.51)
Immunodeficiency	1.21 (0.75, 1.94)	1.01 (0.62, 1.64)
Concurrent central venous access	1.46 (0.99, 2.16)	1.51 (1.01, 2.25)
Concurrent central venous catheter-associated blood-stream infection	2.14 (1.58, 2.88)	1.88 (1.38, 2.56)

*OR: odds ratio; CI: confidence interval; ref: reference level; ICU: intensive care unit.

‡Reference groups for comorbidities are all patients without that comorbidity.

Averaged across the duration of ventilation, medical (OR 0.36, 95%CI 0.27, 0.50) and pediatric patients (OR 0.51, 95%CI 0.40, 0.64) were less likely than

surgical patients to have VAP. The effect of hospital service changed throughout ventilator duration, so we included separate terms in adjusted models for the effect of service through the eleventh day and after eleven days of ventilation. In univariate analysis, prior to the eleventh day of ventilation, medical (OR 0.73, 95%CI 0.40, 1.34) and pediatric patients (OR 1.10, 95%CI 0.72, 1.68) rates were not statistically different from those of surgical patients. After 11 days of ventilation, medical (OR 0.30, 95%CI 0.21, 0.43) and pediatric patients (OR 0.38, 95%CI 0.28, 0.50) had lower risk of VAP compared with surgical patients.

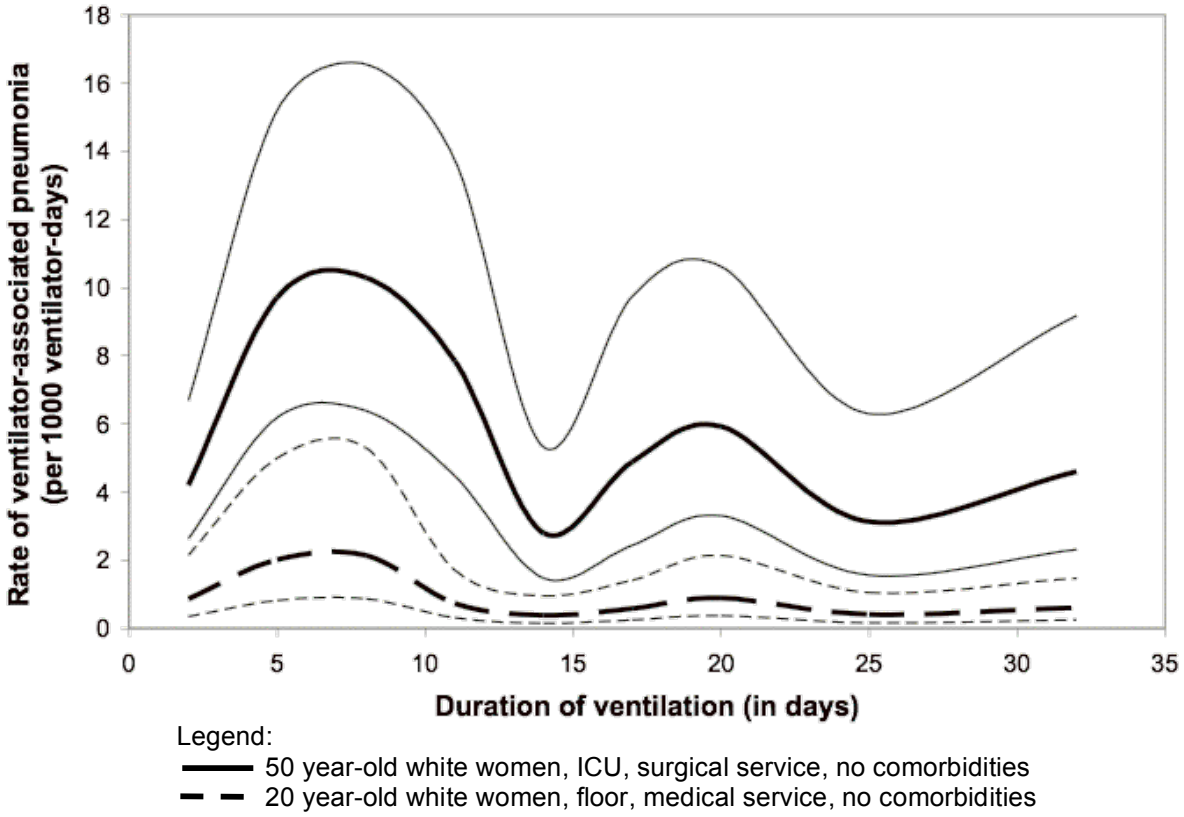
Full model adjusted for all covariates

When adjusting for all covariates, the trends in VAP rate remained similar to the unadjusted trends across ventilator duration. Rates increased in the first week to a high on days 7-9, then decreased to a low on days 13-15, peaked again on days 19-21 and leveled to a relatively stable rate for any subsequent ventilation duration.

For example (Figure 8), rates of VAP among 50 year-old, white women with no comorbidities, in an ICU and on a surgical service throughout duration of ventilation (i.e. the 'baseline' group, in which all risk factors are at referent levels) peaked at 10.29 per 1000 ventilator-days (95%CI 6.38, 16.56) on days 7-9, dropped to 2.79 per 1000 ventilator-days (95%CI 1.47, 5.31) on days 13-15 and had a second peak of 5.93 per 1000 (95%CI 3.31, 10.62) on days 19-21. The rate of VAP among this group was higher than the unadjusted rate (shown in Figure 6) for the first two weeks, then similar to the unadjusted rate with continuing ventilation. In contrast, the rate of VAP among 20 year-old, white women with no comorbidities, on a floor or step-down unit and a medical service throughout the duration of ventilation

peaked at 2.14 per 1000 ventilator-days (95%CI 0.86, 5.30) on days 7-9. With continuing ventilation, the rate ranged from 0.38 to 0.89 VAP per 1000 ventilator-days. The rate of VAP among this group was lower than the unadjusted rate throughout ventilator duration.

Figure 8. Estimated rate (with 95%CI) of ventilator-associated pneumonia across duration of ventilation among specified groups.



Adjusting for all other covariates (Table 16), having central venous catheter-associated blood-stream infection constituted the greatest elevation of VAP rate (OR 1.88, 95%CI 1.38, 2.56). Rate of VAP was 30-40% lower in the first 10 days of ventilation when patients were on medical (OR 0.61, 95%CI 0.33, 1.13) or pediatric (OR 0.67, 95%CI 0.38, 1.18) rather than surgical services. With subsequent ventilation duration VAP rate was 70% lower in medical (OR 0.30, 95%CI 0.21, 0.43)

and pediatric patients (OR 0.27, 95%CI 0.17, 0.42). VAP rate was higher when patients had a trauma (OR 1.60, 95%CI 1.18, 2.17), or had a concurrent central venous catheter (OR 1.51, 95%CI 1.01, 2.25) during their ventilator duration. Males (OR 0.89, 95%CI 0.72, 1.08) and patients on floors (OR 0.33, 95%CI 0.22, 0.50) had lower incidence of VAP compared with females and patients in ICUs. Race, age, and other comorbidities led to no change or inconclusive changes in VAP over the duration of ventilation.

D. Discussion

Ventilator-associated pneumonia (VAP) is an important cause of morbidity and mortality in hospitalized patients, accounting for 26% of all hospital-associated infections, 83% of all pneumonias, and approximately 30% of nosocomial infection-related mortality in the United States [1-2]. We found that the rate of VAP at UNC Hospitals in 2002-2007 varied across duration of ventilation. We found a peak in VAP rate late in the first week of ventilation, a decrease through the second week, a second peak late in the third week, and a lower rate with continuing ventilation. Saviteer et al. [23] found a similar trend of increasing and decreasing rates when studying all nosocomial infections across duration of hospitalization. Their measured trends were across a wider span, peaking around day 18 and dropping to day 24. Jaimes [10] reported changing hazard rate specifically for VAP which more closely resembles our results. We also found that these changes in rate of VAP over duration of ventilation remain when adjusting for risk factors.

Some risk factors have consistently been associated with increased VAP rate, including presence of a central venous catheter or primary blood-stream infection,

reintubation, aspiration, change of location within the hospital, tracheostomy, and patient positioning [4-5, 7, 9, 17, 24, 26-29]. Others, such as age, gender, hospital service, race/ethnicity, hospital service, and comorbidities have been identified as risk factors in some, but not all studies [5, 9, 10, 17, 27-28]. We did find that when accounting for the changing rate across ventilation duration, risk factors for VAP included gender, patient location, age, hospital service, trauma, and concurrent presence of a central venous catheter or central venous catheter-associated blood-stream infection.

We only included one hospital in this analysis. We were also unable to assess reintubation, aspiration, tracheostomy and patient positioning (i.e., head of bed >30^{o}). While these factors influence VAP, we do not expect them to play a role in VAP rate across ventilator duration. Standard practices at this one hospital are maintained throughout hospitalization, thus we expect that the variation in VAP rate throughout ventilator duration would be seen at other facilities as well.

We assumed that gaps of up to two days in the duration of ventilation from the nursing assessment represented continuous use. We conducted a separate analysis with more than a one-day gap considered to be removal and replacement of the ventilator. Odds ratios for covariates in that analysis were similar to those in the main analysis. Trends in VAP across duration of ventilation remained the same, with peaks at the end of the first and third weeks and a relative plateau with longer ventilator duration.

Ventilator placements with shorter duration may occur in healthier patients who are less likely to have infections, or they may occur in sicker patients who are

more likely to die before VAP occurs. We did not analyze mortality data or other information on competing outcomes, so we were unable to elucidate the causes for the lower rates of VAP in the first few days of ventilation. We did look at how the pool of patients changed across ventilator duration. The proportion of patients on a surgical service or with a trauma increased approximately 10% and the proportion of patients with concurrent central venous catheter-associated blood-stream infection increased 5% across five weeks of ventilation. The proportion of patients in the ICU decreased from 91% to 71% over the five weeks analyzed. The decrease in VAP on days 13-15 was not accompanied by a drastic change in any covariate.

E. Conclusions

Duration of mechanical ventilation influences the rate of VAP. Gender, patient location, hospital service, trauma, concurrent central venous catheter, and prior central venous catheter-associated blood stream infection affect the rate of VAP throughout ventilation duration. Being aware of shifts in the patient population, monitoring at risk patients closely, and timing interventions appropriately could aid in decreasing the incidence of VAP.

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VII. RESULTS: ANALYZING THE EFFECT OF DEVICE DURATION ON THE INCIDENCE OF VENTILATOR-ASSOCIATED PNEUMONIA

A. Introduction

Many longitudinal data analyses assume a constant outcome rate over the duration of exposure. This assumption is not always correct, but without a comparison model including changing rates over time, it is difficult to determine whether the constant-rate model assumption is appropriate for the data.

In some arenas, such as monitoring healthcare associated infections, assuming a constant risk (or incidence) of the outcome across the duration of exposure eases the data collection burden and facilitates the timely provision of surveillance numbers to monitor potential outbreaks [1-4]. However, it has been argued that using a constant rate model when the assumption of a constant rate across the duration of time is not met provides results that are "at best ambiguous, at worst misleading [1]." In particular, if a changing infection rate peaks and then decreases over long hospitalizations, not accounting for this change could mean that following guidelines to decrease exposure time would decrease numbers of infections but lead to higher constant infection rates because lower risk days were removed from the rate calculation.

This paper uses one type of device-associated infection (ventilator-associated pneumonia) as our example for assessing models of changing infection rate across the duration of exposure. Mechanical ventilators are among the medical devices

most commonly associated with nosocomial infection [2-4]. Infection rates are also not constant across duration of ventilation or hospitalization [5-8, Chapter VI]. Despite this, many studies of hospital associated infections in the United States report a single, constant rate for ventilator-associated pneumonia (VAP) in each intensive care unit.

Our objective in this study was to determine the impact of modeling the changing VAP rate throughout duration of ventilation. We hypothesized that a changing VAP rate provides more meaningful incidence estimates than a model assuming a constant rate of infection throughout ventilator duration.

B. Longitudinal Data Modeling Options

The analysis technique that is most commonly used for analysis of rates is the "constant rate" loglinear or Poisson regression model [9]. In its simplest form, this model assumes a constant outcome rate over the duration of exposure and the log of that rate is predicted by the linear vector of the regression covariates. The advantage of Poisson over logistic regression in longitudinal data analysis is that it accounts for variations in time at risk between patients. The disadvantage is that (unless time interactions are included) the outcome rate is presumed constant.

Cox proportional hazard regression allows for a changing (hazard) rate of the outcome over the duration of exposure. However, because Cox regression is based on a semiparametric model, the statistical equations used to maximize the likelihood do not maximize the baseline hazard rate [9, 10]. Discrete-time hazards regression also accounts for a changing outcome rate across the duration of exposure and it includes the changing baseline rate in its maximum likelihood

functions [11]. It does assume that the hazard rate for the outcome is constant over each chosen time interval, however this is a less restrictive assumption than a constant rate over the entire observation period (used in the constant rate model). Discrete-time hazards regression allows for direct estimation of the hazard function across the duration of exposure and allows for multiple time-dependent variables to be incorporated directly into the dataset [11]. This paper compares constant-rate Poisson models, which are widely reported in literature [2-6], to discrete-time hazards models with varying time intervals.

C. Example Study Data

This study included the 9,347 people who were hospitalized at UNC Hospitals between January 1, 2002 and December 31, 2007 and who used a mechanical ventilator for at least two days during their hospitalization. Data were collected as part of usual hospital care. Days of hospitalization and ventilation, gender, age, race/ethnicity, comorbidities derived from ICD-9 codes, patient location (ICU versus floor) on each day, and hospital service (medical, surgical, or pediatric) on each day were recorded for each patient. VAP occurred in 456 patients across 104,443 ventilator-days and 286,599 patient-days. Further description on the cohort and main study results have been provided elsewhere (see ventilator manuscript for aim 1).

For comparison of actual and model-predicted rates of VAP, we censored data after 35 days of ventilation or hospital stay, depending on measure of exposure duration. The 35-day endpoint was chosen because there were few cases of VAP after this point. The median ventilator duration was 4 days (IQR: 2-8) and the

median hospital stay was 7 days (IQR: 3-15). The median time between admission and ventilator placement was 0 days (IQR: 0-7).

D. Methods

Duration of time exposed

The duration between hospital admission and the 35th day of ventilation or discharge date for each patient was used to calculate "ventilator-days." The first two days of ventilation were not included because two days of exposure are required before VAP can occur [12].

Constant Rate Models

Unadjusted, constant rates of pneumonia across duration of ventilation were determined using a Poisson regression model including only the intercept.

$$rate = e^{\alpha}$$

This was equivalent to dividing the total number of pneumonias by the total duration of ventilation for all patients and is analogous to the constant rate models in the literature [2-4].

Discrete-Time Hazards Model Overview

We also modeled the data using discrete-time hazards models to allow the rate of VAP to change across the duration of ventilation [13,14]. A discrete-time hazard is the conditional probability that an individual, i, will experience the event of interest, j, during a time period, T, given that the individual did not experience the event in an earlier time period. The conditional rate of VAP in each discrete interval was the number of events in the interval divided by the number of units at risk (i.e. ventilator-days) during the interval.

$$\hat{h}(t_j) = \frac{number\_of\_VAP_j}{ventilator-days_j}$$

Life tables were used to define a risk set and an associated hazard rate for each discrete time interval. After determining the hazard rate for each time interval, logistic regression of the person-period dataset modeled the log odds of the hazard rate throughout the duration of exposure.

$$\log it(h(t_{ij})) = \alpha_1(Time\_Period\_1) + \alpha_2(Period\_2) + \alpha_3(Period\_3) + ... + \alpha_n(Period\_n)$$

The α_n represent the log of the odds for the baseline hazard rate associated with the discrete time intervals. Thus, α_n can be likened to the intercept of a logistic model, measured separately for each time interval.

Hazard rates were calculated for each time interval using the associated α_n.

$$hazard_n = \frac{1}{1 + e^{(\alpha_n)}}$$

Thus, discrete-time hazard models allowed us to estimate the changing rate of VAP across duration of hospitalization or ventilation.

Typically, the hazard for a discrete time period is the conditional probability of an event that can only occur once per patient. VAP can occur multiple times in one person, one admission, or even during one ventilator placement. We used generalized estimating equations [15] to account for multiple admissions or ventilator placements in one person and multiple VAP per placement. Because only a few ventilator placements had more than one VAP, we used an exchangeable correlation matrix, requiring only one parameter, but allowing for non-zero correlation between multiple ventilator placements and VAP within a person.

Longer versus shorter time periods in discrete-time hazards models

We conducted two discrete-time hazards analyses. The first had time periods of longer length to allow for smoothing and visualization of underlying trends. The second used shorter time periods, lengthening later time periods due to sparse data with longer duration of exposure.

The longer period discrete-time hazards analysis split the duration of ventilation or hospitalization into three-day time periods for the first three weeks and seven-day time periods for the fourth and fifth weeks. The shorter analysis time periods were one-day for the first 11 days, two-day for days 12-21, and seven-day with subsequent duration of exposure.

F-tests comparing modeled rates of VAP

The rate from each of the three models was multiplied by the number of continuing ventilator placements in order to calculate an expected number of VAP for each day based on that rate. The modeled rates were subtracted from the actual daily rate of infection for each day of exposure duration. The difference between the modeled rate and the actual rate was squared and summed across the duration of exposure to calculate the sum of squared error term for each of the three models. F-tests were used to compare the fit to the data of the three models (constant rate model, longer time interval discrete-time hazards model, and shorter time interval discrete-time hazards model).

Comparing Poisson and discrete-time hazards models

In Poisson models, log rate ratios (constant across time) are estimated to compare index to reference levels for each covariate. In discrete-time hazards

models, log odds of hazard ratios are estimated. Because rates are small (less than 10 per 1000 at all time points), the odds ratios of hazard rates approximate hazard rate ratios and we can utilize the asymptotic nature of the two models in order to compare the model estimates from the various models.

Competing risks

VAP is not the only possible outcome for patients with mechanical ventilation. None of these models count for competing risks, such as death. Also, since we did not have information about why ventilators were removed, patients who died during ventilation and patients who were well enough for ventilation removal are treated equally in these data.

Specific subpopulations of interest

In addition to modeling the overall population, we assessed five subgroups to determine whether models performed differently for different groups of interest. These five subgroups were: patients over age 65, patients under age 18, patients in an intensive care unit (ICU), patients on a surgical service, and patients on a surgical service with a trauma diagnosis.

Supplemental analyses using other denominators

Infection rates in many studies use the ventilator-day denominator required for CDC surveillance, but some use days in the hospital or “patient-days” as their denominator or only assess duration of exposure until first infection [4]. Thus, we also assessed differences in VAP across duration of hospitalization, and duration of ventilation/hospitalization until first infection.

E. Results

There were 425 VAPs in the first 35 days of ventilation. The number of VAP was highest on the fourth day of exposure (n=48) and the rate was highest on the sixth day (9.53 VAP per 1000 ventilator-days). The rate of VAP increased over the first week, decreased in the second week, increased again in the third week, and was variable with subsequent duration due to small numbers of VAP each day. Half of ventilator placements were less than five days, and 75% were less than 10 days. Half of VAP occurred on or before the ninth day of ventilation and 75% occurred by the 13th day. Half of hospitalizations were less than 16 days, and 75% were less than 32 days. Half of VAP occurred on or before the ninth day of hospitalization and 75% of VAP occurred by the 19th day.

Constant rate model

The constant infection rate across the first 35 days of ventilation was 5.22 per 1000 ventilator-days (95% CI 4.72, 5.71). The same number of infections were predicted across the duration of ventilation as actually occurred. The largest difference in expected and actual number of infections was on the sixth day of ventilation in which the constant rate predicted 25 VAP, but 45 occurred. The largest rate difference between the constant rate model and the observed incidence also occurred at the end of the first week, when the actual VAP rate peaked (Figure 9). The predicted rate was higher than the actual rate of VAP for the first 3 days, then lower through day 11. With longer ventilator duration, the constant rate model generally overestimated the actual rate.

The total error (sum of errors) across the duration was an excess of 17 VAP per 1000 ventilator-days (Table 17). In the first 10 days, during which 75% of ventilator placements completed duration, the total error was a decrease of 13 VAP per 1000 ventilator-days (Table 18).

Figure 9. Actual and model-predicted rate of ventilator-associated pneumonia throughout duration of mechanical ventilation.

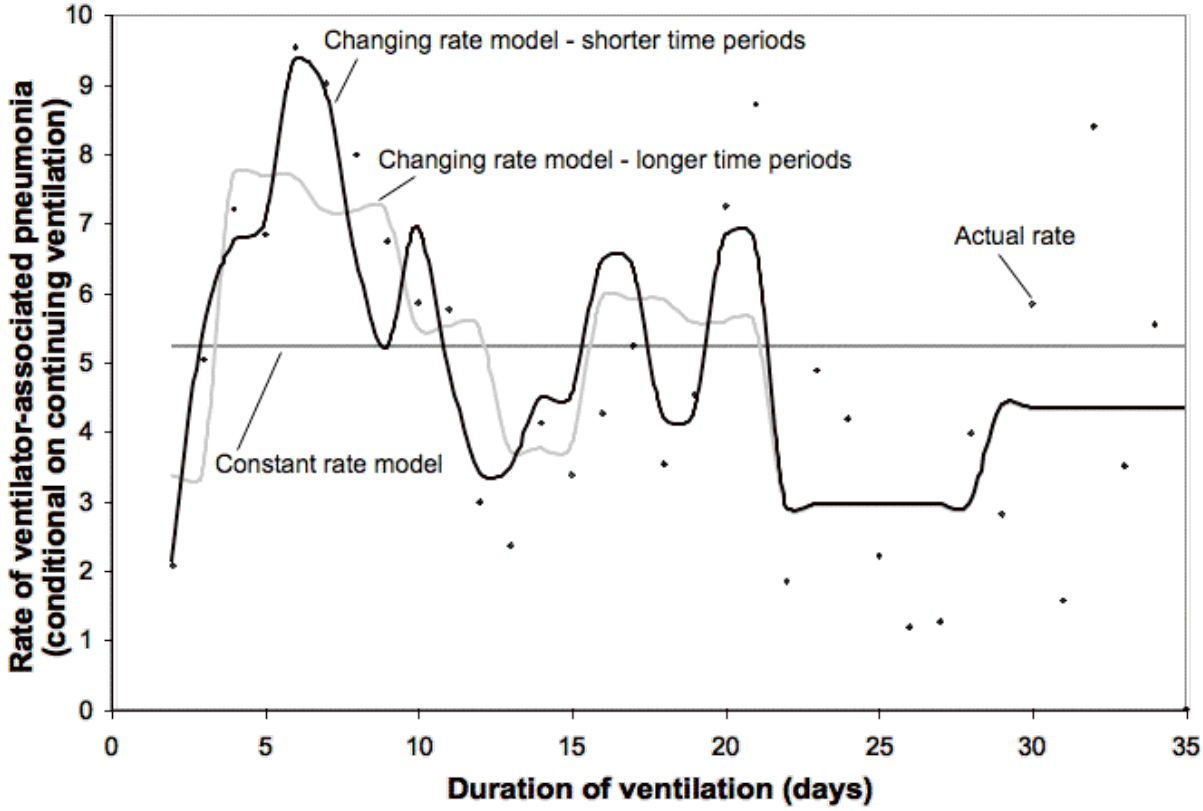

Table 17. Model performance across entire period of observation (35 days of ventilation)

		Discrete-time hazards	
	Constant-rate	Longer time-periods	Shorter time-periods
Number of parameters estimated	1	9	17
Average error (per 1000 ventilator-days)	0.53	0.11	0.14
Sum of errors (per 1000 ventilator-days)	17.86	3.99	4.71
Sum of squared errors	0.000213	0.000108	0.000083
	F-tests		
	Longer vs. Shorter time- periods	Longer time-periods vs. Constant rate	Shorter time-Periods vs Constant rate
F-test	0.62	3.07	1.66
p-value	0.75	0.01	0.16

Discrete-hazards model with longer time periods

In the model with longer time periods, the predicted rate ranged between 3 and 8 VAP per 1000 ventilator-days (Figure 9). This model predicted 3 more VAP predicted than actually occurred across the 35 day duration of ventilation. The largest difference between actual and predicted number of infections was on the second day, when the predicted number was 16 higher than the actual number of VAP. The largest difference in rate between the predicted and actual VAP occurred on the 35th day of ventilation when no VAP occurred but 4 per 1000 ventilator-days (n=2) were expected. The modeled rate was generally higher than the actual rate for the first 5 days, lower through day 10, then higher through day 19. Differences between modeled and observed rates were generally larger in the last two weeks, when seven-day time intervals were used and the number of actual infections on any day was small.

The total error (sum of errors) across the duration of ventilation was an excess of 4 VAP per 1000 ventilator-days (Table 17). In the first 10 days, the sum of

errors from the model were 4 per 1000 ventilator-days lower than the observed rate (Table 18).

Table 18. Performance of model for subgroups of interest.

		Discrete-time hazards	
	Constant-rate	Longer time-periods	Shorter time-periods
Across first 10 days of mechanical ventilation			
Number of parameters estimated	1	4	9
Sum of errors (per 1000 ventilator-days)	-13.32	-3.69	2.31
Sum of squared errors	0.000059	0.000013	0.000006
		F-tests	
	Longer vs. Shorter time- periods	Longer time-periods vs. Constant rate	Shorter time-Periods vs Constant rate
F-test	0.24	5.82	1.10
p-value	0.90	0.04	0.63
Number of parameters estimated for all models below	1	9	17
Over 65 years old			
Sum of errors (per 1000 ventilator-days)	21.54	7.09	7.88
Sum of squared errors	0.000975	0.000767	0.000738
		F-tests	
	Longer vs. Shorter time- periods	Longer time-periods vs. Constant rate	Shorter time-Periods vs Constant rate
F-test	0.09	0.85	0.34
p-value	0.99	0.57	0.98
Under 18 years old			
Sum of errors (per 1000 ventilator-days)	-6.82	-17.59	-17.62
Sum of squared errors	0.000413	0.000324	0.000299
		F-tests	
	Longer vs. Shorter time- periods	Longer time-periods vs. Constant rate	Shorter time-Periods vs Constant rate
F-test	0.18	0.86	0.41
p-value	0.99	0.56	0.96

Table 18. continued. Performance of model for subgroups of interest.

ICU			
Sum of errors (per 1000 ventilator-days)	15.43	5.02	5.54
Sum of squared errors	0.000284	0.000154	0.000131
		F-tests	
	Longer vs. Shorter time- periods	Longer time-periods vs. Constant rate	Shorter time-Periods vs Constant rate
F-test	0.38	2.61	1.23
p-value	0.92	0.03	0.34
Surgical Service			
Sum of errors (per 1000 ventilator-days)	51.00	24.22	28.74
Sum of squared errors	0.000681	0.000312	0.000273
		F-tests	
	Longer vs. Shorter time- periods	Longer time-periods vs. Constant rate	Shorter time-Periods vs Constant rate
F-test	0.31	3.69	1.59
p-value	0.95	0.01	0.18
Surgical service and Trauma diagnosis			
Sum of errors (per 1000 ventilator-days)	57.41	37.04	38.28
Sum of squared errors	0.001502	0.001065	0.001005
		F-tests	
	Longer vs. Shorter time- periods	Longer time-periods vs. Constant rate	Shorter time-Periods vs Constant rate
F-test	0.13	1.28	0.53
p-value	0.99	0.30	0.90

Discrete-hazards model with shorter time periods

In the model with shorter time periods, the modeled rate ranged between 2 and 9 VAP per 1000 ventilator-days. The largest difference between the actual and predicted number of infections was on days 8 and 9, when five fewer VAP were expected from the model than actually occurred. The largest rate difference between the modeled and actual VAP was on the 35th day of ventilation (Figure 9).

As with the larger time period discrete-hazard model, there were zero actual VAP, but 4 per 1000 ventilator-days were expected from the model.

The total error (sum of errors) across the duration of ventilation was an excess of 5 VAP per 1000 ventilator-days (Table 17). In the first 10 days, the sum of errors from the model were 2 per 1000 ventilator-days lower than the observed rate (Table 18).

Comparison of models

Residual differences between the shorter time period discrete-time hazards model and the observed incidence were consistently smaller than the longer time period model and the constant rate model. While all of the models overestimated the actual incidence, models that allowed flexibility in measuring rate across the duration of ventilation were a better fit to the data than the constant rate model (Table 17). The average error for discrete-hazards models was approximately one-quarter of that in the constant model.

Over 75% of ventilator placements had been removed by the end of the tenth day. During this time, all of the models underestimated the actual VAP rate conditional on continuing ventilator duration. The constant rate model had larger sum of squared error, total error, and average error than the variable rate models.

The F-test comparing the constant rate model to the longer time period discrete-time hazards model was statistically significant across the entire 35 days (Table 17) and the first 10 days of ventilation (Table 18), indicating better fit of the changing rate model. The F-test comparing the constant rate model to the shorter-time period discrete-time hazards model did not provide a statistically significant

better fit to the observed incidence. The constant rate model does not account for the variation in VAP rate over duration of exposure, but the shorter-time period model includes too much random error for estimating trends in the data. Thus, for ventilator-days, the changing rate model with longer time periods provides the best fit to the observed incidence.

F. Patient subgroups

Selected patient groups for comparison of models across duration of time
All models underestimated VAP rate across the duration of ventilation for patients under age 18 (Table 18). All models overestimated VAP rates for patients over age 65, in the ICU, on surgical service, and on a surgical service with trauma diagnosis. While models were consistently over- or underestimated the rate, the magnitude of the constant rate model was smaller among patients under 18 and larger for all other groups of interest when compared to the changing rate models. The F-test indicated that the longer time period changing rates model was a better fit to the actual VAP rate for ICU and surgical service patients. The changing rate models did not have a statistically better fit than the constant rate model among patients with younger or older ages or among surgical patients with a trauma diagnosis.

G. Other denominators

Results were replicated in using duration of hospitalization and duration of ventilation/hospitalization prior to infection as denominators. For all denominator choices, at least one of the changing rates models were statistically a better fit than the constant rate model when accounting for time at risk.

H. Discussion

In this study, we compared constant and variable rate models to observed incidence for VAP throughout duration of ventilation and hospitalization. The actual rate of VAP, conditional on continuing ventilation or hospitalization, changed across time. While all models overestimated the observed incidence, models that allowed flexibility in measuring rate across time had approximately half of the sum of squared error compared to the constant rate model (Table 17). The average error for discrete-hazards models was less than one-third of that in the constant model.

Over 75% of ventilator placements had been removed by the end of the tenth day of ventilation. During this initial 10-day period, all of the models underestimated the actual VAP rate conditional on continuing ventilator duration.

The degree to which each model underestimated the VAP rate during the first ten days was at least half as large as the degree to which it was overestimated across the total duration studied (35 days). Inclusion of these longer-lasting ventilator placements in the data decreased the estimated constant rate. Thus, the benefit of the changing rate models was that earlier time periods were more accurately modeled without being influenced by extended ventilation.

Limiting to selected patient groups, ventilator-day models performed similarly to the overall population. In all situations in which a single model was a superior, the longer time period changing rate model was the best predictor of the observed incidence. In three of the target groups, including both of those based on age, the three models did not have statistically different fit to the observed incidence. The

constant rate model was also a poorer estimate of the actual VAP rate in target groups across the duration of hospitalization and the duration at risk.

Ideally, all data used to compare across different patient populations or different hospitals should be adjusted for the changing rate of VAP across ventilator duration. This is frequently not possible, since the duration of device placement for each person is often unavailable. Without data on duration of ventilation and the day of VAP, it is impossible to know whether it is important to account for the time-varying nature of the incidence of VAP and other device-related infections. Thus, investigators should be aware that bias may be introduced when comparing differences between patient groups within a hospital, or comparing between hospitals without accounting for differences in rate across device exposure.

I. Conclusion

Most surveillance reports assume a constant rate model. In some target populations, there is not enough variation among the modeling strategies to warrant accounting for changes across the duration of ventilation or hospitalization. However, in some populations, including the overall population with ventilators at UNC Hospitals, there is sufficient variation in rate of VAP over duration of ventilation and hospitalization to warrant accounting for the changing rate. Investigators comparing different hospitals, or patient subgroups within a hospital, should be aware that bias may be introduced by failing to account for the time-varying nature of device-related infection rates.

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VIII. RESULTS: SUPPLEMENTAL RESULTS FOR ANALYZING THE EFFECTS OF DEVICE DURATION AND EXPOSURE DEFINITION

A. Scope of Chapter

This chapter is intended to cover the results for specific aim 2 which were not included in the previous chapter. It consists of five main sections:

a. Results for the effect of patient characteristics on ventilator-associated pneumonia (VAP) rates as measured by ventilator-days

b. Results for the effect of exposure definition (i.e. denominator choice) on ventilator-associated pneumonia (VAP)

c. Results for the effect of patient characteristics on central line-associated bloodstream infections (CLABSI) as measured by line-days

d. Results for the effect of device duration on CLABSI (assessed across 8 weeks (56 days))

e. Results for the effect of denominator choice on CLABSI

This chapter is not intended to provide information in a format appropriate for publication. Rather, since the results of the device duration analysis were similar across mechanical ventilator and central line associated infections and across different denominator choices, the tables and graphs in this chapter are intended as supplemental material for the previous results chapter.

Each section begins with a short paragraph summarizing the tables and graphs to follow and noting any differences from the results of “Analyzing the effect of device duration on the incidence rate of ventilator-associated pneumonia.”

B. Effect of covariates on rate of VAP

Across the three analysis methods, increased rate of VAP over the duration of ventilation was associated with being in an ICU, on a surgical service, trauma complication, having a central line and having a central line-associated blood-stream infection (Table 19 shows rate ratios for ventilator-days). The three models led to similar conclusions about covariates, and the estimated coefficients and width of confidence intervals did not vary considerably across covariates. While all confidence intervals between the models overlapped the estimates of the other models, the constant rate model implied greater risk of VAP in patients with central lines and less risk increase associated with central line-associated blood-stream infection. This might be due to the estimation of ever concurrently having a central line versus estimating concurrent presence of a central line during each time period in the discrete-time hazards models. In the constant-rate model, initial location and hospital service were included rather than as time-dependent variables (like they were included in discrete-time hazards models and in previous manuscripts). While these variables were allowed to change, very few did over the course of one ventilation placement, thus the estimates from the constant and changing-rate models are fairly comparable.

Table 19. Comparison of rate ratios* across VAP models.

Covariates	Fully Adjusted Model Rate Ratios* (95% Confidence Intervals)		
	Poisson	Discrete-time hazards	
	Constant Rate	Longer Time-Periods	Shorter Time-Periods
Gender			
Female	ref	ref	ref
Male	0.87 (0.72, 1.07)	0.88 (0.73, 1.06)	0.88 (0.73, 1.06)
Race			
White	ref	ref	ref
Black	0.97 (0.78, 1.20)	0.94 (0.77, 1.16)	0.94 (0.76, 1.15)
Hispanic	1.11 (0.74, 1.65)	1.11 (0.75, 1.64)	1.11 (0.76, 1.64)
Other race	0.65 (0.40, 1.07)	0.64 (0.40, 1.04)	0.95 (0.59, 1.32)
Age			
50 years old	ref	ref	ref
Per 10 year increase	0.94 (0.88, 1.00)	0.95 (0.89, 1.01)	0.95 (0.89, 1.00)
Patient location			
ICU	2.86 (1.94, 4.21)	2.58 (1.78, 3.73)	2.59 (1.80, 3.75)
Floor or step-down unit	ref	ref	ref
Hospital service			
Medicine	ref	ref	ref
Surgery	3.31 (2.37, 4.61)		
Pediatrics	1.14 (0.70, 1.85)		
First 11 days - Surgery	N/A	1.24 (0.74, 2.06)	3.51 (2.38, 5.18)
Pediatrics	N/A	1.08 (0.60, 1.93)	1.30 (0.71, 2.39)
After 11 days - Surgery	N/A	3.06 (2.18, 4.29)	1.05 (0.64, 1.75)
Pediatrics	N/A	0.97 (0.59, 1.59)	1.03 (0.54, 1.96)
Comorbidities^			
Cardiovascular complications	0.87 (0.54, 1.39)	0.97 (0.63, 1.51)	1.00 (0.64, 1.56)
Trauma	1.49 (1.10, 2.01)	1.63 (1.24, 2.14)	1.62 (1.23, 2.12)
Acute respiratory distress syndrome	1.07 (0.87, 1.33)	0.95 (0.77, 1.15)	0.95 (0.78, 1.16)
Acute renal failure	0.94 (0.53, 1.65)	0.79 (0.44, 1.41)	0.79 (0.44, 1.40)
Immunodeficiency	0.97 (0.60, 1.57)	1.04 (0.68, 1.60)	1.06 (0.69, 1.62)
Concurrent central line	1.96 (1.07, 3.58)	1.39 (0.96, 2.00)	1.35 (0.94, 1.96)
Concurrent central line-associated blood-stream infection	1.36 (1.02, 1.82)	1.77 (1.34, 2.32)	1.77 (1.35, 2.33)

* Discrete-hazards models provide "odds of hazard rate ratios." Since rates are small, we assume that the rate ratios and odds of hazard rate ratios are approximately equal and comparable across models to determine trends.

^Reference level for comorbidities and concurrent central line variables is all ventilator placements without that comorbidity or concurrent central line.

C. Effect of denominator choice on VAP

Reason for assessment

Infection rates in many studies use the ventilator-day denominator required for national surveillance reporting, but some use days in the hospital or "patient-days" as their denominator [4]. VAP also does not necessitate removal of the device, and multiple infections are possible, so a patient may contribute time to the ventilator-day or patient-day denominators after infection occurs. There is a possibility that some studies only include duration of exposure prior to infection as their time-at-risk. Therefore, we assessed these different denominator choices to determine whether changing rate models were appropriate across all options for defining exposure-time.

Findings

As with ventilator-days, all denominator choices indicated that changing rate models were better estimates of the observed incidence for at least one subgroup assessed.

Table 20. Summary of error in models compared to observed across different denominators for ventilator-associated-pneumonia.

		Discrete-time hazards	
Patient-days	Constant-rate	Longer time-periods	Shorter time-periods
Average error (per 1000 patient-days)	0.25	0.09	0.03
Sum of errors (per 1000 patient-days)	8.51	3.28	1.11
Sum of squared errors	0.000033	0.000012	0.000008
	Longer vs. Shorter time-periods	Longer time-periods vs. Constant rate	Shorter time-Periods vs Constant rate
F-test	1.03	5.34	3.21
p-value	0.45	<0.01	0.01
Ventilator-days-at-risk			
Average error (per 1000 ventilator-days)	3.10	0.02	0.02
Sum of errors (per 1000 ventilator-days)	10.55	0.83	0.79
Sum of squared errors	0.000238	0.000153	0.000095
		F-tests	
	Longer vs. Shorter time-periods	Longer time-periods vs. Constant rate	Shorter time-Periods vs Constant rate
F-test	1.28	1.74	1.55
p-value	0.32	0.14	0.18
Patient-days-at-risk			
Average error (per 1000 patient-days)	0.25	0.07	0.01
Sum of errors (per 1000 patient-days)	8.47	2.43	0.22
Sum of squared errors	0.000011	0.000001	<0.000001
		F-tests	
	Longer vs. Shorter time-periods	Longer time-periods vs. Constant rate	Shorter time-Periods vs Constant rate
F-test	1.04	4.49	2.79
p-value	0.45	<0.01	0.02

Table 21. Summary of error in models compared to actual VAP across **patient-days** for subgroups of interest.

		Discrete-time hazards	
	Constant-rate	Longer time-periods	Shorter time-periods
Across first 10 days of hospitalization			
Sum of errors (per 1000 patient-days)	-6.16	0.21	0.03
Sum of squared errors	0.000012	0.000001	<0.000001
		F-tests	
	Longer vs. Shorter time- periods	Longer time-periods vs. Constant rate	Shorter time-Periods vs Constant rate
F-test	878.98	15.23	5569.99
p-value	0.03	<0.01	0.01
Over 65 years old			
Sum of errors (per 1000 patient-days)	7.20	-0.15	-2.57
Sum of squared errors	0.000084	0.000063	0.000055
		F-tests	
	Longer vs. Shorter time- periods	Longer time-periods vs. Constant rate	Shorter time-Periods vs Constant rate
F-test	0.29	1.05	0.55
p-value	0.96	0.43	0.88
Under 18 years old			
Sum of errors (per 1000 patient-days)	4.69	1.62	0.36
Sum of squared errors	0.000033	0.000027	0.000025
		F-tests	
	Longer vs. Shorter time- periods	Longer time-periods vs. Constant rate	Shorter time-Periods vs Constant rate
F-test	0.15	0.71	0.33
p-value	0.99	0.68	0.98
ICU			
Sum of errors (per 1000 patient-days)	8.93	3.32	1.16
Sum of squared errors	0.000036	0.000013	0.000009
		F-tests	
	Longer vs. Shorter time- periods	Longer time-periods vs. Constant rate	Shorter time-Periods vs Constant rate
F-test	0.84	5.41	2.98
p-value	0.58	<0.01	0.02

Table 21 cont. Summary of error in models compared to actual VAP across **patient-days** for subgroups of interest.

		Discrete-time hazards	
	Constant-rate	Longer time-periods	Shorter time-periods
Surgical service			
Sum of errors (per 1000 patient-days)	17.33	9.22	5.98
Sum of squared errors	0.000110	0.000045	0.000031
		F-tests	
	Longer vs. Shorter time- periods	Longer time-periods vs. Constant rate	Shorter time-Periods vs Constant rate
F-test	0.97	4.51	2.72
p-value	0.49	<0.01	0.02
Surgical service and trauma diagnosis			
Sum of errors (per 1000 patient-days)	22.15	21.59	17.47
Sum of squared errors	0.000381	0.000256	0.000230
		F-tests	
	Longer vs. Shorter time- periods	Longer time-periods vs. Constant rate	Shorter time-Periods vs Constant rate
F-test	0.24	1.51	0.70
p-value	0.98	0.20	0.77

Table 22. Summary of error in models compared to actual VAP across **ventilator-days-at-risk** for subgroups of interest.

		Discrete-time hazards	
	Constant-rate	Longer time-periods	Shorter time-periods
Across first 10 days of mechanical ventilation			
Sum of errors (per 1000 ventilator-days)	-12.73	4.35	-0.17
Sum of squared errors	0.000063	0.000015	0.000001
		F-tests	
	Longer vs. Shorter time-periods	Longer time-periods vs. Constant rate	Shorter time-Periods vs Constant rate
F-test	7.70	5.18	20.15
p-value	0.27	0.05	0.18
Over 65 years old			
Sum of errors (per 1000 ventilator-days)	20.91	11.23	12.56
Sum of squared errors	0.001080	0.000884	0.000860
		F-tests	
	Longer vs. Shorter time-periods	Longer time-periods vs. Constant rate	Shorter time-Periods vs Constant rate
F-test	0.06	0.70	0.27
p-value	0.99+	0.69	0.99
Under 18 years old			
Sum of errors (per 1000 ventilator-days)	-15.31	31.54	-24.58
Sum of squared errors	0.000535	0.000439	0.000397
		F-tests	
	Longer vs. Shorter time-periods	Longer time-periods vs. Constant rate	Shorter time-Periods vs Constant rate
F-test	0.22	0.68	0.37
p-value	0.98	0.70	0.98
ICU			
Sum of errors (per 1000 ventilator-days)	4.05	-2.67	-1.75
Sum of squared errors	0.000354	0.000232	0.000204
		F-tests	
	Longer vs. Shorter time-periods	Longer time-periods vs. Constant rate	Shorter time-Periods vs Constant rate
F-test	0.28	1.66	0.78
p-value	0.96	0.16	0.69

Table 22. cont. Summary of error in models compared to actual VAP across **ventilator-days-at-risk** for subgroups of interest.

		Discrete-time hazards	
	Constant-rate	Longer time-periods	Shorter time-periods
Surgical service			
Sum of errors (per 1000 ventilator-days)	48.60	30.27	31.75
Sum of squared errors	0.000742	0.000405	0.000363
		F-tests	
	Longer vs. Shorter time-periods	Longer time-periods vs. Constant rate	Shorter time-Periods vs Constant rate
F-test	0.25	2.60	1.11
p-value	0.98	0.03	0.41
Surgical service and trauma diagnosis			
Sum of errors (per 1000 ventilator-days)	46.86	46.21	47.15
Sum of squared errors	0.001724	0.001370	0.001288
		F-tests	
	Longer vs. Shorter time-periods	Longer time-periods vs. Constant rate	Shorter time-Periods vs Constant rate
F-test	0.14	0.81	0.36
p-value	0.99+	0.60	0.98

Table 23. Summary of error in models compared to actual VAP across **patient-days-at-risk** for subgroups of interest.

		Discrete-time hazards	
	Constant-rate	Longer time-periods	Shorter time-periods
Across first 10 days of hospitalization			
Sum of errors (per 1000 patient-days)	-5.76	0.18	<0.01
Sum of squared errors	0.000011	0.000001	<0.000001
		F-tests	
	Longer vs. Shorter time- periods	Longer time-periods vs. Constant rate	Shorter time-Periods vs Constant rate
F-test	751890	15.052	4713900
p-value	0.001	0.006	<0.01
Over 65 years old			
Sum of errors (per 1000 patient-days)	7.65	-0.75	-3.19
Sum of squared errors	0.000097	0.000074	0.000066
		F-tests	
	Longer vs. Shorter time- periods	Longer time-periods vs. Constant rate	Shorter time-Periods vs Constant rate
F-test	0.25	0.96	0.49
p-value	0.97	0.49	0.92
Under 18 years old			
Sum of errors (per 1000 patient-days)	4.58	1.20	-0.14
Sum of squared errors	0.000034	0.000030	0.000027
		F-tests	
	Longer vs. Shorter time- periods	Longer time-periods vs. Constant rate	Shorter time-Periods vs Constant rate
F-test	0.18	0.50	0.27
p-value	0.99	0.84	0.99
ICU			
Sum of errors (per 1000 patient-days)	8.88	2.48	0.27
Sum of squared errors	0.000036	0.000015	0.000010
		F-tests	
	Longer vs. Shorter time- periods	Longer time-periods vs. Constant rate	Shorter time-Periods vs Constant rate
F-test	0.87	4.65	2.66
p-value	0.56	<0.01	0.03

Table 23. cont. Summary of error in models compared to actual VAP across **patient-days-at-risk** for subgroups of interest.

		Discrete-time hazards	
	Constant-rate	Longer time-periods	Shorter time-periods
Surgical service			
Sum of errors (per 1000 patient-days)	18.32	8.55	5.22
Sum of squared errors	0.000114	0.000051	0.000036
		F-tests	
	Longer vs. Shorter time- periods	Longer time-periods vs. Constant rate	Shorter time-Periods vs Constant rate
F-test	0.86	3.90	2.29
p-value	0.57	<0.01	0.05
Surgical service and trauma diagnosis			
Sum of errors (per 1000 patient-days)	24.64	23.01	18.74
Sum of squared errors	0.000408	0.000294	0.000265
		F-tests	
	Longer vs. Shorter time- periods	Longer time-periods vs. Constant rate	Shorter time-Periods vs Constant rate
F-test	0.24	1.20	0.58
p-value	0.98	0.34	0.86

D. Effect of covariates on rate of CLABSI

Across the three analysis methods, increased rate of CLABSI over the duration of central line placement was associated with Black or other race (not Hispanic), being in an ICU, on a surgical service, acute respiratory distress syndrome, and acute renal failure (Table 24 shows rate ratios for central line-days). The three models led to similar conclusions about covariates, and the estimated coefficients and width of confidence intervals did not vary considerably across covariates. In the constant-rate model, initial location and hospital service were included rather than as time-dependent variables (like they were included in discrete-time hazards models and in the previous manuscript). While these variables were allowed to change, very few did over the course of one central line

placement, thus the estimates from the constant and changing-rate models are comparable.

Table 24. Comparison of rate ratios* across CLABSI models.

	Fully Adjusted Model Rate Ratios* (95% Confidence Intervals)		
	Poisson	Discrete-time hazards	
Covariates	Constant-Rate	Longer Time-Periods	Shorter Time-Periods
Gender			
Female	ref	ref	ref
Male	1.11 (0.99, 1.23)	n/a	n/a
Male ≤ 7 days	n/a	1.32 (1.12, 1.54)	1.34 (1.13, 1.60)
Male > 7 days	n/a	0.98 (0.85, 1.13)	0.96 (0.83, 1.12)
Race			
White	ref	ref	ref
Black	1.32 (1.18, 1.48)	1.37 (1.22, 1.54)	1.37 (1.22, 1.54)
Hispanic	1.05 (0.82, 1.33)	1.07 (0.83, 1.38)	1.07 (0.83, 1.39)
Other race	1.41 (1.14, 1.75)	1.40 (1.11, 1.77)	1.40 (1.11, 1.77)
Age			
50 years old	ref	ref	ref
Per 10 year increase	0.98 (0.95, 1.02)	1.01 (0.98, 1.05)	1.01 (0.98, 1.05)
Patient location			
Floor or step-down unit	ref	ref	ref
ICU	1.36 (1.20, 1.53)	1.32 (1.16, 1.48)	1.31 (1.16, 1.48)
Hospital service			
Medicine	ref	ref	ref
Surgery	1.15 (1.01, 1.31)	1.15 (1.00, 1.31)	1.14 (1.00, 1.31)
Pediatrics	0.86 (0.67, 1.10)	0.63 (0.45, 0.90)	0.63 (0.45, 0.89)
Other	0.47 (0.31, 0.71)	0.46 (0.30, 0.71)	0.47 (0.30, 0.72)
Comorbidities^			
Cardiovascular complications	0.63 (0.47, 0.84)	0.64 (0.47, 0.86)	0.64 (0.47, 0.87)
Trauma	0.99 (0.78, 1.25)	1.00 (0.77, 1.28)	1.00 (0.78, 1.28)
Acute respiratory distress syndrome	1.15 (1.00, 1.32)	1.09 (0.95, 1.26)	1.09 (0.95, 1.26)
Acute renal failure	1.29 (0.99, 1.68)	1.30 (0.99, 1.72)	1.30 (0.99, 1.71)
Immunodeficiency	0.87 (0.72, 1.04)	0.88 (0.72, 1.08)	0.88 (0.72, 1.08)

* Discrete-hazards models provide "odds of hazard rate ratios." Since rates are small, we assume that the rate ratios and odds of hazard rate ratios are approximately equal and comparable across models to determine trends.
^Reference level for comorbidities and concurrent central line variables is all ventilator placements without that comorbidity or concurrent central line.

E. Effect of device duration on CLABSI

As with ventilator-days, the constant rate central-line day models were associated with more error than the changing rate models. The F-test comparing

the constant rate model to the shorter-time period discrete-hazards model did not provide a statistically significant better fit to the observed incidence (Table 7). But, the F-test comparing the constant rate to the longer-time period model was statistically significant across the 8 weeks of duration assessed. Thus, for central line-days, as for ventilator-days, the changing rate model with longer time periods provides the best fit to the observed incidence. The constant rate model does not account for the variation in CLABSI rate over the duration of exposure, but the shorter-time period changing rate model includes too much random error for estimating trends in the data.

The only subgroup with statistically significant F-tests indicating better fit for the changing rate models was the assessment of the first 10 days of central line placement. Thus, it appears that no subgroup of patients drives the overall variation in CLABSI rate across duration of central line placement. In this case, bias may be introduced when comparing the overall group of UNC Hospitals patients to only a subset of patients without accounting for the changing rate across device placement.

Table 25. Summary of error in models compared to actual CLABSI across **central line-days**.

		Discrete-time hazards	
	Constant-rate	Longer time-periods	Shorter time-periods
Average error (per 1000 central line-days)	-1.52	-0.05	-0.03
Sum of errors (per 1000 central line-days)	-85.11	-2.83	-1.45
Sum of squared errors	0.000359	0.000175	0.000160
		F-tests	
	Longer vs. Shorter time- periods	Longer time-periods vs. Constant rate	Shorter time-Periods vs Constant rate
F-test	0.12	4.19	0.96
p-value	0.99+	<0.01	0.55

Table 26. Summary of error in models compared to actual CLABSI across **central line-days** for subgroups of interest.

		Discrete-time hazards	
	Constant-rate	Longer time-periods	Shorter time-periods
Across first 10 days of central line placement			
Sum of errors (per 1000 central line-days)	1.06	0.02	0.03
Sum of squared errors	0.000014	0.000003	<0.000001
		F-tests	
	Longer vs. Shorter time- periods	Longer time-periods vs. Constant rate	Shorter time-Periods vs Constant rate
F-test	4277	6.56	12205
p-value	0.01	0.03	0.01
Over 65 years old			
Sum of errors (per 1000 central line-days)	-96.88	-7.15	-4.86
Sum of squared errors	0.001921	0.001693	0.001689
		F-tests	
	Longer vs. Shorter time- periods	Longer time-periods vs. Constant rate	Shorter time-Periods vs Constant rate
F-test	<0.01	0.54	0.11
p-value	0.99+	0.87	0.99+
Under 18 years old			
Sum of errors (per 1000 central line-days)	-82.13	-14.90	-14.33
Sum of squared errors	0.000730	0.000542	0.000502
		F-tests	
	Longer vs. Shorter time- periods	Longer time-periods vs. Constant rate	Shorter time-Periods vs Constant rate
F-test	0.10	1.39	0.35
p-value	0.99+	0.21	0.99+
ICU			
Sum of errors (per 1000 central line-days)	-75.34	0.52	1.27
Sum of squared errors	0.000602	0.000439	0.000406
		F-tests	
	Longer vs. Shorter time- periods	Longer time-periods vs. Constant rate	Shorter time-Periods vs Constant rate
F-test	0.10	1.49	0.37
p-value	0.99+	0.17	0.99+

Table 26. cont. Summary of error in models compared to actual CLABSI across **central line-days** for subgroups of interest.

		Discrete-time hazards	
	Constant-rate	Longer time-periods	Shorter time-periods
Surgical service			
Sum of errors (per 1000 central line-days)	-58.59	24.01	25.49
Sum of squared errors	0.000547	0.000512	0.000519
		F-tests	
	Longer vs. Shorter time- periods	Longer time-periods vs. Constant rate	Shorter time-Periods vs Constant rate
F-test	-0.015	0.27	0.04
p-value	n/a	0.99	0.99+
Surgical service and trauma diagnosis			
Sum of errors (per 1000 central line-days)	-4.05	67.48	69.55
Sum of squared errors	0.002142	0.002313	0.002377
		F-tests	
	Longer vs. Shorter time- periods	Longer time-periods vs. Constant rate	Shorter time-Periods vs Constant rate
F-test	-0.03	-0.30	-0.08
p-value	n/a	n/a	n/1

F. Effect of denominator choice on CLABSI

Constant rate models were appropriate for many subgroups with all of the different denominators for central line exposure. But, as with ventilators and central line-days, all denominator choices indicated that changing rate models were better estimates of the observed incidence for at least the overall group at UNC Hospitals or one subgroup assessed.

Table 27. Summary of error in models compared to actual CLABSI across different denominators for central line duration.

		Discrete-time hazards	
Patient-days	Constant-rate	Longer time-periods	Shorter time-periods
Average error (per 1000 patient-days)	-0.45	-0.07	-0.07
Sum of errors (per 1000 patient-days)	-25.26	-4.05	-3.83
Sum of squared errors	0.000062	0.000036	0.000032
		F-tests	
	Longer vs. Shorter time-periods	Longer time-periods vs. Constant rate	Shorter time-Periods vs Constant rate
F-test	0.14	2.95	0.73
p-value	0.99+	0.01	0.80
Central line-days-at-risk			
Average error (per 1000 central line-days)	-1.3	-0.02	0.01
Sum of errors (per 1000 central line-days)	-72.64	-1.20	0.78
Sum of squared errors	0.000331	0.000195	0.000178
		F-tests	
	Longer vs. Shorter time-periods	Longer time-periods vs. Constant rate	Shorter time-Periods vs Constant rate
F-test	0.12	2.78	0.67
p-value	0.99+	0.01	0.86
Patient-days-at-risk			
Average error (per 1000 patient-days)	-0.37	-0.03	-0.02
Sum of errors (per 1000 patient-days)	-20.76	-1.63	-1.30
Sum of squared errors	0.000064	0.000038	0.000033
		F-tests	
	Longer vs. Shorter time-periods	Longer time-periods vs. Constant rate	Shorter time-Periods vs Constant rate
F-test	0.18	2.76	0.73
p-value	0.99+	0.01	0.79

Table 28. Summary of error in models compared to actual CLABSI across **patient-days** for subgroups of interest.

		Discrete-time hazards	
	Constant-rate	Longer time-periods	Shorter time-periods
Across first 10 days of hospitalization			
Sum of errors (per 1000 patient-days)	2.75	-0.01	-0.04
Sum of squared errors	0.000010	0.000002	<0.000001
		F-tests	
	Longer vs. Shorter time- periods	Longer time-periods vs. Constant rate	Shorter time-Periods vs Constant rate
F-test	936.9	9.390	3558
p-value	0.025	0.011	0.01
Over 65 years old			
Sum of errors (per 1000 patient-days)	-19.52	0.32	-1.19
Sum of squared errors	0.000298	0.000282	0.000279
		F-tests	
	Longer vs. Shorter time- periods	Longer time-periods vs. Constant rate	Shorter time-Periods vs Constant rate
F-test	0.01	0.23	0.05
p-value	0.99+	0.99	0.99+
Under 18 years old			
Sum of errors (per 1000 patient-days)	-19.09	-1.82	-1.02
Sum of squared errors	0.000122	0.000084	0.000096
		F-tests	
	Longer vs. Shorter time- periods	Longer time-periods vs. Constant rate	Shorter time-Periods vs Constant rate
F-test	-0.15	1.801	0.21
p-value	n/a	0.08	0.99+
ICU			
Sum of errors (per 1000 patient-days)	-15.96	1.29	-168.6
Sum of squared errors	0.000103	0.000083	0.000605
		F-tests	
	Longer vs. Shorter time- periods	Longer time-periods vs. Constant rate	Shorter time-Periods vs Constant rate
F-test	-1.04	0.96	-0.64
p-value	n/a	0.49	n/a

Table 28. cont. Summary of error in models compared to actual CLABSI across **patient-days** for subgroups of interest.

		Discrete-time hazards	
	Constant-rate	Longer time-periods	Shorter time-periods
Surgical service			
Sum of errors (per 1000 patient-days)	-10.82	4.36	3.49
Sum of squared errors	0.000148	0.000142	0.000142
		F-tests	
	Longer vs. Shorter time- periods	Longer time-periods vs. Constant rate	Shorter time-Periods vs Constant rate
F-test	<0.01	0.17	0.03
p-value	0.99+	0.99+	0.99+
Surgical service and trauma diagnosis			
Sum of errors (per 1000 patient-days)	23.98	28.09	28.33
Sum of squared errors	0.000387	0.000417	0.000411
		F-tests	
	Longer vs. Shorter time- periods	Longer time-periods vs. Constant rate	Shorter time-Periods vs Constant rate
F-test	0.02	-0.29	-0.05
p-value	0.99+	n/a	n/a

Table 29. Summary of error in models compared to actual CLABSI across **central line-days-at-risk** for subgroups of interest.

		Discrete-time hazards	
	Constant-rate	Longer time-periods	Shorter time-periods
Across first 10 days of central line-placement			
Sum of errors (per 1000 central line-days)	-0.11	0.06	<-0.01
Sum of squared errors	0.000014	0.000003	<0.000001
		F-tests	
	Longer vs. Shorter time- periods	Longer time-periods vs. Constant rate	Shorter time-Periods vs Constant rate
F-test	2835655	6.52	8051666
p-value	<0.01	0.03	0.01
Over 65 years old			
Sum of errors (per 1000 central line-days)	-105.6	-27.13	-24.25
Sum of squared errors	0.002614	0.002371	0.002356
		F-tests	
	Longer vs. Shorter time- periods	Longer time-periods vs. Constant rate	Shorter time-Periods vs Constant rate
F-test	<0.01	0.41	0.09
p-value	0.99+	0.94	0.99+
Under 18 years old			
Sum of errors (per 1000 central line-days)	-56.89	0.61	1.73
Sum of squared errors	0.000681	0.000539	0.000500
		F-tests	
	Longer vs. Shorter time- periods	Longer time-periods vs. Constant rate	Shorter time-Periods vs Constant rate
F-test	0.09	1.06	0.28
p-value	0.99+	0.42	0.99+
ICU			
Sum of errors (per 1000 central line-days)	-61.40	3.06	4.45
Sum of squared errors	0.000604	0.000493	0.000461
		F-tests	
	Longer vs. Shorter time- periods	Longer time-periods vs. Constant rate	Shorter time-Periods vs Constant rate
F-test	0.08	0.90	0.24
p-value	0.99+	0.55	0.99+

Table 29. cont. Summary of error in models compared to actual CLABSI across **central line-days-at-risk** for subgroups of interest.

		Discrete-time hazards	
	Constant-rate	Longer time-periods	Shorter time-periods
Surgical service			
Sum of errors (per 1000 central line-days)	-45.43	27.72	29.79
Sum of squared errors	0.000544	0.000562	0.000563
		F-tests	
	Longer vs. Shorter time- periods	Longer time-periods vs. Constant rate	Shorter time-Periods vs Constant rate
F-test	-0.01	-0.13	-0.03
p-value	n/a	n/a	n/a
Surgical service and trauma diagnosis			
Sum of errors (per 1000 central line-days)	-5.00	63.78	66.62
Sum of squared errors	0.002142	0.002294	0.002373
		F-tests	
	Longer vs. Shorter time- periods	Longer time-periods vs. Constant rate	Shorter time-Periods vs Constant rate
F-test	-0.04	-0.26	-0.08
p-value	n/a	n/a	n/a

Table 30. Summary of error in models compared to actual CLABSI across **patient-days-at-risk** for subgroups of interest.

		Discrete-time hazards	
	Constant-rate	Longer time-periods	Shorter time-periods
Across first 10 days of hospitalization			
Sum of errors (per 1000 patient-days)	1.91	-0.03	<-0.01
Sum of squared errors	0.000009	0.000002	<0.000001
		F-tests	
	Longer vs. Shorter time- periods	Longer time-periods vs. Constant rate	Shorter time-Periods vs Constant rate
F-test	27284	9.214	101987
p-value	0.01	0.01	<0.01
Over 65 years old			
Sum of errors (per 1000 patient-days)	-21.62	-5.88	-5.44
Sum of squared errors	0.000333	0.000310	0.000308
		F-tests	
	Longer vs. Shorter time- periods	Longer time-periods vs. Constant rate	Shorter time-Periods vs Constant rate
F-test	0.01	0.30	0.06
p-value	0.99+	0.98	0.99+
Under 18 years old			
Sum of errors (per 1000 patient-days)	-11.34	1.88	2.29
Sum of squared errors	0.000139	0.000097	0.000092
		F-tests	
	Longer vs. Shorter time- periods	Longer time-periods vs. Constant rate	Shorter time-Periods vs Constant rate
F-test	0.07	1.73	0.40
p-value	0.99+	0.10	0.99
ICU			
Sum of errors (per 1000 patient-days)	-10.94	3.86	4.29
Sum of squared errors	0.000115	0.000090	0.000083
		F-tests	
	Longer vs. Shorter time- periods	Longer time-periods vs. Constant rate	Shorter time-Periods vs Constant rate
F-test	0.10	1.12	0.30
p-value	0.99+	0.37	0.99+

Table 30. cont. Summary of error in models compared to actual CLABSI across **patient-days-at-risk** for subgroups of interest.

		Discrete-time hazards	
	Constant-rate	Longer time-periods	Shorter time-periods
Surgical service			
Sum of errors (per 1000 patient-days)	-9.21	5.50	5.75
Sum of squared errors	0.000123	0.000120	0.000118
		F-tests	
	Longer vs. Shorter time- periods	Longer time-periods vs. Constant rate	Shorter time-Periods vs Constant rate
F-test	0.02	0.11	0.04
p-value	0.99+	0.99+	0.99+
Surgical service and trauma diagnosis			
Sum of errors (per 1000 patient-days)	24.54	28.51	28.74
Sum of squared errors	0.000429	0.000464	0.000458
		F-tests	
	Longer vs. Shorter time- periods	Longer time-periods vs. Constant rate	Shorter time-Periods vs Constant rate
F-test	0.02	-0.30	-0.05
p-value	0.99+	n/a	n/a

IX. CONCLUSIONS

A. Recapitulation of overall study aims, findings and degree to which the goals of the doctoral research have been met

The focus of this dissertation research has been on determining whether and how the rate of device-associated nosocomial infections change across duration of time at risk. We focused specifically on central line and mechanical ventilator associated infections, as these devices are associated with many nosocomial infections and over 60% of nosocomial infection related mortality.

The dissertation had two specific aims. The first was to clarify how the rate of device-associated infections varies over time in the hospital for patients who utilize ventilators or CL. We achieved this aim by merging the electronic health and claims records from patients at UNC Hospitals between 2002 and 2007 and determining the time from device insertion to infection and device removal for these patients. We then assessed and modeled the changing rate of CLABSI and VAP across duration of time with each device. Further, we adjusted for changes in risk factor distribution across the duration of device use to clarify the extent to which risk factors determined rate of infection.

This aim was realized by the writing of two manuscripts, one for each type of device. In the first manuscript, we assess the rate of CLABSI across 8 weeks of central line placement. The rate of CLABSI increased from 1.60 per 1000 CL-days in the first three days to 5.07 per 1000 CL-days in the beginning of the third week

with a central line. After dropping to 4.12 per 1000 CL-days in the fourth week, CLABSI increased again to 5.58 per 1000 CL-days among patients who had CL for seven weeks. Rates of CLABSI across the duration of central line placement were similar among whites and Hispanics, among trauma and non-trauma patients, and among immunodeficient and non-immunodeficient patients. CLABSI rate increased among blacks and other races compared with whites. CLABSI rate also increased among ICU patients, surgical and pediatric patients compared with medical patients, and was higher in patients with acute respiratory distress syndrome and acute renal failure. Children (under age 16) and older patients (1% increase in risk with each decade of life) were at increased risk of CLABSI across the duration of central line placement. Males differed from females in that they were at increased risk of CLABSI in the first week, but with subsequent central line duration both genders had similar risk of CLABSI.

The second manuscript reported VAP across the first five weeks of mechanical ventilation. The rate of VAP increased from 3.27 per 1000 ventilator-days in the first three days with a ventilator to 8.43 per 1000 ventilator-days at the beginning of the second week. As with CLABSI, there was a dip and another peak, but with VAP this occurred in a shorter time frame. VAP reached 7.54 per 1000 ventilator-days at the end of the third week then decreased to 4-5 per 1000 across the fifth week and with subsequent ventilation. Males had a slightly lower VAP rate across the duration of ventilation compared with females; patients with cardiovascular complications, acute respiratory distress syndrome, acute renal failure, or immunodeficiency were similar to those without those conditions. White,

black, and Hispanic patients had similar rates of VAP across duration of ventilation. Increasing age and being on a floor or step-down unit rather than in an ICU decreased risk of VAP across duration of ventilation. Trauma patients and those with concurrent CL or CLABSI were at increased risk for VAP. Medical and pediatric patients were less likely to have VAP than surgical patients. After 11 days of ventilation, the risk of VAP among medical and pediatric patients decreased further compared with surgical patients.

The second specific aim was to determine the impact of denominator choice and modeling the changing infection rate over time for ventilator-associated pneumonia and central line-associated blood stream infections on the infection rates obtained. We accomplished this through comparing constant and changing rate models of VAP and CLABSI using two types of denominators. The device-day denominator was used in the first aim and accounted for the duration of time between device placement and removal. A patient-day denominator accounted for the duration of time between admission and discharge. We also assessed the impact of risk adjustment on denominator and modeling choice by including risk factors in our analyses.

The manuscript for this aim focused on VAP and a supplemental results chapter provided information on CLABSI. As expected, patient-day models consistently indicated lower rates of infection across the duration of hospitalization compared with device-day models. For both VAP and CLABSI, unadjusted, constant rate models had approximately twice the sum of squared error across duration of device placement compared to changing rate models. When looking at

risk factors of interest, constant rate device-day models continued to have higher error compared with changing rate device-day models. The constant and changing rate models led to similar conditional rate ratios among covariates. But, the increased error associated with the constant rate model implied that it was a poor choice for monitoring the rate of these infections throughout device and hospital duration. Results from F-tests indicated that constant rate models were appropriate for many subgroups with all of the different denominators for both MV and CL. But, for both devices, all denominator choices indicated that changing rate models were better estimates of the observed incidence for at least the overall group at UNC Hospitals or at least one subgroup assessed. Comparison of these groups without adjusting for variation in rate over the duration of device exposure would lead to biased estimates.

B. Strengths

The three previous studies in time to nosocomial infection have been limited by small numbers, examining only ICU patients, short duration of time studied, use of patient-days as denominator of choice, and, in the largest study to date, all nosocomial infections were included. The two prior studies of time to device-associated nosocomial infection both assessed VAP. Cook, et al. presented data on VAP in 1,014 ICU patients from Canada between 1992 and 1996. Jaimes, et al. presented data on VAP in 270 patients from Columbia between 2002 and 2003. Both of these studies used Cox proportional hazards regression, used a denominator comprising duration between admission and ICU discharge, and provided information on changing rate of VAP for less than 20 days with ventilation.

Saviteer, et al. assessed time to any nosocomial infection between admission and discharge among 102,665 patients at UNC Hospitals from 1980 to 1984 and provided information on the changing rate of nosocomial infection across 23 days of hospitalization.

A strength of this research is that we have extended the previous work in each of the following aspects:

1) Six years of data provided us with over 9,000 ventilated patients and over 27,000 patients with CL. The number of ventilated patients is much larger than studies to date. And, this is the first study of time to CLABSI to our knowledge. These larger numbers allowed us to assess changes in rate of infection as well as adjust for changes in risk factor distribution over duration of device use.
2) Secondary analysis of hospital-wide surveillance provided records of both ICU and floor or step-down unit patients. While most ventilated patients are located in an ICU, some patients on a floor or step-down unit are ventilated and VAP can still occur on the floor when a patient is transferred from an ICU. Central line use is prevalent in both the ICU and floor or step-down units. Assessing these device-associated infections throughout the hospital provided us with a complete picture of VAP and CLABSI rates at UNC Hospitals.
3) The larger number of patients allowed us to assess infections across longer duration of device use. Prior studies provided information about changing rate of infection for less than three weeks. Many patients use a ventilator or

central line for a longer period of time. We were able to assess changes in the rate of VAP for up to 5 weeks with mechanical ventilation and changes in CLABSI for up to 8 weeks of central line use.

4) Collection of data regarding duration of device usage allowed us to assess and compare device-days and patient-days. While national surveillance of VAP and CLABSI uses device-day denominators, previous time to infection studies have utilized patient-day denominators. The work in this dissertation provided manuscripts of time to infection across only the duration of device use and then compared duration of device use to duration of admission as potential denominator choices.

5) Conducting this study in a tertiary-care center with low rates of nosocomial infection allowed us to update the literature while providing current incidence data to which new interventions can be compared. Rates of nosocomial infection have been decreasing in the past several years and patient safety goals include decreasing these rates. Thus, timely data from a hospital with low rates can identify potential points of intervention given the current situation in a hospital adhering to guidelines.

An additional strength of the dissertation research is its specific focus on timing of infection. Because previous information on time to infection in published literature has been a byproduct of other research questions, proportional hazards regression has been utilized. Other studies assessing risk factors for VAP and CLABSI have used logistic regression. While both of these models can be appropriate for studying exposure-outcome relationships, neither of them allows for

explicit modeling of conditional infection rates across the duration of device use. Logistic regression does not allow for assessing time-dependent risk factors. Proportional hazards regression does allow for time dependent covariates and accounts for changing rates over time. But, it uses a partial likelihood technique to determine hazard ratios, thus not optimizing the models for the underlying conditional hazard rates. We used discrete-time hazards analysis for our studies, allowing us to explicitly model the underlying conditional rate across duration of device use. In addition, this type of model is comparable to logistic regression and provided us with log odds of hazard ratios for risk factors, which could be compared to other literature.

C. Limitations

While obtaining electronic health records and claims data from UNC Hospitals allowed us to assess timing of CLABSI and VAP in thousands of patients over six years, it also provided some limitations for our analyses.

1) The electronic data did not include information on the number of CL that patients had, only that at least one central line was present. Thus, we were unable to determine whether patients with central line(s) were more likely to have CLABSI if they had more lines or whether the timing of CLABSI different with more CL. This lack of information about number of CL is typical of this literature. In the future, determining the increase in risk of CLABSI with each central line insertion would help to fill this knowledge gap.

2) The electronic data did not include information on aspiration. Since aspiration is a known risk factor of VAP, we were unable to assess whether the timing of VAP varied by whether patients had aspiration.

3) Device utilization was captured from daily nursing assessment. This data included gaps when assessment information was not entered. We assumed that gaps equivalent to the definition-based time requirements for attributing blood-stream infection and pneumonia to CL and MV, respectively, could be considered continuous use. When extending "continuous" use to gaps of 5 days, 70% of device placements were still included. But, we felt that this gap was too long and represented removal and replacement rather than forgetting to enter an electronic record of the assessment for multiple days.

4) The electronic data did not provide information on occurrences outside of the hospital setting. If patients came into the hospital with a central line, we were unable to determine this with the electronic data. We assessed whether this influenced our assessment of time to CLABSI by including a sensitivity analysis using only patients who had at least one day between admission and central line use. If patients had either a central line or ventilator removed just before leaving the hospital, they could have a device-associated infection outside the hospital which would not be captured in our data. We were unable to assess the incidence of this occurrence.

5) We did not have access to other outcomes, such as death, which would compete with device-associated nosocomial infection. Thus, patients who did not get infections because they died look similar to patients who had the

device removed because they were well enough for discharge. Accounting for comorbidities and ICU versus floor or step-down unit allowed us to adjust for some patient severity information, but did not fully capture differences between those more and less likely for device-associated infections or more severe competing outcomes.

A potential source of error is not capturing CLABSI or VAP or including an infection when one has not occurred. Clinical suspicion and laboratory confirmation of CLABSI and VAP are included in their definitions and infection control nurses and doctors review each case before it is entered into the Hospital Infection Database. Thus, it is unlikely that false positives are entered or false negatives are missed in the data. The date of each infection is the date that the laboratory test was taken. It is possible that the date entered into the database is the date of laboratory confirmation, but due to multiple reviews, this is also unlikely.

D. Public Health Impact

While the public health impact of a single study is difficult, if not impossible, to assess, this project has provided insight into timing of MV and CL-associated nosocomial infections. Variation in rate of infection is measurable, even when accounting for changing risk factors across device duration and with all typical exposure-time assessments. Thus, there are time-periods during which patients are at increased risk and during which they may benefit from more intense, targeted interventions. This study provides a method for assessing baseline risk over exposed time for patients with general hospital devices and a framework around which future interventions can be built.

Ideally, all data used to compare across different patient populations or different hospitals should be adjusted for the changing rate of device-associated infections across duration of exposure. This is often not possible, since the duration of device placement for each person is often unavailable. Without data on duration of device placement and the day of infection, it is impossible to know whether it is important to account for the time-varying nature of the incidence rate of device-related infections. Thus, comparing differences between hospitals or patient groups within a hospital without accounting for differences in rate across device exposure can provide misleading results. In order to provide a basis for comparison between hospitals and patient groups, analyses of surveillance data reported in published studies should include assessment of patient characteristics as well as timing of device utilization and subsequent infection.

E. Future directions

Future analyses in this data should look at pathogen-specific infections. *Staphylococcus* infections (*Staph.*) occur earlier than *Pseudomonas* infections. As the amount of *Staph.* and specifically oxacillin-resistant *Staph.* present in hospitals and communities is increasing, the rate of device-associated infections may be increasing because more patients are exposed to *Staph.* while using CL or MV. If *Staph.* infections make up an increasing proportion of infections throughout the six years in this data, then *Staph.* may be an appropriate intervention target.

Given our finding that time to CLABSI is longer than time to VAP, analysis of time to infection among patients with urinary catheters, surgical site infections, and other specific nosocomial infections of interest would provide information to infection

control practitioners on when to expect increased risk and target interventions. As most cases of nosocomial infection are associated with medical devices, further investigation on timing of device-associated infection adjusting for changes in risk factor distribution should be conducted to confirm timing of CLABSI and VAP as well as to find target times for intervention with other infection prone devices.

X. APPENDICES

A. Residual Error Graphs

Figure 10. Residual error in ventilator-associated pneumonia models across duration of ventilation.

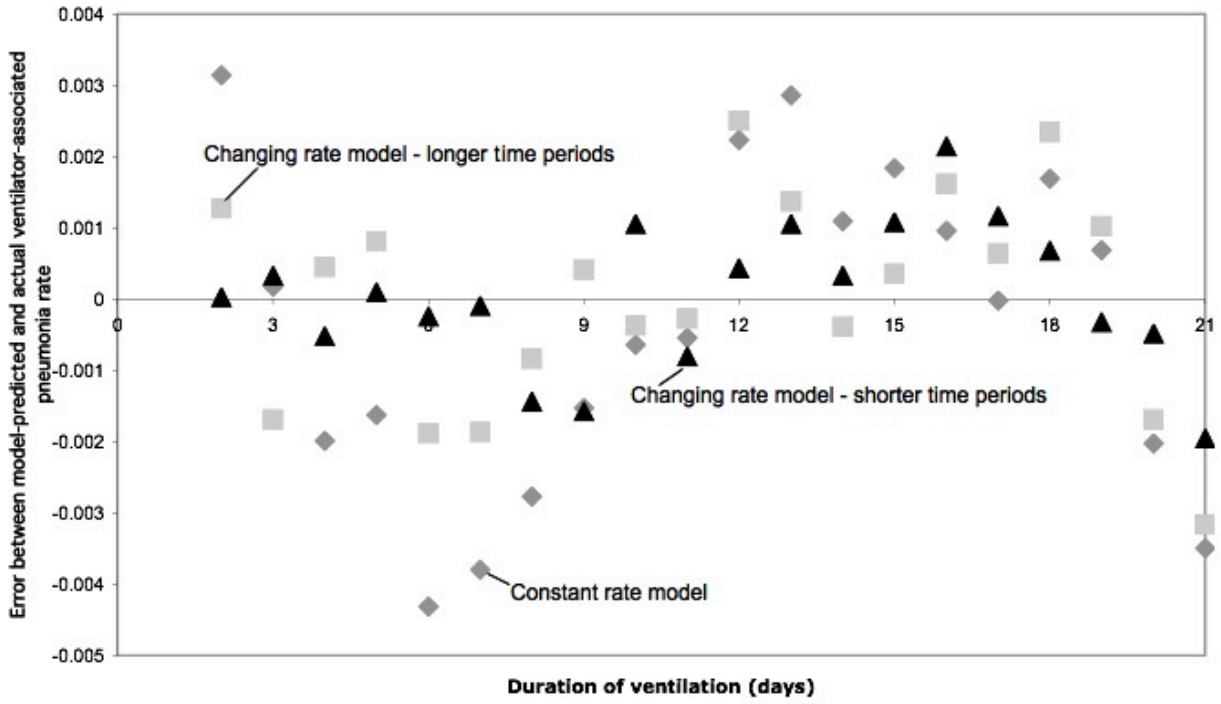

Figure 11. Residual error in ventilator-associated pneumonia models across hospitalization.

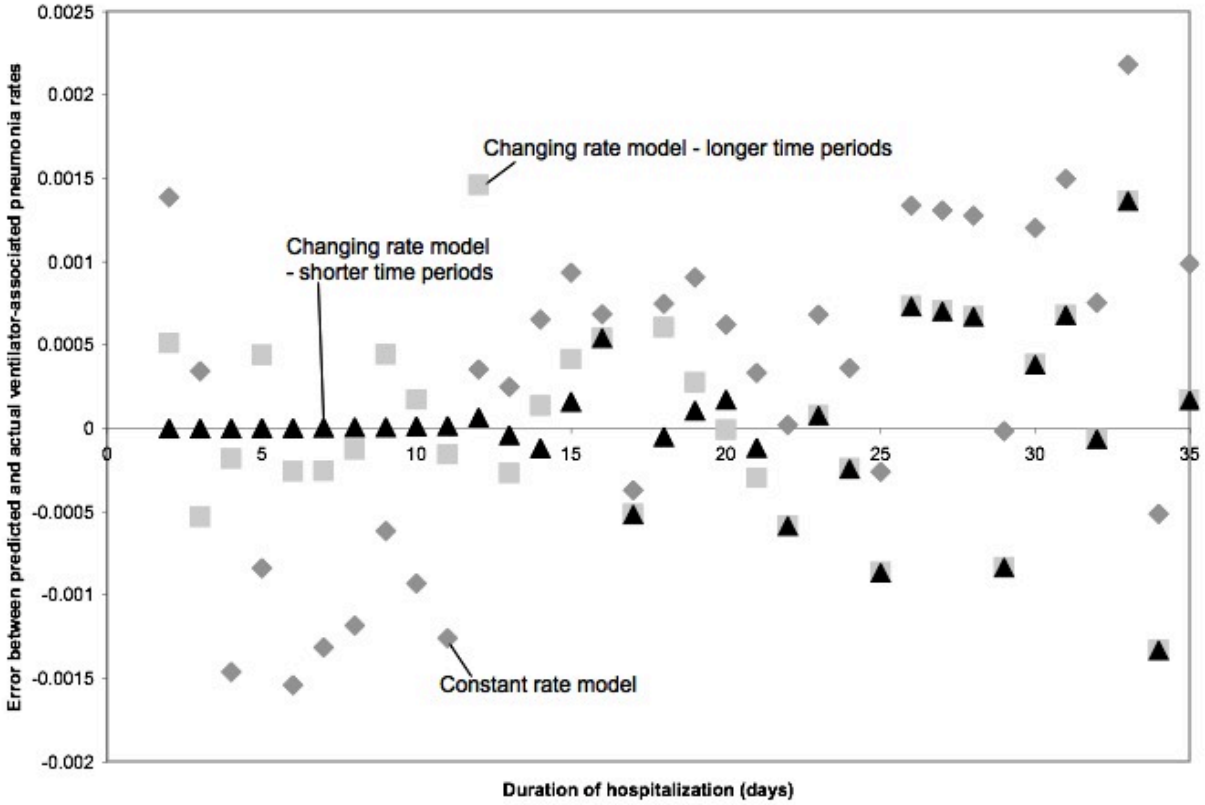

Figure 12. Residual error in CLABSI models across duration of central line placement.

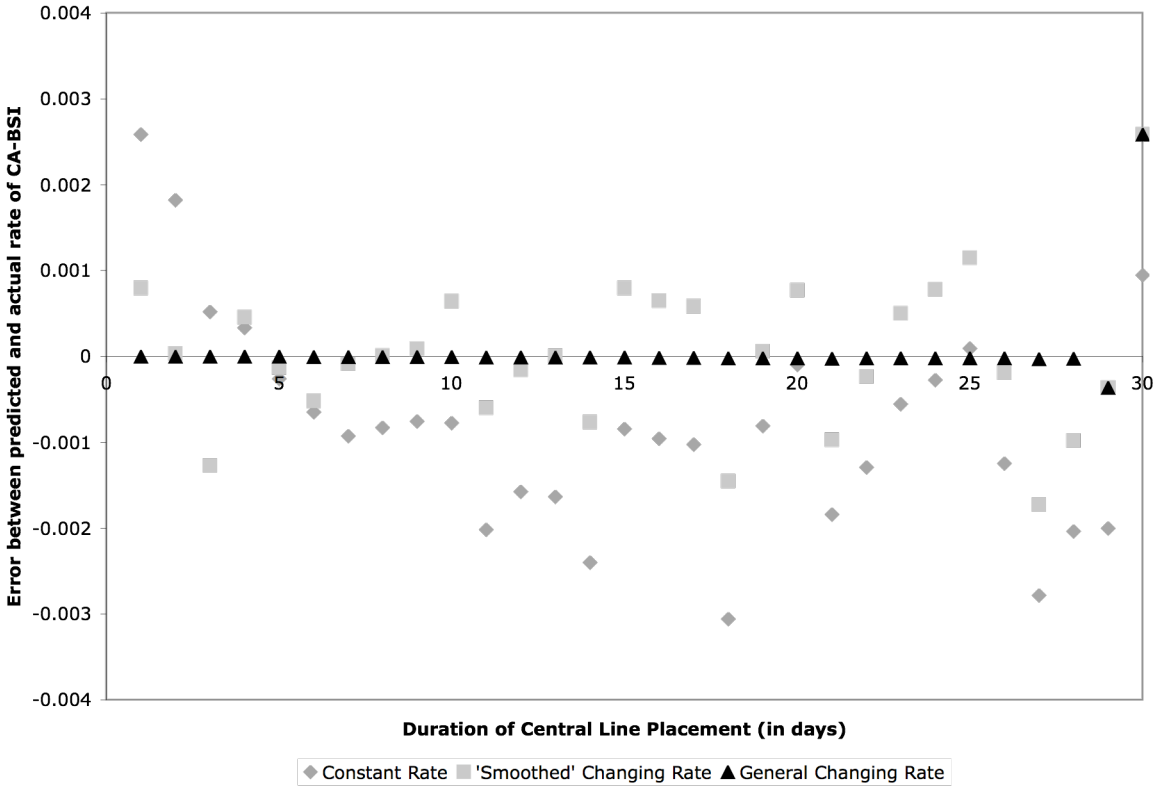

Figure 13. Residual error in CLABSI models across hospitalization.