INCIDENCE AND RISK FACTORS FOR NON-DEVICE ASSOCIATED HEALTHCARE ASSOCIATED INFECTIONS

Paula D. Strassle

A dissertation submitted to the faculty at the University of North Carolina at Chapel Hill in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Department of Epidemiology.

Chapel Hill
2019

Approved by:

David J. Weber

Emily E. Sickbert-Bennett

Jennifer L. Lund

Paul W. Stewart

Michael Klompas

ABSTRACT

Paula D. Strassle: Incidence and Risk Factors for Non-Device Associated Healthcare Associated Infections
(Under the direction of David J Weber)

Due to current targeted surveillance programs of healthcare associated infections (HAIs), there is a paucity of research on non-device associated urinary tract infections (ND-UTIs), non-device associated pneumonia (ND-pneumonia), and non-device associated bloodstream infections (ND-BSIs). However, limited data that do exist suggest that the proportion of all HAIs that were non-device associated have increased over the last decade. Thus, the purpose of this study was to update current estimates of ND-HAI rates and their frequency relative to device associated infections, assess temporal trends, and identify potential risk factors for ND-HAIs among adult patients hospitalized at the University of North Carolina (UNC) Hospitals between 2013 – 2017.

Between 2013 and 2017, the rates of ND-UTIs and ND-pneumonia remained relatively stable, and the rate of ND-BSIs increased. Additionally, ND-UTIs and ND-pneumonia cases represent the majority of infections, with almost 3 in 4 UTIs and pneumonia cases being non-device associated in 2017. One in three BSIs are non-device associated at UNC Hospitals.

Females, older adults, peptic ulcer disease, paralysis, immunosuppression, opioid use, TPN, and trauma patients all had a higher risk of ND-UTI. Urinary retention, suprapubic catheters and nephrostomy tubes may also increase patient risk of ND-UTI, although estimates

were imprecise. Risk factors for ND-pneumonia included male sex, older age, ICU admission, and chronic bronchitis/emphysema, congestive heart failure, paralysis, and immunosuppression. Finally, risk factors for ND-BSIs included male sex, peptic ulcer disease, paralysis, general anesthesia, opioids, and peripheral venous catheters; higher Morse Fall Risk score, beta-blockers, and UTIs (device or non-device associated) also appeared to increase patient risk. These results all suggest that specific patient and clinical characteristics may increase the risk for certain ND-HAIs, and future studies should explore targeting modifiable risk factors for potential prevention strategies.

I dedicate this work to my entire family- who are too numerous to name- but especially my parents Brian and Diane Strassle, who have been my constant cheerleaders with everything I do and have supported me at every step throughout my life; my brother Michael Strassle; and to my partner, Julian Bradford-Hill, whose support, patience, and cooking made this dissertation possible.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

ACE	angiotensin converting enzyme
ACIP	Advisory Committee on Immunization Practices
ARB	angiotensin II receptor blockers
BMI	body mass index
BSI	bloodstream infection
CA-UTI	catheter associated urinary tract infection
CCI	Charlson comorbidity index
CDC	Centers for Disease Control and Prevention
CDW-H	Carolina Data Warehouse for Health
CI	confidence interval
CLA-BSI	central line associated bloodstream infection
CMS	Centers for Medicare & Medicaid Services
COPD	chronic obstructive pulmonary disease
CPT	Current Procedural Terminology
CVC	central venous catheter
DX1	admitting diagnosis
EMR	electronic medical records
GEMS	general equivalence mapping
H2 blockers	histamine-type 2 receptor blockers
HAI	healthcare associated infection
HIV/AIDS	human immunodeficiency viruses/acquired immunodeficiency syndrome
HR	hazard ratio

ICD-9-CM	International Classification of Diseases, 9th Edition, Clinical Modification
ICD-10-CM	International Classification of Diseases, 10th Edition, Clinical Modification
ICU	intensive care unit
IPMW	inverse-probability of missing weights
ISDA	Infectious Diseases Society of America
IQR	interquartile range
LOS	length of stay
MAR	medication administration record
MEWS	Modified Early Warning System
MI	myocardial infarction
MRN	Medical Record Number
NCATS	National Center for Advancing Translational Sciences
ND	non-device associated
NHSN	National Healthcare Safety Network
NIH	National Institutes of Health
NIS	National Inpatient Sample
NNIS	National Nosocomial Infection Surveillance
NSAID	nonsteroidal anti-inflammatory medications
PPI	proton pump inhibitor
PVC	peripheral venous catheter
PVD	peripheral vascular disease
TPN	total parenteral nutrition
UTI	urinary tract infection

UNC	University of North Carolina
VAP	ventilator associated pneumonia
WBC	white blood cell

CHAPTER 1: STATEMENT OF SPECIFIC AIMS

Healthcare associated infections (HAIs) are a substantial source of morbidity and mortality, are considered one of the most common sources of preventable harm in the inpatient setting, and pose a major burden on the United States healthcare system.[1-5] In 2015, it was estimated that 3.2% of patients, or roughly 1 in every 31 hospitalized adults, has at least one HAI on any given day in the US, which corresponds to almost 700,000 infections a year.[2] Three major types of HAIs include urinary tract infections (UTIs), pneumonia, and bloodstream infections (BSIs). These infections can be largely classified as being either device associated, specifically catheter associated UTIs (CA-UTIs), ventilator associated pneumonia (VAP), and central line associated BSIs (CLA-BSIs), or non-device associated (ND-HAIs), which are defined as HAIs that occur when the devices listed above are not present.

Historically, devices have been considered one of the biggest risk factors for HAIs (causing the vast majority of infections), and since the 1990s, surveillance programs managed by the Centers for Disease Control and Prevention (CDC) have focused on these infections to maximize efficiency.[5-7] Subsequently, research and evidence-based prevention guidelines have also focused on CA-UTI, VAP, and CLA-BSI.[8-11] In the past 10 years, there have been substantial decreases in the rates of device associated HAIs, largely driven by this research and the identification of successful prevention strategies which target the placement, maintenance, removal, and properties of the associated devices.[1,2,6,12] Unsurprisingly, these interventions have had little effect on the rates of ND-HAIs, and these infections represent a growing proportion of

the HAI burden in US hospitals.[7,13-17] However, despite this growing impact, little is known about ND-HAIs infections.

Thus, the overall goals of this research are to estimate the incidence of ND-HAIs, assess any changes in their rates over time, and to identify modifiable and non-modifiable risk factors for non-device associated HAIs, specifically non-device associated UTIs (ND-UTIs), non-device associated pneumonia (ND-pneumonia), and non-device associated BSIs (ND-BSIs).

1.1 SPECIFIC AIM 1

Describe the epidemiology of ND-HAIs- specifically ND-UTIs, ND-pneumonia, and ND-BSIs, in hospitalizations of non-prisoner adults (≥18 years old) admitted to University of North Carolina (UNC) Hospitals between 2012-2017. Calculate quarterly incidence rates of ND-HAIs and the proportion of HAIs that are device- and non-device associated, and assess temporal trends during this time. Additionally, part of this investigation will explore how the rates of ND-HAIs change depending on whether they are defined as the number of infections per:

(1) All-hospitalization days (CDC definition)[18]

(2) At-risk days only

(3) At-risk, non-device days only

1.2 SPECIFIC AIM 2

Assess the association between patient demographics, comorbidities, illness severity, and inpatient treatments (medication use, device-use, procedures) and the incidence of ND-HAIs, among hospitalizations of non-prisoner adults (≥18 years old) admitted for ≥2 days to UNC

Hospitals between 2015-2017. This aim will be composed of three separate analyses, for each ND-HAI:

(1) Non-device associated urinary tract infections (ND-UTIs),

(2) Non-device associated pneumonia (ND-pneumonia), and

(3) Non-device associated bloodstream infections (ND-BSIs).

Each infection type will have its own list of potential risk factors and will reflect relevant (i.e. non-device associated) risk factors for the device associated HAI counterpart (e.g. CA-UTI risk factors will be included in ND-UTI analysis), as well as other potentially clinically relevant covariates. All treatments, as well as hospital unit, will be treated as time-varying exposures.

CHAPTER 2: REVIEW OF THE LITERATURE

2.1 BACKGROUND

Healthcare associated infections pose a significant burden on the healthcare system.

Healthcare associated infections (HAIs) are a substantial source of morbidity and mortality, are considered one of the most common sources of preventable harm in the inpatient setting, and pose a major burden on the United States healthcare system.[1-5] In 2015, it was estimated that 3.2% of patients, or roughly 1 in every 31 hospitalized adults, has at least one HAI on any given day in the US, which corresponds to almost 700,000 infections a year.[2] In national hospital prevalence surveys conducted in 2011 and 2015 by the Centers for Disease Control and Prevention (CDC), the mortality rate of HAIs was estimated to be over 10%[1,2], although it does vary based on the type of infection and patient-specific factors[4,19-21]. HAIs have also been found to cause prolonged lengths of stay (LOS)[5,20,22,23], although the magnitude of their impact on LOS is somewhat unclear due to inappropriate methodology that overestimates the effect[24,25]. Overall, it is estimated that HAIs cost the US healthcare system between $3.2 to $9.8 billion dollars a year.[5,23]

The shifting landscape of healthcare associated infections.

Between 1992 and 1998, reports from the National Nosocomial Infection Surveillance (NNIS, a voluntary network of US hospitals collaborating with the CDC to monitor HAIs that was established in 1970) system found that almost 70% of all healthcare associated infections

(formerly referred to as nosocomial infections) were attributed to just three infection types- urinary tract infections (UTIs), pneumonia, and bloodstream infections (BSIs).[26,27] Moreover, the same system found that 97% of UTIs were catheter associated UTIs (CA-UTIs), 83% of pneumonia cases were ventilator associated pneumonia (VAP), and 87% of BSIs were central line associated BSIs (CLA-BSIs).[26] These findings shifted support among hospitals in NNIS from comprehensive (i.e. all HAIs) and hospital-wide (i.e. all units and patients) surveillance to more efficient, targeted surveillance, and by 1998 NNIS officially switched practices.[21,28] In fact, targeted surveillance is still the standard today, and currently, the National Healthcare Safety Network (NHSN, established in 2005 and replaced NNIS), national reporting is only required for CA-UTIs and CLA-BSIs, as well as surgical site infections (SSIs) after colon surgery and abdominal hysterectomy, positive blood cultures for methicillin-resistant *Staphylococcus aureus*, and positive cultures for *Clostridium difficile*.[6,7,29] Reporting of VAP is supported, but is not currently required.

In 2011, the CDC conducted a multistate prevalence survey in order to estimate the total burden of HAIs at acute care hospitals, given that national surveillance no longer captured all infections.[1,2] This survey found that the overall incidence of HAIs was 4.0% (95% confidence interval [CI] 3.7, 4.4), and that CA-UTI, VAP, and CLA-BSI, the infections that 'have traditionally been the focus of programs to prevent health care associated infections' now only accounted for 26% of all HAIs in the US that year.[1] This dramatic decrease in device associated HAIs is likely due to the evidence-based guidelines on how to reduce CA-UTIs[8], VAP[9,10], and CLA-BSIs[11] that the CDC released in the decade prior. Moreover, when the same survey was performed again in 2015, they found the HAI rate had decreased to 3.2% (95% CI 2.9, 3.5), and that patients were 16% less likely to develop an HAI compared to four years prior (risk ratio

[RR] 0.84, 95% CI 0.74, 0.95).[2] The study also found that 61% of pneumonia cases were non-device associated (67 infections vs. 43 infections) and 38% of UTIs were non-device associated (21 vs. 34); almost all BSIs were CLA-BSI (42 out of 50 BSIs).[2]

Epidemiology of non-device associated healthcare associated infections

Despite the changing landscape of HAIs and the role ND-HAIs now play in the incidence of hospital infections, relatively little is known about the incidence and epidemiology of these infections in the US. Additionally, of the studies that do exist on ND-UTIs, ND-pneumonia, and ND-BSIs, the majority are either dated or have used flawed methods for identifying HAIs.[7,13-17,30]

Several of these studies have come from the University of North Carolina (UNC) Hospitals, which has conducted comprehensive, hospital-wide surveillance of all HAIs (device and non-device associated) in accordance with CDC definitions and methodology since 1978.[13,31] From 2006-2009, they found that 28% of all UTIs were non-device associated, an ND-UTI rate of 6.4 infections per 10,000 non-device days[14], and in 2010 ND-UTIs accounted for 38% of all urinary infections.[13] Additionally, in 2010 ND-BSIs accounted for 22% of all BSIs and ND-pneumonia accounted for 30% of all pneumonia cases.[13] Finally, DiBiase et al. reported that from 2008-2012, the rates of CA-UTI, CLA-BSI, and VAP decreased significantly (similar to other findings), but that ND-UTI, ND-BSI, and ND-pneumonia rates remained consistent.[7] Overall, while these studies use robust methods for capturing infections and support the growing need to measure ND-HAI incidence and identify prevention strategies, whether these trends have continued in the past five years needs to be assessed.

There have also been a handful studies estimating the incidence of ND-pneumonia from other research teams which assessed rates across multiple institutions[15,17] or by utilizing a nationally available database of hospital discharge records (e.g. National Inpatient Sample)[16]. Davis and Finley (2012) utilized state-mandated comprehensive surveillance data from Pennsylvania, and found that between 2009 and 2011 that 71% of cases of pneumonia were non-device associated (5,597 ND-pneumonia, 2,299 VAP), and that mortality rates were similar between the two groups (18.7% and 18.9%, respectively).[15] In a 2014 convenience sample of 21 hospitals across the US, the rate of ND-pneumonia ranged from 0.12 to 2.28 cases per 1,000 patient days, and that all units have some risk for ND-pneumonia.[17] There was also a study which estimated the rate of ND-pneumonia in 2012 was to be 3.36 per 1,000 hospital days; however, this is likely overestimated because of how they identified their ND-pneumonia cases.[16]

Giuliano et al. (2017)[16] conducted their study in the National Inpatient Sample (NIS, a stratified random sample of hospital discharges in the US), and had to identify ND-pneumonia cases using International Classification of Diseases, 9th Edition, Clinical Modification (ICD-9-CM) diagnosis codes to identify cases of ND-pneumonia, which is problematic for a few reasons. First, several systematic reviews have found that administrative codes are poor predictors of HAIs, which can cause a high prevalence of false positives.[32-34] Additionally, there appears to have been a shift in coding practices during this time period where hospitalizations of patients with community-acquired pneumonia, would have their infection coded secondary to more severe complications of the disease, like respiratory failure, sepsis, and pleural effusion.[35] These coding changes would also increase the rate of false positives utilizing ICD-9-CM codes on discharge records.

Finally, to date, there have been no studies on the risk factors of ND-UTIs or ND-BSIs in the US. And while a few studies have looked at the effect of oral care on ND-pneumonia[30,36,37], there are still no evidence-based guidelines for preventing ND-pneumonia, and other risk factors (and potential prevention strategies) remain essentially unknown.[38]

2.2 SUMMARY

HAIs represent a substantial source of morbidity and mortality, and are one of the most common sources of preventable harm in the inpatient setting.[1-5] In the US, changes in HAI surveillance practices from comprehensive and hospital-wide to targeted in the 1990s have resulted in HAI efforts to focus on device associated infections (CA-UTIs, VAP, and CLA-BSIs).[21] Moreover, as significant reductions in the rates of device associated HAIs over the past decade have been seen, ND-HAIs rates have remained stagnant[1,2,7] and ND-UTIs, ND-pneumonia, and ND-BSIs now represent a growing proportion of all hospital infections.[1,7,13-15] And despite the growing need to understand the epidemiology of ND-HAIs, there is a paucity of research on the incidence and risk factors of ND-UTIs, ND-pneumonia, and ND-BSIs.

CHAPTER 3: STUDY METHODOLOGY

3.1 DATA SOURCES

Carolina Data Warehouse for Health (CDW-H)

Electronic medical records (EMR) from non-prisoner adults (≥18 years old) admitted to the University of North Carolina (UNC) Hospitals between January 1, 2013 and December 31, 2017 were obtained from the Carolina Data Warehouse for Health (CDW-H), a central repository for clinical and administrative data from the UNC Healthcare System. Patients were allowed to have multiple hospitalizations during the study period.

Among patients all patients, medical record numbers (MRNs), full name, date of birth, admission and discharge dates for inpatient hospitalizations were obtained from either the legacy healthcare system or Epic healthcare system, which went live at UNC Hospitals on April 4, 2014. Additionally, among patients admitted between 2015 and 2017 (i.e. years where all patient EMR were in Epic), patient demographics, inpatient procedures, dispensed inpatient medications, laboratory test results, hospital locations throughout the entire hospitalization, information on all lines, drains, and airway devices, and discharge disposition were also collected.

UNC Hospitals Epidemiology Database

UNC Hospitals Epidemiology database is a database of all HAIs, including both device and non-device associated HAIs, captured through comprehensive, hospital-wide active surveillance, in accordance with the Centers for Disease Control and Prevention (CDC) case definitions and methodology since 1978.[13,31] Variables included in the Hospital Epidemiology database include: MRN, full name, date of birth, admission date, date of HAI diagnosis, infection site (UTI, pneumonia, or BSI) and device status (i.e. device or non-device associated).

3.2 DATA LINKAGING

Overall, there were 163,389 hospitalization records obtained from the CDW-H and 2,853 HAIs captured in the Hospital Epidemiology database. These two data sources were then deterministically linked using combinations of medical record numbers (MRNs), date of admission, and/or first and last names. UTIs, pneumonia cases, and BSIs were linked to hospitalization records separately, 93% (n=2,651) HAIs were able to be linked using the full admission date (month, day, and year) and MRN in both data sources. Additionally, 2% (n=63) of records were linked using full admission date and full name, 4% (n=123) were linked using the full admission date, first name, and last name, and <1% (n=8) were linked using admission month and year only and MRN.

Initially, 10 infections (5 UTIs, 3 pneumonia cases, and 2 BSIs) were unable to be linked. These records were then manually reviewed using chart review to identify additional MRNs or data entry errors in the record. After this process, the 2 BSIs were able to be linked to hospitalization records.

3.1 STUDY POPULATION

All hospitalizations of non-prisoner adults (≥18 years old) admitted between January 1, 2013 and December 31, 2017 were included. Patients will be allowed to contribute multiple hospitalizations during this time. Only patients admitted for ≥2 days (i.e. those at risk for an HAI as per CDC definitions[18]) and admitted between January 1, 2015 and December 31, 2017 were included for the risk factor analyses, as several variables of interest were either not recorded or not extractable from the legacy healthcare system.

3.2 CALCULATING INCIDENCE RATES

For Aim 1, quarterly incidence rates for ND-HAIs were calculated between 2013 and 2017, and expressed as the number of infections per 10,000 hospitalization days. Hospitalization days will be defined using CDC definitions, which means that all hospitalization days, irrespective of patient risk or ND-HAI status, were included.[18] For each hospitalization, admission and discharge dates were used to allocate person-time to each quarter. Patients could contribute multiple ND-HAIs at each site to the numerator.

Poisson regression was used to assess potential linear trends in the quarterly rates of ND-UTIs, ND-pneumonia, and ND-BSIs during the 5-year study period. The model used to assess said trends is detailed below.

$$\log(\mu) = \boldsymbol{X_i\beta} + \log(n), \text{where i} = 1, \ldots, 20$$

$\log(\mu)$ is the log rate of non-device associated HAI

$\boldsymbol{X_i}$ is an 20 × 2 fixed effect design matrix for the *i*-th quarter where

$$\boldsymbol{X}_i = \begin{bmatrix} 1 & \delta_{11} \\ \vdots & \vdots \\ 1 & \delta_{1i} \end{bmatrix}$$

$\delta_{1i} = quarter$, when $year = 2010$ (i. e. $1, 2, 3,$ or 4), and

$= \big((year - 2010) \times 4\big) + quarter$, when year > 2010 (i. e. $5, 6, \dots, 20$)

$\boldsymbol{\beta} = (\beta_0 \quad \beta_1)'$ is the 2×1 vector of unknown regression parameters:

- β_0 is the log rate of ND-HAIs in January-March 2010
- β_1 is the increment in the log rate of ND-HAIs for every quarter after January-March 2010, assuming the rate increases linearly

$\log(n)$ is log of the number of patients admitted each quarter (i.e. offset)

Two sensitivity analyses on the denominator definitions were also conducted. First, among hospitalizations between 2013 and 2017, rates of ND-HAIs per 10,000 *at-risk* hospitalization days were calculated to observe the impact of including not-at-risk time in the CDC-definition rates. For these rates, patients began contributing person time after being hospitalized for 2 days (i.e. the first 2 days are excluded), as per CDC definitions for HAIs, and stopped contributing person-time after they become infected with their first ND-HAI at the site of interest. Only a patient's first ND-HAI for each site was included in the numerator. While in practice a patient is able to re-enter the at-risk pool after their ND-HAI is treated (and why patients are able to have multiple ND-HAIs at the same site in a single hospitalization), we were unable to assess when that occurs as a 'cured' date is not captured in the Hospital Epidemiology database.

Finally, among hospitalization between 2015 and 2017, rates of ND-HAIs per 10,000 *non-device* days were also calculated. Non-device days were obtained by removing device days- obtained from the lines, drains, and airway device data from the CDW-H- from the at-risk days calculated above. Similar to the 2-day lag after admission to meet the definition for an HAI, the CDC also applies a 2-day lag on device-days, where an infection occurring within 2 days of a device being placed would not be associated with the new device, and any infections occurring within 2 days of a device being removed would be affiliated with said device. This criteria was also taken into account when calculating non-device day rates. Only a patient's first ND-HAI at each site will be included in the numerator. Rates of device associated HAIs per 10,000 device days were also be calculated for this time period.

3.3 MEASURING POTENTIAL RISK FACTORS

Multivariable Cox proportional hazards regression was used to estimate the direct effect of potential risk factors on the incidence of ND-UTIs, ND-pneumonia, and ND-BSIs. Only a patient's first HAI (device or non-device associated) was included. Correlation between repeat hospitalizations of the same patients were taken into account by the utilizing robust sandwich covariance matrix estimates described by Lee et al. (1992).[39] Both inpatient mortality and device associated infections were treated as a competing risk using the Fine and Gray (1999) model, and the outcome of interest was categorized as censored (no event and no competing risk), event (ND-HAI), or competing risk (death or device associated HAI).[40] The hazard at time *t* can be written out as follows:

$$log(\lambda(t)|\boldsymbol{X}) = log\big(\lambda_0(t)\big) + \boldsymbol{X\beta}, \text{where}$$

$\lambda_0(t)$ is the expected or baseline hazard at time *t*

$\boldsymbol{X}$ is an $n_i \times k$ known fixed effects design matrix, where *k* is the number of risk factors included in the model, and

$\boldsymbol{\beta}$ is the k × 1 vector of unknown fixed effect regression parameters

Potential risk factors for each ND-HAI will be determined by identifying all known risk factors for device associated HAI counterpart (e.g. CA-UTI risk factors for ND-UTI) and other factors were identified through expert opinion (DJW, EESW, MK, AM).

Patient Demographics

Patient age and sex were included in all three risk-factor analyses. Age was categorized by decade (18-29 years old [reference], 30-39 years old, 40-49 years old, 50-59 years old, 60-69 years old, 70-79 years old, and ≥80 years old). Patient race was also captured and categorized as White [reference], Black, or Other race. Information on race was missing from 3% hospitalizations (n=2,820).

Patient Comorbidities

Patient comorbidities were captured using the discharge diagnosis ICD-9-CM (January 2015 – September 2015) and ICD-10-CM (October 2015 – December 2017) codes on each record. Deyo et al. (1992) and Quan et al. (2005) algorithms were adapted to identify components of the Charlson comorbidity index (CCI) score.[41,42] Diagnosis codes for incident events (e.g. acute myocardial infarction) were dropped from all component definitions, as codes came from the index hospitalizations only.[41] Peripheral vascular disease (PVD) was excluded

from analyses due to low incidence (n=201) and human immunodeficiency viruses (HIV) was incorporated into the broader classification of 'immunocompromised' (described below).

Immunocompromised patients were defined using the Advisory Committee on Immunization Practices (ACIP) and Infectious Diseases Society of America (IDSA) classification, which is used to identify persons who cannot receive live-attenuated vaccinations (e.g. chickenpox).[43] Diagnoses of immunosuppressive conditions were identified using discharge diagnosis codes; relevant ICD-9-CM codes were identified using the Greenberg et al. (2016)[44] algorithm and ICD-10-CM codes were identified from that list using General Equivalence Mappings (GEMS). Patients receiving chemotherapeutic agents, corticosteroids, or immune-modulating agents were identified using inpatient medications fills during the first 2 days of their hospitalization. A full list of diagnoses and medications used can be found in Tables 3.1 and 3.2, respectively.

In addition to diagnosis codes, neutropenia was also defined as having 2 labs with white blood cell [WBC] count <500 cells/mm^3 during the first 2 hospitalization days. Medications and laboratory results were restricted to this timeframe in order to minimize the potential of misclassifying conditions and events occurring after an ND-HAI as a potential risk factor, which could bias results. Low albumin, also measured within 2 days of admission, was also assessed as a potential risk factor, and defined as <3.4 g/dL. Patients who did not undergo a blood test were assumed to have normal levels.

BMI was calculated using patient height and weight, and categorized as underweight (<18.5), normal weight (18.5 – 24.9), overweight (25.0 – 29.9), and obese (≥30).

Severity of Illness

Illness severity was captured using the Modified Early Warning System (MEWS) score[45,46] and the Morse Fall Scale[47,48], both of which are captured and calculated in Epic. The MEWS uses vital signs- specifically systolic blood pressure, heart rate, respiratory rate, temperature, level of consciousness, and hourly urine output (for two hours)- to detect patients at risk for imminent clinical deterioration.[49] The Morse Fall Scale is a simple prediction score designed to identify patients at risk for falling in the hospital. The Morse Fall Scale includes the following variables: history of falling, number of secondary diagnoses, whether ambulatory aid is needed, intravenous therapy/heparin lock, gait, and mental status.[50] For each patient, the first MEWS and Morse Fall Scale score within the first 2 days of admission was captured and categorized using clinically relevant cut points (MEWS: <1 [reference], 2, 3, ≥4; Morse Fall Scale: 0 [reference], 1-24, 25-45, >45). A MEWS ≥4 and a Morse Fall Scale score >45 are both considered indicators of severe illness.[49,50]

Inpatient Medication Use

Inpatient medications of interest included systemic antibiotics (all ND-HAIs), anesthetics (local and general, all ND-HAIs), benzodiazepines (all ND-HAIs), opioids (all ND-HAIs), anticholinergics (ND-UTIs, ND-BSIs only), alpha-2 agonists (ND-BSIs only), nonsteroidal anti-inflammatory medications (NSAIDs, ND-BSIs only), calcium channel blockers (ND-BSIs only), and acid-suppressing medications (histamine-type 2 receptor blockers [H2 blockers] and proton pump inhibitors [PPIs], ND-pneumonia only). Total parenteral nutrition (TPN, all ND-HAIs) and chlorhexidine mouthwash (ND-pneumonia only) utilization was also assessed as potential risk

factors and captured through inpatient medication files. Finally, inpatient urinary retention (ND-UTIs only) was measured using suggestive medications for the disease. Generic medication for all medications are described in Table 3.2.

All medication administration, including TPN, chlorhexidine mouthwash, and urinary retention treatment, was confirmed using the medication administration record (MAR) and treated as a time-varying exposure, meaning patients were considered unexposed until the time of their first administration, and remained exposed for the remainder of follow-up. If a patient did not receive a medication until after their ND-HAI or device associated HAI event, they were considered unexposed for their entire at-risk time.

Inpatient Procedures

Current Procedural Terminology (CPT) codes were used to identify inpatient procedures that may be risk factors for ND-HAIs, specifically urologic surgery (ND-UTIs only), and dialysis (ND-pneumonia). Undergoing any surgical procedure (all ND-HAIs) was also assessed. Procedures were also treated as a time-varying exposure.

Prior Device Use

Prior device use was also considered potential risk factors. Among ND-UTIs, urinary catheters (CA-UTI device), suprapubic catheters, and nephrostomy tubes were each assessed. Endotracheal tubes and tracheostomy (both VAP devices) were assessed as a potential risk factor for ND-pneumonia, and both central venous catheter (CVC, CLA-BSI device), and peripheral venous catheter (PVC) were included. Device use was treated as a time-varying exposure.

Other Variables of Interest

Other potential risk factors of interest include trauma admission (all ND-HAIs), hospital location/service (all ND-HAIs), being admitted for a urinary disease (ND-UTIs only), being admitted with pneumonia (ND-pneumonia) only, and prior HAI (device or non-device related) (ND-BSIs only). Service, specifically intensive care unit (ICU) , and prior HAI were treated as time-varying exposures.

3.6. HANDLING MISSING DATA

Due to missing values of BMI (n=15,146, 17%), MEWS (n=18,761, 21%), Morse Fall Scale (n=8,571, 10%), and location/discharge disposition (n=8,482, 10%), inverse-probability of missing weights (IPMW) were calculated.[51] Weights were estimated using multivariable logistic regression, which modeled the probability of being a complete case as a function of the year and season of admission, cause of admission, patient age, sex, Charlson score comorbidities (excluding HIV and cancer), immunosuppression, TPN, target medication usage anytime during hospitalization (antibiotics, antipsychotics, local anesthetics, general anesthetics, benzodiazepines, opioids, alpha-2 agonists, NSAIDs, calcium channel blockers, statins, angiotensin converting enzyme [ACE] inhibitors, angiotensin II receptor blockers [ARBs], H2 blockers, PPIs), device use (urinary catheter, ventilator, central venous catheter, peripheral venous catheter), whether they underwent any surgery (CPT 10021 – 69990), and LOS, as well as interaction terms between admission date (year and quarter) and both cause of admission and LOS. Age and LOS were modeled as restricted quadratic splines.[52] Because 99% of hospitalizations from January-March 2015 were missing MEWS (28% of all the missing data), all hospitalizations in this time period were excluded from multivariable analysis.

Table 3.1. International Classification of Diseases 9th and 10th edition, Clinical Modification (ICD-9-CM and ICD-10-CM) codes used to capture selected comorbidities and immunosuppressive conditions.

	ICD-9-CM code(s)	ICD-10-CM code(s)
CCI comorbidities[a]		
History of MI	412	I25.2
Congestive heart failure	428.0 – 428.9	I50.1 – I50.9
Cerebrovascular disease	438.0 – 438.9	I69.00 – I69.998
Dementia	290.0 – 290.9	F01.5 – F03.91
Chronic pulmonary disease[b]	490 – 496, 500 – 505, 506.4	J40 – J47.9, J60 – J67.9, J68.4
Rheumatic disease	710.0, 710.1, 710.4, 714.0 – 714.2, 714.81, 725	M05.00 – M05.9, M06.00 – M06.9
Peptic ulcer disease	531.4 – 531.7, 532.4 – 532.7, 533.4 – 533.7, 534.4 – 534.7	K25.4 – K25.7, K26.4 – K26.7, K27.4 – K27.7, K28.4 – K28.7
Mild liver disease	571.2, 571.4 – 571.6	K70.30, K70.31, K74.0, K74.3, K74.4, K74.5, K74.60, K74.69
Moderate or severe liver disease	572.2 – 572.8	K72.10, K72.90, K72.91, K76.6, K76.7
Diabetes without chronic complications	250.0 – 250.3, 250.7	E10.10, E10.11, E10.61 – E10.69, E10.8, E10.9, E11.00, E11.01, E11.10, E11.11, E11.61 – E11.69, E11.8, E11.9, E12.00, E12.01, E12.10, E12.11, E12.61 – E12.69, E12.8, E12.9, E13.00, E13.01, E13.10, E13.11, E13.61 – E13.69, E13.8, E13.9, E14.00, E14.01, E14.10, E14.11, E14.61 – E14.69, E14.8, E14.9
Diabetes with chronic complication	250.4 –250.6	E10.21 – E10.29, E10.31 – E10.39, E10.40 – E10.49, E10.51 – E10.59, E10.71 – E10.79, E11.21 – E11.29, E11.31 – E11.39, E11.40 – E11.49, E11.51 – E11.59, E11.71 – E11.79, E12.21 – E12.29, E12.31 – E12.39, E12.40 – E12.49, E12.51 – E12.59, E12.71 – E13.79, E13.21 – E13.29, E13.31 – E13.39, E13.40 – E13.49,

		E13.51 – E13.59, E13.71 – E13.79, E14.21 – E14.29, E14.31 – E14.39, E14.40 – E14.49, E14.51 – E14.59, E14.71 – E14.79
Hemiplegia or paraplegia	342.0 – 342.9, 344.1	G81.0 – G82.54
Renal disease	582.0 – 582.9, 583.0 – 583.7, 585.1 – 585.9, 586, 588.0 – 588.9	N03.0 – N03.9, N05.0 – N05.9, N18.1 – N18.9, N19, N25.0 – N25.9
Chronic pulmonary disease[b]		
Bronchitis/emphysema[c]	490, 491.0 – 491.9, 492.0, 492.8	J40 – J44.1
Asthma[c]	493.0 – 493.92	J45.20 – J45.998
Bronchiectasis[c]	494.0, 494.1	J47.0 – J47.9
Other COPD[c]	496	J44.9
Immunosuppressive conditions		
HIV/AIDS	042, 079.53	B20
Neutropenia	288.00 – 288.9	D70.0 – D70.9
Organ transplant	996.80 – 996.99, V42.0 – V42.9	T86.00 – T86.99, Z94.0 – Z94.9
Hematological malignancy	200.0 – 208.92	C81. 00 – C96.9
Solid malignancy	140.0 – 199.2, 209.0 – 209.79, 235.0 – 239.9	C00.0 – C80.2, C7A, C7B, D37.01 – D49.9
Rheumatologic/inflammatory condition	135, 277.30 – 277.39, 340, 341.0 – 341.9, 357.0 – 357.9, 422.0 – 422.99, 446.0 – 446.7, 495.9, 516.0 – 516.9, 555.0 – 558.9, 695.4, 710.0 – 712.99, 714.0 – 714.9, 720.0 – 720.9	D86.0 – D86.9, E10.40, E10.42, E11.40, E11.42, E12.40, E12.42, E13.40, E13.42, E14.40, E14.42, E85.0 – E85.9, G35, G36.0 – G36.9, G61.0 – G65.2, I40.0 – I40.9, I41, J67.9, J84.01 – J84.09, K50.00 – K52.9, K55.0 – K55.9, L93.0, L93.2, M00.00 – M00.9, M01.X0 0 M01.X9, M02.10 – M02.19, M02.30 – M02.39, M04.1, M05.00 – M05.9, M06.00 – M06.9, M08.00 – M08.99, M11.00 – M11.9, M12.00 – M12.09, M30.0 – M30.8, M32.0 – M34.9, M35.00 – M35.3, M35.8, M35.9, M45.0 – M46.1, M46.50 – M46.59, M46.80 – M46.99, M49.80 – M49.89

Other immune conditions	279.0 – 279.9, 288.0 – 288.2, 288.50 – 279.59, 288.8, 288.9, 288.00 – 288.9, 289.83, 289.89, 289.9, 795.71, 795.79	D47.4, D71, D72.0, D72.810 – D72.819, D72.89, D72.9, D75.81, D75.89, D75.9, D80.0 – D80.9, D89.2, R75, R76.0, R76.8, R76.9
Cause of admission		
Trauma	800.0 – 959.9	S00.00XA – T34.99XS, T79.0XXA – T79.9XXS
Urologic disease[c]	590.0 – 599.9, 996.64, 997.5	N10 – N13.9, N16, N20.0 – N22, N28.0 – N37, N39.0 – N39.9, N99.0 – N99.89, T83.510 – T83.598S R80.2

Abbreviations; ICD-9-CM, International Classification of Diseases, 9th edition, Clinical modification; ICD-10-CM, International Classification of Diseases, 10th edition, Clinical modification; CCI, Charlson Comorbidity Index; MI, myocardial infarction: HIV/AIDS, human immunodeficiency virus/acquired immunodeficiency syndrome

[a] Only codes which could be applied to the index hospitalization were used; e.g. history of MI (ICD-9-CM 412) was included, but acute MI (ICD-9-CM 410-410.92) was excluded

[b] For ND-pneumonia analyses only, chronic pulmonary disease were broken into smaller, more granular categories

[c] Captured by assessing admitting diagnoses (DX1) only

Table 3.2. Generic medication names used to identify and classify medications of interest.

	Generic medication name(s)
Antibiotics, systemic	
β-lactams	Amoxicillin, Ampicillin, Benzathine penicillin, Dicloxacillin, Nafcillin, Oxacillin, Penicillin G, Penicillin V, Piperacillin
	Cefaclor, Cefadroxil, Cefazolin, Cefdinir, Cefepime, Cefixime, Cefotetan, Cefoxatime, Cefoxitin, Cefpodoxime, Ceftriaxone, Ceftaroline, Ceftazidime, Cefuroxime, Cephalexin, Cepodoxime proxetil
	Aztreonam
	Ertapenem, Imipenem, Meropenem
	Avibactam, Clavulanic acid, Sulbactam
	Ampicillin/Sulbactam, Amoxicillin/Clavulanate, Ceftolozane/tazobactam, Piperacillin/Tazobactam
	Colistin (colistamethate sodium), Daptomycin, Ethambutol, Isoniazid, Polymyxin B, Pyrazinamide, Metronidazole
Aminoglycosides	Amikacin, Gentamicin, Neomycin, Paromomycin, Tobramycin
Chloramphenicol	Chloramphenicol
Glycopeptides	Telavancin, Vancomycin
Macrolides	Azithromycin, Clarithromycin, Erythromycin, Fidaxomicin, Telithromycin
Oxazolidinones	Linezolid, Tedizolid
Quinolones	Ciprofloxacin, Levofloxacin, Moxifloxacin, Ofloxacin
Rifaximin	Rifaximin
Sulfonamides	Sulfadiazine, Sulfamethoxazole, Trimethoprim
Tetracyclines	Doxycycline, Minocycline, Rifampin, Tetracycline, Tigecycline
Lincosamides	Clindamycin
Lipopeptides	Daptomycin
Nitrofurans	Nitrofuratoin
Anesthetics	
General	Etomidate, Ketamine, Midazolam, Propofol
Local	Benzocaine, Bupivacaine, Chloroprocaine, Lidocaine, Ropivacaine, Tetracaine
Anticholinergics	
Antipsychotics/neuroleptics	Amitriptyline, Aripiprazole, Chlorpromazine, Clozapine, Desipramine, Doxepin, Droperidol, Fluphenazine, Haloperidol, Imipramine, Lurasidone, Nortriptyline, Olanzapine, Paliperidone, Paroxetine, Perphenazine, Prochlorperazine, Promazine, Promethazine, Protriptyline,

	Quetiapine, Risperidone, Thioridazine, Thiothixene, Trifluoperazine, Ziprasidone
Other	Amantadine, Atropine, Baclofen, Benztropine, Carisoprodol, Cetirizine, Chlorpheniramine, Colchicine, Cyclobenzaprine, Cyproheptadine, Dexchlorpheniramine, Dicyclomine, Digoxin, Diphenhydramine, Diphenoxylate, Darifenacin, Fesoterodine, Hydroxyzine, Hyoscyamine, Loperamide, Loratadine, Meclizine, Pseudoephedrine, Ranitidine, Scopolamine, Solifenacin, Tizanidine, Tolterodine, Trospium
Antipsychotics/neuroleptics	Amitriptyline, Aripiprazole, Chlorpromazine, Clozapine, Desipramine, Doxepin, Droperidol, Fluphenazine, Haloperidol, Imipramine, Lurasidone, Nortriptyline, Olanzapine, Paliperidone, Paroxetine, Perphenazine, Prochlorperazine, Promazine, Promethazine, Protriptyline, Quetiapine, Risperidone, Thioridazine, Thiothixene, Trifluoperazine, Ziprasidone
Benzodiazepines	Alprazolam, Chlordiazepoxide, Clobazam, Clomipramine, Clonazepam, Clorazepate, Diazepam, Flurazepam, Lorazepam, Midazolam, Oxazepam, Temazepam
Histamine 2-agonists	Cimetidine, Famotidine, Ranitidine
Proton pump inhibitors	Dexlansoprazole, Esomeprazole, Lansoprazole, Omeprazole, Pantoprazole
Opioids	Buprenorphine, Codeine, Fentanyl, Hydromorphone, Meperidine, Methadone, Morphine, Nalbuphine, Oxycodone, Oxymorphone, Sufentanil, Tapentadol, Tramadol
Urinary retention medication	Doxazosin, Tadalafil, Tamsulosin, Tarazosin
Immunosuppressive medications	
Chemotherapeutic agents (alkylating)	Bendamustine hydrochloride, Busulfan, Carmustine, Cyclophosphamide, Darabazine, Ifosfamide, Melphalan, Thiotepa
Chemotherapeutic agents (antibiotics)	Bleomycin sulfate, Dactinomycin, Daunorubicin, Doxorubicin, Epirubicin, Idarubicin
Chemotherapeutic agents (antimetabolites)	Capecitabine, Cladribine, Clofarabine, Cytarabine, Fludarabine, Fluorouracil, Gemcitabine, Mercaptopurine, Methotrexate, Pemetrexed, Pentostatin
Chemotherapeutic agents (antimitotics)	Docetaxel, Paclitaxel, Vinblastine, Vincristine, Vinorelbine
Chemotherapeutic agents (monoclonal antibodies)	Alemtuzumab, Bevacizumab, Cetuximab, Gemtuzumab, Ofatumumab, Rituximab
Chemotherapeutic agents (other)	Aldesleukin, Arsenic trioxide, Asparaginase, Azacitidine, Brentuximab vedotin, Bortezomib, Carboplatin, Carfilzomib, Cisplatin, Dasatinib, Decitabine, Erlotinib, Etoposide, Everolimus, Imatinib, Irinotecan, Lapatinib,

	Mitoxantrone, Nelarabine, Nilotinib, Oxaliplatin, Pazopanib, Pegaspargase, Pralatrexate, Procarbazine, Romidepsin, Sorafenib, Sunitinib, Temozolomide, Temsirolimus, Topotecan, Tretinoin, Vorinostat
Immune-modulating agents	Abatacept, Adalimumab, Alefacept, Anakinra, Azathioprine, Basiliximab, Belatacept, Belimumab, Certolizumab pegol, Cyclosporine, Daclizumab, Denosumab, Eculizumab, Efalizumab, Etanercept, Fingolimod, Glatiramer, Golimumab, Infliximab, Interferon alfa-2a, Interferon alfa-2b, Interferon alfa-n3, Interferon alfacon-1, Interferon beta-1a, Interferon beta-1b, Interferon gamma-1b, Leflunomide, Lenalidomide, Muromonab-CD3, Mycophenolate acid, Mycophenolate mofetil, Natalizumab, Palifermin, Palivizumab, Pomalidomide, Pegademase bovine, Peginterferon alfa-2a, Peginterferon alfa-2b, Sirolimus, Tacrolimus, Tocilizumab, Ustekinumab
Systemic corticosteroids	Betamethasone, Budesonide, Dexamethasone, Methylprednisolone, Prednisolone, Triamcinolone

CHAPTER 4: INCIDENCE AND RISK FACTORS OF NON-DEVICE ASSOCIATED URINARY TRACT INFECTIONS IN AN ACUTE CARE HOSPITAL

4.1 INTRODUCTION

Healthcare associated infections (HAIs) pose a major burden on the United States healthcare system. HAIs are a substantial source of morbidity and mortality and are considered one of the most common sources of preventable harm in the inpatient setting.[1-5,21] In 2015, 3.2% of patients, or roughly 1 in every 31 hospitalized adults, had at least one HAI on any given day in the US, which corresponds to almost 700,000 infections a year.[2] Urinary tract infections (UTIs) are one of the most common types of HAIs, accounting for almost 15% of all HAIs and one-third of HAIs outside of intensive care units.[1,2,21] And while mortality and cost of UTIs may be low (2% and $589, respectively), because they are so common the estimated overall burden is substantial (13,000 deaths and $340 million per year).[21,53]

Historically the vast majority of UTIs have been considered catheter associated (CA-UTIs).[21,26,28] However, there is increasing appreciation that non-device associated UTIs (ND-UTIs) account for a substantial fraction and sometimes the majority of hospital-onset UTIs. Rates of CA-UTIs have dramatically decreased over the past decade but the rate of non-device associated UTIs (ND-UTIs) have remained stagnant.[2,7,13,14] Despite the increasing importance of ND-UTIs in the acute care setting, there is a paucity of research on the incidence, risk factors, and optimal prevention strategies for these infections. Thus, the purpose of this study was to

update current estimates of ND-UTI rates and their frequency relative to CA-UTI, assess temporal trends, and identify potential risk factors for ND-UTI.

4.2 METHODS

Data sources and study population

Electronic medical records (EMR) from adults (≥18 years old) admitted to the University of North Carolina (UNC) Hospitals between January 1, 2013 and December 31, 2017 were obtained from the Carolina Data Warehouse for Health (CDW-H), a central repository for clinical and administrative data from the UNC Healthcare System. Prisoners were excluded from analysis. Patients were able to have multiple hospitalizations during the study period. HAIs were identified through the UNC Hospitals' Infection Prevention database, which included both device and non-device associated HAIs, captured through comprehensive, hospital-wide active surveillance, in accordance with the Centers for Disease Control and Prevention (CDC) case definitions and methodology.[13,31] The two databases were then deterministically linked using admission date, medical record numbers, and full name. This study was approved by the UNC Institutional Review Board.

Incidence of ND-UTIs

Quarterly incidence rates, per 10,000 hospitalization days, between 2013 and 2017 were calculated and Poisson regression was used to estimate potential changes in ND-UTI rates over time. The proportion of UTIs that were non-device related each year were also calculated. Cochran-Armitage trend tests (two-sided) were used to test the null hypothesis that the proportion of ND-UTIs did not change between 2013 and 2017.

Risk Factors for ND-UTIs

Only hospitalizations between 2015 and 2017 with a length of stay (LOS) >2 days were included in the risk factor analysis. Potential risk factors of interest included patient sex, age (categorized as 18-39 years old [reference], 40-49 years old, 50-59 years old, 60-69 years old, and ≥70 years old), selected comorbidities, immunosuppression, BMI (categorized as under/normal weight [<25, reference], overweight [25.0 – 29.9], and obese [≥30.0]), trauma admission, being on an intensive care unit (ICU), Modified Early Warning Score, Morse Fall scale, urinary retention, inpatient medications (anesthesia antibiotics, anticholinergics, benzodiazepines, and opioids), total parenteral nutrition (TPN), urinary catheterization, suprapubic catheterization, nephrostomy tube, and having underwent a urologic procedure.

Patient comorbidities were identified using the discharge diagnosis ICD-9-CM (January 2015 – September 2015) and ICD-10-CM (October 2015 – December 2017) codes on each record. Deyo et al. (1992) and Quan et al. (2005) algorithms were adapted to identify components of the Charlson comorbidity index (CCI) score (Table 4.1).[41,42] Diagnosis codes for incident events (e.g. acute myocardial infarction) were removed from all component definitions.[41] Peripheral vascular disease (PVD) was also excluded due to low incidence (n=201) and both malignancy (solid tumor or metastatic disease) and human immunodeficiency viruses (HIV) were incorporated into the broader classification of immunocompromised.

Immunocompromised patients were identified using the Advisory Committee on Immunization Practices (ACIP) and Infectious Diseases Society of America (IDSA) guidelines, which are used to determine persons who cannot receive live-attenuated vaccinations.[43] Diagnoses of immunosuppressive conditions- which included HIV, neutropenia, organ

transplant, and any malignancy- were identified using discharge diagnosis codes; relevant ICD-9-CM codes were identified using the Greenberg et al. (2016)[44] algorithm and ICD-10-CM codes were identified using CMS General Equivalence Mappings (GEMS) (Table 4.1). Patients receiving chemotherapeutic agents, corticosteroids, or immune-modulating agents within the first 2 days of their hospitalization were identified using inpatient medications (Table 4.2). Neutropenia was identified using both diagnosis codes and laboratory blood test results within the first 2 hospitalization days (defined as ≥2 white blood cell [WBC] counts <500 cells/mm^3). Urinary retention was identified through inpatient medication treatment for the condition (Table 4.2).

Severity of illness was captured using the Modified Early Warning Score (MEWS)[45,46] and Morse Fall Scale[47,48], which are captured and calculated within the UNC Hospitals EMR. The MEWS uses vital signs- specifically systolic blood pressure, heart rate, respiratory rate, temperature, level of consciousness, and hourly urine output (for two hours)- to detect patients at risk for imminent clinical deterioration.[49] The Morse Fall Scale is a simple prediction score designed to identify patients at risk for falling in the hospital. The Morse Fall Scale includes the following variables: history of falling, number of secondary diagnoses, whether ambulatory aid is needed, intravenous therapy/heparin lock, gait, and mental status.[50] For each patient, the first MEWS and Morse Fall Scale score within the first 2 days of admission was captured and categorized using clinically relevant cut points (MEWS: <1 [reference], 2, 3, ≥4; Morse Fall Scale: 0 [reference], 1-24, 25-45, >45). A MEWS ≥4 and a Morse Fall Scale score >45 are both considered indicators of severe illness.[49,50]

ICU stay, urinary retention, inpatient medications, TPN, device use, and urologic procedures were treated as time-varying exposures, with the patient being considered as exposed

for the remainder of the hospitalization. For example, once a patient received antibiotics on day 4, they were considered to be exposed from day 4 until discharge, and were classified as unexposed on days 1-3. All medications were identified using orders captured in the EMR and receipt was confirmed using the medication administration record (Table 4.2). Urinary retention was captured through treatment (Table 4.2), and urologic procedures were identified using CPT codes 50010 – 53899.

Multivariable Cox proportional hazards regression was used to simultaneously estimate the association between each potential risk factor and the incidence of ND-UTIs. Correlation between repeat hospitalizations of the same patients were taken into account by utilizing robust sandwich covariance matrix estimates as described by Lee et al. (1992) and CA-UTI and inpatient mortality were treated as competing risks using the Fine and Gray (1999) model.[39,40]

Due to missing values of BMI (n=15,146, 17%), MEWS (n=18,761, 21%), Morse Fall Scale (n=8,571, 10%), and location/discharge disposition (n=8,482, 10%), inverse-probability of missing weights (IPMW) were calculated.[51] Weights were estimated using multivariable logistic regression, which modeled the probability of being a complete case as a function of the year and season of admission, cause of admission, patient age, sex, Charlson score comorbidities (excluding HIV and cancer), immunosuppression, TPN, target medication usage anytime during hospitalization (antibiotics, antipsychotics, local anesthetics, general anesthetics, benzodiazepines, opioids, alpha-2 agonists, non-steroid anti-inflammatory drugs [NSAIDs], calcium channel blockers, statins, angiotensin converting enzyme [ACE] inhibitors, angiotensin II receptor blockers [ARBs], histamine-2 agonists, proton pump inhibitors), device use (urinary catheter, ventilator, central venous catheter, peripheral venous catheter), whether they underwent any surgery (CPT 10021 – 69990), and LOS, as well as interaction terms between admission date

(year and quarter) and both cause of admission and LOS. Age and LOS were modeled as restricted quadratic splines.[52] Because 99% of hospitalizations from January-March 2015 were missing MEWS (28% of all the missing data), all hospitalizations in this time period were excluded from multivariable analysis.

Our statistical analysis strategy is consistent with the American Statistical Association's statements on p-values.[54,55] All statistical computations were performed using SAS 9.4 (SAS Inc., Cary, NC).

4.3 RESULTS

From 2013-2017 there were 163,386 hospitalizations (97,485 unique patients) and 1,273 UTIs (715 ND-UTI, 558 CA-UTI) during 1,234 unique hospitalizations at UNC Hospitals. Of the 1,273 UTIs, 1,268 (99.6%) were successfully linked to a hospitalization record. 87% (n=142,836) of hospitalizations were >2 days (median 5 days, interquartile range [IQR] 3-8 days). Patient demographics and causes of admission are described in Table 4.3.

Median time to first UTI was 8 days for both ND-UTIs (IQR 4 -15) and CA-UTIs (IQR 4-18). Between 2013 and 2017, the rate of ND-UTIs decreased slightly but overall remained stable, with 6.14 ND-UTIs per 10,000 hospitalization days in 2013 and 5.57 ND-UTIs per 10,000 hospitalization days in 2017, p=0.15 (Figure 4.1.A). However, the proportion of UTIs that were non-device related increased from 52% to 72% during this time, p<0.0001 (Figure 4.1.B). From 2015-2017, 15% (n=49) of ND-UTIs occurred in an ICU, 70% (n=229) occurred on a floor, and 14% on a stepdown unit (n=46) (67 could not be classified due to missing location data). In comparison, 55% of CA-UTIs occurred in an ICU (n=137), 32% on the floor (n=81), and 13% on a stepdown unit (n=33) (18 could not be classified). The 30-day and 60-day

cumulative incidence of ND-UTI was 19.9 and 48.7 infections per 10,000 patients, respectively (Figure 4.2).

There were 88,487 hospitalizations between 2015 and 2017 with a LOS >2 days included in the risk factor analysis. Median IPMW was 1.07 (IQR 1.03-1.24, range 1.00 – 21.38); only 27 hospitalizations had a weight >10. After adjustment, female sex (HR 1.94, 95% CI 1.50, 2.50) and increasing age, with patients ≥70 years, compared to 18-25 year old patients, old having the highest incidence (HR 2.06, 95% CI 1.33, 3.21) were associated within increased incidence of ND-UTIs, Table 4.4. Moreover, the effect of female sex appeared to be relatively consistent across age (p=0.57). Patients diagnosed with peptic ulcer disease (HR 2.25, 95% CI 1.04, 4.86) or who were immunosuppressed (HR 1.48, 95% CI 1.15, 1.91) were also at higher risk for ND-UTIs. Trauma admissions were associated with increased patient risk for ND-UTI (HR 1.36, 95% CI 1.02, 1.81). BMI and MEWS did not appear to have any impact.

During the hospitalization, being given TPN (HR 1.99, 95% CI 1.35, 2.94) and opioids (HR 1.62 95% CI 1.10, 2.32) were associated with increased patient risk of ND-UTI, Table 4.4. In the crude analyses, urinary retention, suprapubic catheterization, and nephrostomy tubes were associated with increased risk of infection, but after adjustment for possible confounders, confidence intervals were wide and effects were no longer statistically significant (urinary retention: HR 1.41, 95% CI 0.96, 2.07, suprapubic catheterization: HR 2.28, 95% CI 0.88, 5.91 and nephrostomy tubes: HR 2.02, 95% CI 0.83, 4.93). Local anesthesia (HR 0.70, 95% CI 0.53, 0.92), antibiotics (HR 0.32, 95% CI 0.24, 0.43), non-antipsychotic anticholinergics (HR 0.68, 0.53, 0.87), and benzodiazepines (HR 0.66, 0.51, 0.87) were associated with reduced risk of infection.

4.4 DISCUSSION

Between 2013 and 2017, the incidence of ND-UTIs have remained consistent and 72% UTIs are now non-device associated. Females, older adults, peptic ulcer disease, paralysis, immunosuppression, urinary retention, opioid use, TPN, and trauma patients all had a higher risk of ND-UTI. Suprapubic catheters and nephrostomy tubes may also increase patient risk. To the best of our knowledge, this is the first study to conduct a robust and in-depth analysis of ND-UTI risk factors and most recent assessment of ND-UTI incidence.

Over the past decade, the rate of ND-UTIs has remained relatively consistent but the relative burden of non-device associated has increased. For example, from 2006-2009, 28% of all UTIs at UNC Hospitals were non-device associated and the rate of ND-UTIs was 6.4 infections per 10,000 non-device days[14], but by 2012 it rose to almost 50%.[7] As of 2017, the rate of ND-UTI was 5.57 ND-UTIs per 10,000 hospitalization days and 3 out of every 4 UTIs were non-device associated. This shift towards non-device infections is likely due to implementation of evidence-based guidelines to prevent CA-UTI; these guidelines mainly target catheter placement, maintenance, and removal and thus have limited impact on preventing ND-UTIs.[8,56] Our results suggest that current targeted surveillance practices directed at catheterized patients alone are no longer sufficient to capture the majority of UTIs in acute care settings.

We found that patient demographics and comorbidities, specifically female sex, older age, peptic ulcer disease, paralysis, and immunosuppression, were associated with increased ND-UTI incidence. Female sex, older age, paraplegia, and immunosuppression have also been shown to increase the risk for CA-UTIs, indicating that certain subsets of patients may be at higher risk for all UTIs.[57-59] However, a recent study of CA-UTI found that after accounting for comorbidities and other severity measures age was no longer a predictor of infection, which

likely means that age is a proxy for illness severity or frailty, and not an independent risk factor itself[59]. To the best of our knowledge, peptic ulcer disease has not been reported to be a risk factor for UTIs (or CA-UTIs), but treatments such as ranitidine, may cause drug-induced urinary retention, particularly in new users, females, and those ≥60 years old.[60,61] However, peptic ulcer disease was associated with ND-UTI incidence even after adjusting for urinary retention, indicating that other factors may also be at play.

Inpatient medication use was also associated with ND-UTI incidence. Patients receiving antibiotics, local anesthetics, anticholinergics, and benzodiazepines were at reduced risk for infection, and patients receiving TPN and opioids were at increased risk. Opioids have also been found to cause drug-induced urinary retention[60], although opioid use may also be a proxy for acute pain and limited mobility (particularly after surgery), which may increase risk for UTIs, particularly in older adults[62]. Several studies have also found that TPN was associated with increased fungal infections, including UTIs, in hospitalized patients.[63,64] Interestingly, we found that antibiotic use was associated with reduced incidence of ND-UTIs although antibiotic prophylaxis has not been found to reduce risk of CA-UTIs.[8] And while local anesthetics, anticholinergics, and benzodiazepines are also known to cause urinary retention, anesthetics and benzodiazepines were associated with reduced risk of ND-UTIs, even in unadjusted analyses. It is possible that patients receiving these medications may represent an overall healthier patient population.

Finally, both suprapubic catheters and nephrostomy tubes were associated with increased incidence of ND-UTIs, but estimates were imprecise. A recent Cochrane review (2015) found that there was little or no difference in symptomatic UTI risk between short-term suprapubic versus indwelling catheters, but that patients with suprapubic catheters were catheterized for

longer durations, which could explain the higher cumulative infection risk in this population.[65] Currently, neither suprapubic catheters nor nephrostomy tubes are included in the CDC CA-UTI definition, and the CDC has no recommendations for preventing CA-UTI in these populations, although they do call for further research on the topic.[8]

This study is not without limitations. First, this was a retrospective, single center study and our results may not generalize to other hospitals, particularly if the patient population is different. We also did not account for duration, dose, or underlying indications for medication use. Future studies should assess whether longer exposures or higher doses of opioids and other medications are associated with higher risk for ND-UTI. Additionally, ICD-9-CM and ICD-10-CM codes were used to identify most comorbidities. Using these codes likely underestimates the prevalence of comorbidities, although we expect this misclassification to be non-differential and, if anything, bias results towards the null. Similarly, ND-UTIs and CA-UTIs were captured using CDC definitions, which require laboratory confirmation. Patients who are treated for suspected UTIs but are not cultured would be missed. Likewise, urinary retention was captured using suggestive medications and thus patients managed without medications would also be missed. Finally, although we had a large sample size, the incidence of ND-UTI and prevalence of some risk factors were low, resulting in low levels of precision of the estimators as indicated by the widths of the observed confidence intervals.

In conclusion, between 2013 and 2017, the incidence rate of ND-UTIs remained relatively stable, although non-device infections now represent the majority of UTIs in our acute care hospital. Current targeted surveillance practices for catheter associated UTIs should be reconsidered in light of this changing landscape. Women, older age, peptic ulcer disease, paralysis, immunosuppression, trauma admissions, TPN, and opioids were all identified as risk

factors for ND-UTI. Urinary retention, suprapubic catheters and nephrostomy tubes may also increase patient risk. Future research should attempt to replicate these findings and explore the impact of prevention strategies that target these risk factors.

4.5 ACKNOWLEDGEMENTS

This project was supported by the National Center for Advancing Translational Sciences (NCATS), National Institutes of Health (NIH), through Grant Award Number UL1TR002489. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH. The authors would also like to thank Adam M. Lee at the NC TraCS Institute for his help querying and obtaining EMR data.

Table 4.1. International Classification of Diseases 9th and 10th edition, Clinical Modification (ICD-9-CM and ICD-10-CM) codes used to capture selected comorbidities and immunosuppressive conditions.

	ICD-9-CM code(s)	ICD-10-CM code(s)
Comorbidities[a]		
History of MI	412	I25.2
Congestive heart failure	428.0 – 428.9	I50.1 – I50.9
Cerebrovascular disease	438.0 – 438.9	I69.00 – I69.998
Dementia	290.0 – 290.9	F01.5 – F03.91
Chronic pulmonary disease	490 – 496, 500 – 505, 506.4	J40 – J47.9, J60 – J67.9, J68.4
Rheumatic disease	710.0, 710.1, 710.4, 714.0 – 714.2, 714.81, 725	M05.00 – M05.9, M06.00 – M06.9
Peptic ulcer disease	531.4 – 531.7, 532.4 – 532.7, 533.4 – 533.7, 534.4 – 534.7	K25.4 – K25.7, K26.4 – K26.7, K27.4 – K27.7, K28.4 – K28.7
Mild liver disease	571.2, 571.4 – 571.6	K70.30, K70.31, K74.0, K74.3, K74.4, K74.5, K74.60, K74.69
Moderate or severe liver disease	572.2 – 572.8	K72.10, K72.90, K72.91, K76.6, K76.7
Diabetes without chronic complications	250.0 – 250.3, 250.7	E10.10, E10.11, E10.61 – E10.69, E10.8, E10.9, E11.00, E11.01, E11.10, E11.11, E11.61 – E11.69, E11.8, E11.9, E12.00, E12.01, E12.10, E12.11, E12.61 – E12.69, E12.8, E12.9, E13.00, E13.01, E13.10, E13.11, E13.61 – E13.69, E13.8, E13.9, E14.00, E14.01, E14.10, E14.11, E14.61 – E14.69, E14.8, E14.9
Diabetes with chronic complication	250.4 –250.6	E10.21 – E10.29, E10.31 – E10.39, E10.40 – E10.49, E10.51 – E10.59, E10.71 – E10.79, E11.21 – E11.29, E11.31 – E11.39, E11.40 – E11.49, E11.51 – E11.59, E11.71 – E11.79, E12.21 – E12.29, E12.31 – E12.39, E12.40 – E12.49, E12.51 – E12.59, E12.71 – E13.79, E13.21 – E13.29, E13.31 – E13.39, E13.40 – E13.49,

		E13.51 – E13.59, E13.71 – E13.79, E14.21 – E14.29, E14.31 – E14.39, E14.40 – E14.49, E14.51 – E14.59, E14.71 – E14.79
Hemiplegia or paraplegia	342.0 – 342.9, 344.1	G81.0 – G82.54
Renal disease	582.0 – 582.9, 583.0 – 583.7, 585.1 – 585.9, 586, 588.0 – 588.9	N03.0 – N03.9, N05.0 – N05.9, N18.1 – N18.9, N19, N25.0 – N25.9
Immunosuppressive conditions		
HIV/AIDS	042, 079.53	B20
Neutropenia	288.00 – 288.9	D70.0 – D70.9
Organ transplant	996.80 – 996.99, V42.0 – V42.9	T86.00 – T86.99, Z94.0 – Z94.9
Hematological malignancy	200.0 – 208.92	C81. 00 – C96.9
Solid malignancy	140.0 – 199.2, 209.0 – 209.79, 235.0 – 239.9	C00.0 – C80.2, C7A, C7B, D37.01 – D49.9
Rheumatologic/inflammatory condition	135, 277.30 – 277.39, 340, 341.0 – 341.9, 357.0 – 357.9, 422.0 – 422.99, 446.0 – 446.7, 495.9, 516.0 – 516.9, 555.0 – 558.9, 695.4, 710.0 – 712.99, 714.0 – 714.9, 720.0 – 720.9	D86.0 – D86.9, E10.40, E10.42, E11.40, E11.42, E12.40, E12.42, E13.40, E13.42, E14.40, E14.42, E85.0 – E85.9, G35, G36.0 – G36.9, G61.0 – G65.2, I40.0 – I40.9, I41, J67.9, J84.01 – J84.09, K50.00 – K52.9, K55.0 – K55.9, L93.0, L93.2, M00.00 – M00.9, M01.X0 0 M01.X9, M02.10 – M02.19, M02.30 – M02.39, M04.1, M05.00 – M05.9, M06.00 – M06.9, M08.00 – M08.99, M11.00 – M11.9, M12.00 – M12.09, M30.0 – M30.8, M32.0 – M34.9, M35.00 – M35.3, M35.8, M35.9, M45.0 – M46.1, M46.50 – M46.59, M46.80 – M46.99, M49.80 – M49.89
Other immune conditions	279.0 – 279.9, 288.0 – 288.2, 288.50 – 279.59, 288.8, 288.9, 288.00 – 288.9, 289.83, 289.89, 289.9, 795.71, 795.79	D47.4, D71, D72.0, D72.810 – D72.819, D72.89, D72.9, D75.81, D75.89, D75.9, D80.0 – D80.9, D89.2, R75, R76.0, R76.8, R76.9

Cause of admission		
Trauma	800.0 – 959.9	S00.00XA – T34.99XS, T79.0XXA – T79.9XXS
Urologic disease[b]	590.0 – 599.9, 996.64, 997.5	N10 – N13.9, N16, N20.0 – N22, N28.0 – N37, N39.0 – N39.9, N99.0 – N99.89, T83.510 – T83.598S R80.2

Abbreviations; ICD-9-CM, International Classification of Diseases, 9th edition, Clinical modification; ICD-10-CM, International Classification of Diseases, 10th edition, Clinical modification; CCI, Charlson Comorbidity Index; MI, myocardial infarction: HIV/AIDS, human immunodeficiency virus/acquired immunodeficiency syndrome

[a] Only codes which could be applied to the index hospitalization were used; e.g. history of MI (ICD-9-CM 412) was included, but acute MI (ICD-9-CM 410-410.92) was excluded

[b] Captured by assessing admitting diagnoses (DX1) only

Table 4.2. Generic medication names used to classify medications of interest.

	Generic medication name(s)
Antibiotics, systemic	
β-lactams	Amoxicillin, Ampicillin, Benzathine penicillin, Dicloxacillin, Nafcillin, Oxacillin, Penicillin G, Penicillin V, Piperacillin
	Cefaclor, Cefadroxil, Cefazolin, Cefdinir, Cefepime, Cefixime, Cefotetan, Cefoxatime, Cefoxitin, Cefpodoxime, Ceftriaxone, Ceftaroline, Ceftazidime, Cefuroxime, Cephalexin, Cepodoxime proxetil
	Aztreonam
	Ertapenem, Imipenem, Meropenem
	Avibactam, Clavulanic acid, Sulbactam
	Ampicillin/Sulbactam, Amoxicillin/Clavulanate, Ceftolozane/tazobactam, Piperacillin/Tazobactam
	Colistin (colistamethate sodium), Daptomycin, Ethambutol, Isoniazid, Polymyxin B, Pyrazinamide, Metronidazole
Aminoglycosides	Amikacin, Gentamicin, Neomycin, Paromomycin, Tobramycin
Chloramphenicol	Chloramphenicol
Glycopeptides	Telavancin, Vancomycin
Macrolides	Azithromycin, Clarithromycin, Erythromycin, Fidaxomicin, Telithromycin
Oxazolidinones	Linezolid, Tedizolid
Quinolones	Ciprofloxacin, Levofloxacin, Moxifloxacin, Ofloxacin
Rifaximin	Rifaximin
Sulfonamides	Sulfadiazine, Sulfamethoxazole, Trimethoprim
Tetracyclines	Doxycycline, Minocycline, Rifampin, Tetracycline, Tigecycline
Lincosamides	Clindamycin
Lipopeptides	Daptomycin
Nitrofurans	Nitrofuratoin
Anesthetics	
General	Etomidate, Ketamine, Midazolam, Propofol
Local	Benzocaine, Bupivacaine, Chloroprocaine, Lidocaine, Ropivacaine, Tetracaine
Anticholinergics	
Antipsychotics/neuroleptics	Amitriptyline, Aripiprazole, Chlorpromazine, Clozapine, Desipramine, Doxepin, Droperidol, Fluphenazine, Haloperidol, Imipramine, Lurasidone, Nortriptyline, Olanzapine, Paliperidone, Paroxetine, Perphenazine, Prochlorperazine, Promazine, Promethazine, Protriptyline,

	Quetiapine, Risperidone, Thioridazine, Thiothixene, Trifluoperazine, Ziprasidone
Other	Amantadine, Atropine, Baclofen, Benztropine, Carisoprodol, Cetirizine, Chlorpheniramine, Colchicine, Cyclobenzaprine, Cyproheptadine, Dexchlorpheniramine, Dicyclomine, Digoxin, Diphenhydramine, Diphenoxylate, Darifenacin, Fesoterodine, Hydroxyzine, Hyoscyamine, Loperamide, Loratadine, Meclizine, Pseudoephedrine, Ranitidine, Scopolamine, Solifenacin, Tizanidine, Tolterodine, Trospium
Benzodiazepines	Alprazolam, Chlordiazepoxide, Clobazam, Clomipramine, Clonazepam, Clorazepate, Diazepam, Flurazepam, Lorazepam, Midazolam, Oxazepam, Temazepam
Opioids	Buprenorphine, Codeine, Fentanyl, Hydromorphone, Meperidine, Methadone, Morphine, Nalbuphine, Oxycodone, Oxymorphone, Sufentanil, Tapentadol, Tramadol
Urinary retention medication	Doxazosin, Tadalafil, Tamsulosin, Tarazosin
Immunosuppressive medications	
Chemotherapeutic agents (alkylating)	Bendamustine hydrochloride, Busulfan, Carmustine, Cyclophosphamide, Darabazine, Ifosfamide, Melphalan, Thiotepa
Chemotherapeutic agents (antibiotics)	Bleomycin sulfate, Dactinomycin, Daunorubicin, Doxorubicin, Epirubicin, Idarubicin
Chemotherapeutic agents (antimetabolites)	Capecitabine, Cladribine, Clofarabine, Cytarabine, Fludarabine, Fluorouracil, Gemcitabine, Mercaptopurine, Methotrexate, Pemetrexed, Pentostatin
Chemotherapeutic agents (antimitotics)	Docetaxel, Paclitaxel, Vinblastine, Vincristine, Vinorelbine
Chemotherapeutic agents (monoclonal antibodies)	Alemtuzumab, Bevacizumab, Cetuximab, Gemtuzumab, Ofatumumab, Rituximab
Chemotherapeutic agents (other)	Aldesleukin, Arsenic trioxide, Asparaginase, Azacitidine, Brentuximab vedotin, Bortezomib, Carboplatin, Carfilzomib, Cisplatin, Dasatinib, Decitabine, Erlotinib, Etoposide, Everolimus, Imatinib, Irinotecan, Lapatinib, Mitoxantrone, Nelarabine, Nilotinib, Oxaliplatin, Pazopanib, Pegaspargase, Pralatrexate, Procarbazine, Romidepsin, Sorafenib, Sunitinib, Temozolomide, Temsirolimus, Topotecan, Tretinoin, Vorinostat
Immune-modulating agents	Abatacept, Adalimumab, Alefacept, Anakinra, Azathioprine, Basiliximab, Belatacept, Belimumab, Certolizumab pegol, Cyclosporine, Daclizumab, Denosumab, Eculizumab, Efalizumab, Etanercept, Fingolimod, Glatiramer, Golimumab, Infliximab, Interferon alfa-2a, Interferon alfa-2b, Interferon alfa-n3,

	Interferon alfacon-1, Interferon beta-1a, Interferon beta-1b, Interferon gamma-1b, Leflunomide, Lenalidomide, Muromonab-CD3, Mycophenolate acid, Mycophenolate mofetil, Natalizumab, Palifermin, Palivizumab, Pomalidomide, Pegademase bovine, Peginterferon alfa-2a, Peginterferon alfa-2b, Sirolimus, Tacrolimus, Tocilizumab, Ustekinumab
Systemic corticosteroids	Betamethasone, Budesonide, Dexamethasone, Methylprednisolone, Prednisolone, Triamcinolone

Table 4.3. Hospitalization characteristics.

	2013 – 2014	2015 – 2017
Total hospitalizations, n	62,853	100,533
Unique patients, n	41,941	64,633
Female, n (%)	35,360 (56)	55,985 (56)
Age, median (IQR)	52 (34 – 66)	53 (35 – 66)
Race, n (%)		
White	37,766 (62)	60,089 (62)
Black	16,625 (27)	26,378 (27)
Asian	752 (1)	1,411 (1)
Hawaiian/Pacific Islander	31 (<1)	79 (<1)
Native American	533 (1)	908 (1)
Other race	5,159 (8)	8,166 (8)
Missing	1,987	3,502
Cause of admission[a], n (%)		
Circulatory disease	8,166 (13)	13,440 (14)
Injury or poisoning[b]	8,429 (13)	12,934 (13)
Childbirth/complications of pregnancy	7,938 (13)	12,408 (13)
Digestive disease	5,982 (10)	10,367 (11)
Neoplasms	6,094 (10)	9,882 (10)
Psychological disorders	4,485 (7)	6,738 (7)
Infectious/parasitic disease	3,651 (6)	5,789 (6)
Respiratory disease	2,977 (5)	4,674 (5)
Musculoskeletal disease	2,286 (4)	4,462 (5)
Endocrine/metabolic disease	1,959 (3)	3,233 (3)
Genitourinary disease	2,106 (3)	3,313 (3)
Nervous system disease	1,679 (3)	2,756 (3)
Skin disease	1,116 (2)	1,778 (2)
Blood disease	994 (2)	1,575 (2)
Other or ill-defined	4,862 (8)	4,972 (5)
LOS, days, median (IQR)	5 (3 – 8)	5 (3 – 8)

Abbreviations: IQR, interquartile range; LOS, length of stay

[a] Classified using primary diagnosis on each hospitalization; 2,341 hospitalizations (1%) were unable to be linked to their diagnosis codes

[b] A subset of these codes were used to identify trauma admissions

Table 4.4. Risk factor prevalence and hazard ratios for ND-UTIs, among adults hospitalized for >2 days between 2015 – 2017.

	Prevalence	**Crude**		**Adjusted[a]**	
	N (%)	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Female	49,500 (56)	1.71 (1.37, 2.14)	**<0.0001**	1.94 (1.50, 2.50)	**<0.0001**
Age, years					
18-39 years old	28,007 (32)	ref	–	ref	–
40-49 years old	11,018 (12)	1.78 (1.15, 2.75)	**0.009**	1.60 (1.00, 2.54)	**0.05**
50-59 years old	15,631 (18)	2.12 (1.43, 3.15)	**0.0002**	1.88 (1.21, 2.93)	**0.005**
60-69 years old	16,400 (19)	2.13 (1.46, 3.10)	**<0.0001**	1.70 (1.10, 2.63)	**0.02**
≥70 years old	17,431 (20)	2.86 (1.98, 4.12)	**<0.0001**	2.06 (1.33, 3.21)	**0.001**
Comorbidities					
Prior MI	5,434 (6)	1.47 (1.03, 2.09)	**0.03**	1.44 (0.96, 2.17)	0.08
Heart failure	12,538 (14)	0.90 (0.68, 1.20)	0.47	0.79 (0.56, 1.11)	0.18
Cerebrovascular disease	1,923 (2)	0.85 (0.40, 1.80)	0.67	0.64 (0.28, 1.46)	0.29
Dementia	2,376 (3)	1.37 (0.85, 2.19)	0.20	0.94 (0.55, 1.61)	0.83
Pulmonary disease	18,047 (19)	1.06 (0.82, 1.37)	0.65	0.95 (0.72, 1.27)	0.74
Rheumatoid arthritis	1,708 (2)	1.65 (0.91, 3.01)	0.10	1.17 (0.59, 2.31)	0.65
Peptic ulcer disease	441 (1)	2.45 (1.17, 5.10)	**0.02**	2.25 (1.04, 4.86)	**0.04**
Diabetes	20,821 (23)	1.13 (0.89, 1.44)	0.31	1.10 (0.83, 1.45)	0.52
Liver disease	3,320 (4)	0.93 (0.57, 1.51)	0.76	1.04 (0.59, 1.85)	0.89
Renal disease	13,120 (15)	0.88 (0.66, 1.17)	0.37	0.72 (0.52, 1.01)	0.06
Paralysis	1,915 (2)	3.39 (2.40, 4.80)	**<0.0001**	3.14 (2.10, 4.72)	**<0.0001**
Immunosuppression	35,810 (40)	1.37 (1.10, 1.71)	**0.005**	1.48 (1.15, 1.91)	**0.002**
Body mass index					
Under/normal weight	24,535 (33)	ref	–	ref	–
Overweight	21,129 (29)	1.00 (0.77, 1.32)	0.98	1.03 (0.77, 1.38)	0.85
Obese	27,677 (38)	0.90 (0.70, 1.17)	0.43	0.91 (0.67, 1.22)	0.52
Trauma admission	9,683 (11)	1.21 (0.92, 1.58)	0.17	1.36 (1.02, 1.81)	**0.04**
Intensive care unit stay[b]	15,767 (20)	1.20 (0.94, 1.54)	0.15	1.27 (0.90, 1.78)	**0.17**
MEWS					
0-1	18,917 (27)	ref	–	ref	–

	2	27,062 (39)	0.88 (0.66, 1.17)	0.38	0.98 (0.72, 1.32)	0.88
	3	12,380 (18)	1.00 (0.72, 1.38)	0.99	1.06 (0.76, 1.49)	0.72
	≥4	11,367 (16)	0.82 (0.59, 1.15)	0.25	0.90 (0.63, 1.28)	0.54
Morse fall risk						
	0	4,626 (6)	ref	–	ref	–
	1-24	19,862 (25)	1.28 (0.57, 2.88)	0.55	1.02 (0.43, 2.42)	0.96
	25-45	33,833 (42)	1.99 (0.93, 4.26)	0.08	1.55 (0.67, 3.59)	0.30
	>45	21,595 (27)	2.73 (1.28, 5.84)	**0.01**	1.83 (0.78, 4.33)	0.17
Urinary retention[b]		5,918 (7)	1.29 (0.93, 1.79)	0.12	1.41 (0.96, 2.07)	0.08
Inpatient medications[b]						
	Anesthesia, local	23,820 (27)	0.71 (0.56, 0.89)	**0.003**	0.70 (0.53, 0.92)	**0.01**
	Anesthesia, general	5,278 (6)	0.92 (0.69, 1.22)	0.56	0.95 (0.66, 1.35)	0.75
	Antibiotics	51,841 (59)	0.45 (0.36, 0.56)	**<0.0001**	0.32 (0.24, 0.43)	**<0.0001**
	Anticholinergics, antipsychotics	22,960 (26)	0.88 (0.70, 1.10)	0.27	0.96 (0.75, 1.23)	0.76
	Anticholinergics, other	27,909 (32)	1.01 (0.81, 1.25)	0.95	0.68 (0.53, 0.87)	**0.002**
	Benzodiazepines	28,293 (32)	0.60 (0.48, 0.76)	**<0.0001**	0.66 (0.51, 0.87)	**0.002**
	Opioids	59,813 (68)	1.23 (0.91, 1.66)	0.18	1.62 (1.10, 2.39)	**0.01**
Total parenteral nutrition[b]		1,544 (2)	1.78 (1.26, 2.50)	**0.001**	1.99 (1.35, 2.94)	**0.0006**
Catheterization[b]						
	Urinary catheter	24,424 (28)	1.23 (0.99, 1.53)	0.07	1.16 (0.88, 1.53)	0.30
	Suprapubic catheter	255 (<1)	2.73 (1.12, 6.64)	**0.03**	2.28 (0.88, 5.91)	0.09
	Nephrostomy tube	526 (1)	2.36 (1.06, 5.26)	**0.03**	2.02 (0.83, 4.93)	0.12
Urologic procedure[b]		1,288 (1)	1.86 (1.03, 3.37)	**0.04**	1.44 (0.72, 2.89)	0.30

Abbreviations: HR, hazard ratio; CI, confidence interval; ref, reference; MI, myocardial infarction; MEWS, Modified Early Warning System

[a] Adjusted for all risk factors included in table above; correlation between repeat hospitalizations of the same patients were taken into account using a robust sandwich covariance matrix and inpatient mortality was treated as a competing risk using the Fine and Gray model; inverse-probability of missingness weights were used to account for missing data

[b] Treated as a time-varying exposure; patients were considered exposed for the remainder of the hospitalization

Figure 4.1. A) Quarterly rates of non-device associated urinary tract infections (ND-UTIs), per 10,000 hospitalization days and B) Proportion of urinary tract infections (UTIs) that are device and non-device associated, stratified by year.

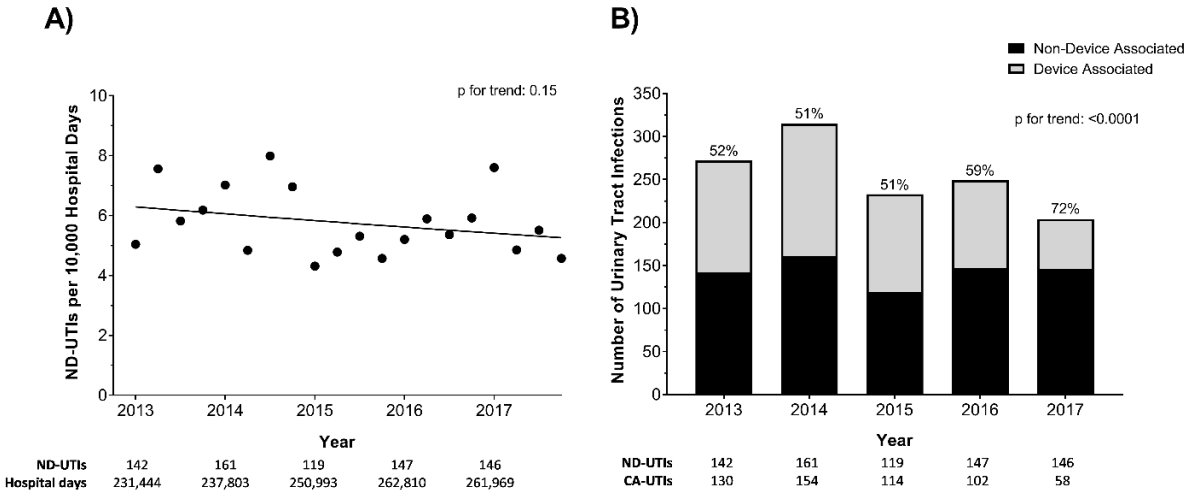
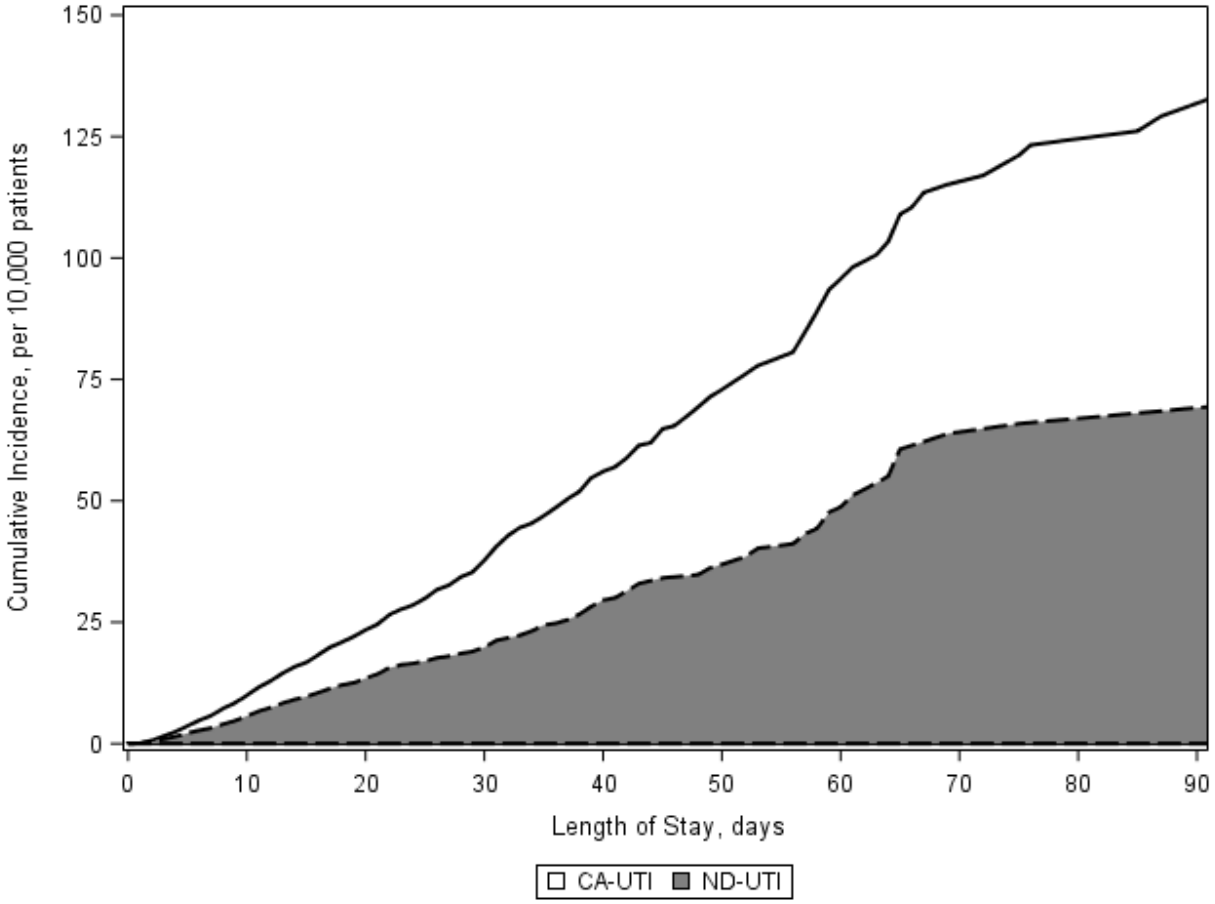


Figure 4.2. Stacked cumulative incidences of non-device (ND-UTI, gray) and catheter associated (CA-UTI, white) urinary tract infections.



CHAPTER 5: INCIDENCE AND RISK FACTORS OF NON-DEVICE ASSOCIATED PNEUMONIA IN AN ACUTE CARE HOSPITAL

5.1 INTRODUCTION

Pneumonia is the most common healthcare associated infection (HAI) in the United States, and accounts for almost 25% of all hospital infections.[1,2] Healthcare associated pneumonia poses a substantial burden on the healthcare system, with a 14% mortality and estimated to cost over $3 billion per year.[5,21] Historically 83% of healthcare associated pneumonia cases have been considered to be ventilator associated (VAP), which is why the U.S. Centers for Disease Control and Prevention have traditionally focused surveillance efforts on VAP.[21,28]

Recent studies have reported dramatic decreases in VAP rates over the past 15 years[9]; however, the rate of non-device associated pneumonia (ND-pneumonia) has remained stagnant during this period and ND-pneumonia now accounts for the majority of nosocomial pneumonia in hospitals settings.[2,7,13,15-17,66] Despite this growing body of literature on the burden and importance of ND-pneumonia in hospitals, little is known about the risk factors for infection and there are currently no evidence-based guidelines for ND-pneumonia prevention.[38,67] Thus, the purpose of this study was to update current estimates of ND-pneumonia rates and their frequency relative to VAP, assess temporal trends, and identify potential risk factors.

5.2 METHODS

Data sources and study population

Electronic medical records (EMR) from adults (≥18 years old) admitted to the University of North Carolina (UNC) Hospitals between January 1, 2013 and December 31, 2017 were obtained from the Carolina Data Warehouse for Health (CDW-H), a central repository for clinical and administrative data from the UNC Healthcare System. Prisoners were excluded from analysis. Patients were able to have multiple hospitalizations during the study period. HAIs were identified through the UNC Hospitals' Epidemiology database, which included both device and non-device associated HAIs, captured through comprehensive, hospital-wide active surveillance, in accordance with the Centers for Disease Control and Prevention (CDC) case definitions and methodology.[13,31] In July 2014, UNC Hospital Epidemiology began also capturing ventilator associated events, a new surveillance concept that CDC developed as an alternative to traditional VAP surveillance.[68] The two databases were then deterministically linked using admission date, medical record numbers, and full name. This study was approved by the UNC Institutional Review Board.

Incidence of ND-pneumonia

Quarterly incidence rates, per 10,000 hospitalization days, between 2013 and 2017 were calculated and Poisson regression was used to assess a potential change in ND-pneumonia rates over time. The proportion of pneumonia cases that were non-device related each year were also calculated. Cochran-Armitage trend tests (two-sided) were used to test the null hypothesis that the proportion of ND-pneumonia cases did not change between 2015 and 2017 (after new definitions were implemented).

Risk Factors for ND-pneumonia

Only hospitalizations between 2015 and 2017 with a length of stay (LOS) >2 days were included in risk factor analyses. Potential risk factors of interest included patient sex, age (categorized as 18-39 years old [reference], 40-49 years old, 50-59 years old, 60-69 years old, and ≥70 years old), comorbidities, body mass index (BMI, categorized as under/normal weight [<25, reference], overweight [25.0 – 29.9], and obese [≥30.0]), immunosuppression (including neutropenia), Modified Early Warning Score (MEWS), Morse Fall scale, inpatient medication usage- specifically anesthetics, antibiotics, antipsychotics, benzodiazepines, opioids, and acid-suppressing medications-, total parenteral nutrition (TPN), chlorhexidine mouthwash, prior endotracheal ventilation, prior tracheostomy, intensive care unit (ICU) stay, and trauma admission..

Patient comorbidities were captured using the discharge diagnosis ICD-9-CM (January 2015 – September 2015) and ICD-10-CM (October 2015 – December 2017) codes on each record. Deyo et al. (1992) and Quan et al. (2005) algorithms were adapted to identify components of the Charlson comorbidity index (CCI) score (Table 5.1).[41,42] Diagnosis codes for incident events (e.g. acute myocardial infarction) were removed from all component definitions.[41] Peripheral vascular disease (PVD) was also excluded due to low incidence (n=201) and both malignancy (solid tumor or metastatic disease) and human immunodeficiency viruses (HIV) were incorporated into the broader classification of immunocompromised. Additionally, chronic pulmonary diseases were broken into more discrete categories (bronchitis/emphysema, asthma, bronchiectasis, and other chronic obstructive pulmonary diseases [COPD]).

Immunocompromised patients were identified using the Advisory Committee on Immunization Practices (ACIP) and Infectious Diseases Society of America (IDSA) guidelines

on which persons cannot receive live-attenuated vaccinations.[43] Diagnoses of immunosuppressive conditions- which included HIV, neutropenia, organ transplant, and malignancy- were identified using discharge diagnosis codes; relevant ICD-9-CM codes were identified using the Greenberg et al. (2016)[44] algorithm and ICD-10-CM codes were identified using Centers for Medicare & Medicaid Services (CMS) General Equivalence Mappings (GEMS) (Table 5.1). Patients receiving chemotherapeutic agents, corticosteroids, or immune-modulating agents within the first 2 days of their hospitalization were identified using inpatient medications (Table 5.2). Neutropenia was identified using both diagnosis codes and laboratory blood test results within the first 2 hospitalization days (defined as ≥2 white blood cell [WBC] counts <500 cells/mm^3).

Severity of illness and frailty were measured using the MEWS[45] and Morse Fall Scale[47,48], respectively. These metrics are both automatically calculated within the UNC Hospitals EMR. The MEWS uses vital signs- specifically systolic blood pressure, heart rate, respiratory rate, temperature, conscious level, and hourly urine output (for two hours)- to identify patients at risk for imminent deterioration. The Morse Fall Scale includes history of falling, number of secondary diagnoses, whether ambulatory aid is needed, intravenous therapy/heparin lock, gait, and mental status and is used to predict future falls in hospitalized patients. For each patient, the first MEWS and Morse Fall Scale score within the first 2 days of admission was captured and categorized using the clinically relevant cut points (MEWS: <1 [reference], 2, 3, ≥4; Morse Fall Scale: 0 [reference], 1-24, 25-45, >45). A MEWS ≥4 and a Morse Fall Scale score >45 are both considered indicators of severe illness.

ICU stay, inpatient medications, chlorohexidine mouthwash, TPN, and device use were treated as time-varying exposures, with the patient being considered as exposed for the

remainder of the hospitalization. For example, once a patient received antibiotics on day 4, they were considered to be exposed from day 4 until discharge, and were classified as unexposed on days 1-3. All medications were identified using orders captured in the EMR and receipt was confirmed using the medication administration record (Table 5.2).

Multivariable Cox proportional hazards regression was used to simultaneously estimate the association between each potential risk factor and the incidence of ND-pneumonia. Correlation between repeat hospitalizations of the same patients were taken into account by utilizing robust sandwich covariance matrix estimates as described by Lee et al. (1992) and both VAP and inpatient mortality were treated as competing risks using the Fine and Gray (1999) model.[39,40]

Due to missing values of BMI (n=15,146, 17%), MEWS (n=18,761, 21%) Morse Fall Scale (n=8,571, 10%), and location/discharge disposition (n=8,482, 10%), inverse-probability of missing weights (IPMW) were calculated.[51] Weights were estimated using multivariable logistic regression, which modeled the probability of being a complete case as a function of the year and season of admission, cause of admission, patient age, sex, Charlson score comorbidities (excluding HIV and cancer), immunosuppression, TPN, medication usage anytime during hospitalization (antibiotics, antipsychotics, local anesthetics, general anesthetics, benzodiazepines, opioids, alpha-2 agonists, non-steroidal anti-inflammatory drugs [NSAIDs], calcium channel blockers, statins, angiotensin converting enzyme [ACE] inhibitors, angiotensin II receptor blockers [ARBs], histamine-2 agonists, proton pump inhibitors), device use (urinary catheter, ventilator, central venous catheter, peripheral venous catheter), whether they underwent any surgery (CPT 10021 – 69990), and LOS, as well as interaction terms between admission timing and both cause of admission and LOS. Age and LOS were modeled as restricted quadratic

splines.[52] Because 99% of hospitalizations from January-March 2015 were missing MEWS (28% of all missing), all hospitalizations in this time period were excluded.

Our statistical analysis strategy is consistent with the American Statistical Association's statements on p-values.[54,55] All statistical computations were performed using SAS 9.4 (SAS Inc., Cary, NC).

5.3 RESULTS

From 2013-2017 there were 163,386 hospitalizations (97,485 unique patients) and 771 cases of healthcare associated pneumonia (520 ND-pneumonia, 191 VAP) during 666 unique hospitalizations at UNC Hospitals. Of the 771 pneumonia cases, 768 (99.6%) were successfully linked to a hospitalization record. 87% (n=142,836) of hospitalizations were >2 days (median 5 days, interquartile range [IQR] 3-8 days). Patient demographics and causes of admission are described in Table 5.3.

Median time to diagnosis was 9 days for ND-pneumonia (IQR 5-19) and 11 days for VAP (IQR 6-21). Between 2013 and 2017, the rate of ND-pneumonia was stable, with 4.15 ND-pneumonia cases per 10,000 hospitalization days in 2013 and 4.54 ND-pneumonia cases per 10,000 hospitalization days in 2017, p=0.65 (Figure 5.1.A). In 2013-2014 (prior to the implementation of the CDC's updated definition for VAP), over 80% of pneumonia cases were non-device associated. Between 2015 and 2017 (after CDC ventilator associated event definition was implemented), the proportion of non-device infections ranged from 64% to 74%, p=0.09 (Figure 5.1.B). From 2015-2017, only 36% (n=107) of ND-pneumonia cases occurred on the ICU, 45% (n=137) occurred on a floor, and 18% on a stepdown unit (n=55) (25 events could not be attributed to a specific location due to missing location data). In comparison, 96% of all VAPs

occurred on an ICU (n=140). The 30-day and 60-day cumulative incidence of ND-pneumonia was 19.7 and 41.7 infections per 10,000 patients, respectively (Figure 5.2).

There were 88,487 hospitalizations between 2015 and 2017 with a LOS>2 days included in the risk factor analysis. Median IPMW was 1.07 (IQR 1.03-1.24, range 1.00 – 21.38); only 27 hospitalizations had a weight >10. After adjustment, male sex and older age were associated with increased incidence of ND-pneumonia, Table 5.4. Additional risk factors included diagnoses for bronchitis or emphysema (HR 2.07, 95% CI 1.40, 3.06), congestive heart failure (HR 1.48, 95% CI 1.07, 2.05), paralysis (HR 1.72, 95% CI 1.09, 2.73), and immunosuppression (HR 1.50, 95% CI 1.16, 1.95). Being in an ICU was also associated with increased ND-pneumonia (HR 1.49, 95% CI 1.06, 2.09). Conversely, patients with dementia were at lower risk of infection (HR 0.41, 95% CI 0.18, 0.95). Our study failed to detect a change in ND-pneumonia risk for the following variables: use of chlorhexidine mouthwash, TPN, all medications of interest, and prior ventilation variables. For chlorhexidine mouthwash, for example, while the hypothesis test of "HR=1" was inconclusive, the point- and interval- estimates (HR 0.90, 95% CI 0.54, 1.52) indicate that the data are compatible with hazard ratios as small as 0.54 and as large as 1.52 in the target population.[55]

5.4 DISCUSSION

Between 2013 and 2017 the rate of ND-pneumonia cases remained constant in UNC Hospitals, and non-device infections continue to account for the majority of hospital associated pneumonia cases. Risk factors for ND-pneumonia included male sex, older age, ICU admission, and chronic bronchitis/emphysema, congestive heart failure, paralysis, and immunosuppression.

To the best of our knowledge, this is the most comprehensive analysis of ND-pneumonia rates and risk factors in an acute care setting.

The incidence and proportion of ND-pneumonia cases in our study are similar to rates reported by other centers. Davis and Finley, for example, utilized state-mandated comprehensive surveillance data from Pennsylvania and found that 71% of cases of pneumonia between 2009 and 2011 were non-device associated (5,597 ND-pneumonia, 2,299 VAP).[15] In a 2014 convenience sample of 21 hospitals across the US, the rate of ND-pneumonia ranged from 0.12 to 2.28 cases per 1,000 patient days.[17] Our findings are also consistent with a prior report from our institution. Between 2008 and 2012, the proportion of non-device associated pneumonias increased from roughly 40% to 60%, predominantly due a decrease in device associated infections without concomitant change in the incidence of non-device associated infections.[7]

Older age, pulmonary disease, and ICU stays have been associated with increased risk of VAP[69]. In our study, we found that these same risk factors extend to ND-pneumonia as well, albeit with some nuances. We noted increased risk in middle-aged adults (40-49 and 50-59 years old) were at higher risk compared to patients 18-39 years old, and only specific types of pulmonary disease (bronchitis and emphysema) were at increased risk (differences in ND-pneumonia risk among patients with asthma, bronchiectasis, and 'other' COPD were not detected). We also found that paralysis was associated with increased incidence of ND-pneumonia. Paralytic agents and coma/stupor have been associated with VAP[69,70], suggesting that limited mobility may increase a patient's risk. Patients with paralysis may also have other neurological issues, like impaired swallowed or decreased level of consciousness, that could also account for the increased pneumonia risk. Male sex, chronic pulmonary disease, and congestive heart failure have also been shown to increase the risk of community-acquired pneumonia in

older adults.[71] Overall, these finding suggest that there are certain characteristics that may predispose some adults to pneumonia infections.

Interestingly, our study failed to detect an association between acid-suppressing medication (i.e. histamine-2 agonists and proton pump inhibitors [PPIs]), although they have been associated with increased risk of VAP.[69] However, the literature for VAP is mixed. Additionally, evidenced-based guidelines and awareness of potential adverse effects have narrowed indications for acid suppression therapies in the acute care setting and UNC Hospitals implemented changes to the clinical guidelines for stress ulcer prophylaxis prior to the study period. Similarly, antipsychotics have also been associated with aspiration pneumonia in both the hospital[72] and community setting[73] but in our study failed to detect association between antipsychotic use and ND-pneumonia as well.

There have been a few recent studies that have found the use of oral care prevented ND-pneumonia in high-risk patients (e.g. neurologic injury patients, older adults).[30,37,74] While we failed to detect an association between chlorhexidine mouthwash and ND-pneumonia rates, this discrepancy could be due to targeted use of oral care with chlorhexidine at UNC Hospitals. As opposed to the universal use in prior studies, only 8% of hospitalized patients included in this analysis received the treatment. It is possible that these individuals were selected to receive oral care with chlorhexidine specifically due to perceived higher risk for respiratory infections-(although indication for chlorhexidine could not be determined) which could explain our inconclusive finding. Chlorhexidine mouthwash has also been associated with increased inpatient mortality.[75] Studies assessing the utility of chlorhexidine mouthwash and oral care with VAP are mixed and there are currently no recommendations on its use for device associated infections.[9]

This study is not without limitations. First, this was a single center study and results may not generalize to other hospitals, particularly if the patient population is different. We also did not account for duration, dose, or underlying indications for medication use. Additionally, ICD-9-CM and ICD-10-CM codes were used to identify comorbidities. Using these codes likely underestimates the prevalence of comorbidities, although we expect this misclassification to be non-differential and, if anything, bias results towards the null. Similarly, ND-pneumonia and VAP were captured using CDC definitions, some of which require laboratory confirmation, and patients who are treated for suspected pneumonia but are not cultured would be missed. Finally, although we had a large sample size, the incidence of ND-pneumonia and prevalence of some risk factors were low, resulting in low levels of precision of the estimators as indicated by the widths of the observed confidence intervals.

In conclusion, between 2013 and 2017, the incidence rate of ND-pneumonia was unchanged, and non-device infections represent the majority of healthcare associated pneumonia cases in our acute care hospital. Our study and similar findings by others suggest that hospital infection prevention programs should consider expanding the scope of surveillance and prevention programs to include non-ventilated patients. Male sex, older age, bronchitis/emphysema, congestive heart failure, paralysis, immunosuppression, and ICU stays were all associated with increased risk of ND-pneumonia. Future research should continue to look for modifiable risk factors and assess potential prevention strategies.

5.5 ACKNOWLEDGEMENTS

This project was supported by the National Center for Advancing Translational Sciences (NCATS), National Institutes of Health, through Grant Award Number UL1TR002489. The

content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH. The authors would also like to thank Adam M. Lee at the NC TraCS Institute for his help querying and obtaining EMR data.

Table 5.1. Diagnosis codes used to identify comorbidities and immunosuppressive conditions.

	ICD-9-CM code(s)	ICD-10-CM code(s)
Comorbidities[a]		
History of MI	412	I25.2
Congestive heart failure	428.0 – 428.9	I50.1 – I50.9
Cerebrovascular disease	438.0 – 438.9	I69.00 – I69.998
Dementia	290.0 – 290.9	F01.5 – F03.91
Rheumatic disease	710.0, 710.1, 710.4, 714.0 – 714.2, 714.81, 725	M05.00 – M05.9, M06.00 – M06.9
Peptic ulcer disease	531.4 – 531.7, 532.4 – 532.7, 533.4 – 533.7, 534.4 – 534.7	K25.4 – K25.7, K26.4 – K26.7, K27.4 – K27.7, K28.4 – K28.7
Mild liver disease	571.2, 571.4 – 571.6	K70.30, K70.31, K74.0, K74.3, K74.4, K74.5, K74.60, K74.69
Moderate or severe liver disease	572.2 – 572.8	K72.10, K72.90, K72.91, K76.6, K76.7
Diabetes without chronic complications	250.0 – 250.3, 250.7	E10.10, E10.11, E10.61 – E10.69, E10.8, E10.9, E11.00, E11.01, E11.10, E11.11, E11.61 – E11.69, E11.8, E11.9, E12.00, E12.01, E12.10, E12.11, E12.61 – E12.69, E12.8, E12.9, E13.00, E13.01, E13.10, E13.11, E13.61 – E13.69, E13.8, E13.9, E14.00, E14.01, E14.10, E14.11, E14.61 – E14.69, E14.8, E14.9
Diabetes with chronic complication	250.4 –250.6	E10.21 – E10.29, E10.31 – E10.39, E10.40 – E10.49, E10.51 – E10.59, E10.71 – E10.79, E11.21 – E11.29, E11.31 – E11.39, E11.40 – E11.49, E11.51 – E11.59, E11.71 – E11.79, E12.21 – E12.29, E12.31 – E12.39, E12.40 – E12.49, E12.51 – E12.59, E12.71 – E13.79, E13.21 – E13.29, E13.31 – E13.39, E13.40 – E13.49, E13.51 – E13.59, E13.71 – E13.79, E14.21 – E14.29, E14.31 – E14.39, E14.40 –

		E14.49, E14.51 – E14.59, E14.71 – E14.79
Hemiplegia or paraplegia	342.0 – 342.9, 344.1	G81.0 – G82.54
Renal disease	582.0 – 582.9, 583.0 – 583.7, 585.1 – 585.9, 586, 588.0 – 588.9	N03.0 – N03.9, N05.0 – N05.9, N18.1 – N18.9, N19, N25.0 – N25.9
Chronic pulmonary conditions[b]		
Bronchitis/emphysema	490, 491.0 – 491.9, 492.0, 492.8	J40 – J44.1
Asthma	493.0 – 493.92	J45.20 – J45.998
Bronchiectasis	494.0, 494.1	J47.0 – J47.9
Other COPD	496	J44.9
Immunosuppressive conditions		
HIV/AIDS	042, 079.53	B20
Neutropenia	288.00 – 288.9	D70.0 – D70.9
Organ transplant	996.80 – 996.99, V42.0 – V42.9	T86.00 – T86.99, Z94.0 – Z94.9
Hematological malignancy	200.0 – 208.92	C81. 00 – C96.9
Solid malignancy	140.0 – 199.2, 209.0 – 209.79, 235.0 – 239.9	C00.0 – C80.2, C7A, C7B, D37.01 – D49.9
Rheumatologic/inflammatory condition	135, 277.30 – 277.39, 340, 341.0 – 341.9, 357.0 – 357.9, 422.0 – 422.99, 446.0 – 446.7, 495.9, 516.0 – 516.9, 555.0 – 558.9, 695.4, 710.0 – 712.99, 714.0 – 714.9, 720.0 – 720.9	D86.0 – D86.9, E10.40, E10.42, E11.40, E11.42, E12.40, E12.42, E13.40, E13.42, E14.40, E14.42, E85.0 – E85.9, G35, G36.0 – G36.9, G61.0 – G65.2, I40.0 – I40.9, I41, J67.9, J84.01 – J84.09, K50.00 – K52.9, K55.0 – K55.9, L93.0, L93.2, M00.00 – M00.9, M01.X0 0 M01.X9, M02.10 – M02.19, M02.30 – M02.39, M04.1, M05.00 – M05.9, M06.00 – M06.9, M08.00 – M08.99, M11.00 – M11.9, M12.00 – M12.09, M30.0 – M30.8, M32.0 – M34.9, M35.00 – M35.3, M35.8, M35.9, M45.0 – M46.1, M46.50 – M46.59, M46.80 – M46.99, M49.80 – M49.89
Other immune conditions	279.0 – 279.9, 288.0 – 288.2, 288.50 – 279.59, 288.8,	D47.4, D71, D72.0, D72.810 – D72.819,

	288.9, 288.00 – 288.9, 289.83, 289.89, 289.9, 795.71, 795.79	D72.89, D72.9, D75.81, D75.89, D75.9, D80.0 – D80.9, D89.2, R75, R76.0, R76.8, R76.9
Trauma	800.0 – 959.9	S00.00XA – T34.99XS, T79.0XXA – T79.9XXS

Abbreviations; ICD-9-CM, International Classification of Diseases, 9th edition, Clinical modification; ICD-10-CM, International Classification of Diseases, 10th edition, Clinical modification; CCI, Charlson Comorbidity Index; MI, myocardial infarction: HIV/AIDS, human immunodeficiency virus/acquired immunodeficiency syndrome

[a] Only codes which could be applied to the index hospitalization were used; e.g. history of MI (ICD-9-CM 412) was included, but acute MI (ICD-9-CM 410-410.92) was excluded

[b] Chronic obstructive pulmonary disease (COPD) from Charlson Comorbidity Index was broken into more granular categories for analyis

Table 5.2. Generic medication names used to classify medications of interest.

	Generic medication name(s)
Antibiotics, systemic	
β-lactams	Amoxicillin, Ampicillin, Benzathine penicillin, Dicloxacillin, Nafcillin, Oxacillin, Penicillin G, Penicillin V, Piperacillin
	Cefaclor, Cefadroxil, Cefazolin, Cefdinir, Cefepime, Cefixime, Cefotetan, Cefoxatime, Cefoxitin, Cefpodoxime, Ceftriaxone, Ceftaroline, Ceftazidime, Cefuroxime, Cephalexin, Cepodoxime proxetil
	Aztreonam
	Ertapenem, Imipenem, Meropenem
	Avibactam, Clavulanic acid, Sulbactam
	Ampicillin/Sulbactam, Amoxicillin/Clavulanate, Ceftolozane/tazobactam, Piperacillin/Tazobactam
	Colistin (colistamethate sodium), Daptomycin, Ethambutol, Isoniazid, Polymyxin B, Pyrazinamide, Metronidazole
Aminoglycosides	Amikacin, Gentamicin, Neomycin, Paromomycin, Tobramycin
Chloramphenicol	Chloramphenicol
Glycopeptides	Telavancin, Vancomycin
Macrolides	Azithromycin, Clarithromycin, Erythromycin, Fidaxomicin, Telithromycin
Oxazolidinones	Linezolid, Tedizolid
Quinolones	Ciprofloxacin, Levofloxacin, Moxifloxacin, Ofloxacin
Rifaximin	Rifaximin
Sulfonamides	Sulfadiazine, Sulfamethoxazole, Trimethoprim
Tetracyclines	Doxycycline, Minocycline, Rifampin, Tetracycline, Tigecycline
Lincosamides	Clindamycin
Lipopeptides	Daptomycin
Nitrofurans	Nitrofuratoin
Anesthetics	
General	Etomidate, Ketamine, Midazolam, Propofol
Local	Benzocaine, Bupivacaine, Chloroprocaine, Lidocaine, Ropivacaine, Tetracaine
Antipsychotics/neuroleptics	Amitriptyline, Aripiprazole, Chlorpromazine, Clozapine, Desipramine, Doxepin, Droperidol, Fluphenazine, Haloperidol, Imipramine, Lurasidone, Nortriptyline, Olanzapine, Paliperidone, Paroxetine, Perphenazine, Prochlorperazine, Promazine, Promethazine, Protriptyline, Quetiapine, Risperidone, Thioridazine, Thiothixene, Trifluoperazine, Ziprasidone

Benzodiazepines	Alprazolam, Chlordiazepoxide, Clobazam, Clomipramine, Clonazepam, Clorazepate, Diazepam, Flurazepam, Lorazepam, Midazolam, Oxazepam, Temazepam
Histamine 2-agonists	Cimetidine, Famotidine, Ranitidine
Proton pump inhibitors	Dexlansoprazole, Esomeprazole, Lansoprazole, Omeprazole, Pantoprazole
Opioids	Buprenorphine, Codeine, Fentanyl, Hydromorphone, Meperidine, Methadone, Morphine, Nalbuphine, Oxycodone, Oxymorphone, Sufentanil, Tapentadol, Tramadol
Immunosuppressive medications[a]	
Chemotherapeutic agents (alkylating)	Bendamustine hydrochloride, Busulfan, Carmustine, Cyclophosphamide, Darabazine, Ifosfamide, Melphalan, Thiotepa
Chemotherapeutic agents (antibiotics)	Bleomycin sulfate, Dactinomycin, Daunorubicin, Doxorubicin, Epirubicin, Idarubicin
Chemotherapeutic agents (antimetabolites)	Capecitabine, Cladribine, Clofarabine, Cytarabine, Fludarabine, Fluorouracil, Gemcitabine, Mercaptopurine, Methotrexate, Pemetrexed, Pentostatin
Chemotherapeutic agents (antimitotics)	Docetaxel, Paclitaxel, Vinblastine, Vincristine, Vinorelbine
Chemotherapeutic agents (monoclonal antibodies)	Alemtuzumab, Bevacizumab, Cetuximab, Gemtuzumab, Ofatumumab, Rituximab
Chemotherapeutic agents (other)	Aldesleukin, Arsenic trioxide, Asparaginase, Azacitidine, Brentuximab vedotin, Bortezomib, Carboplatin, Carfilzomib, Cisplatin, Dasatinib, Decitabine, Erlotinib, Etoposide, Everolimus, Imatinib, Irinotecan, Lapatinib, Mitoxantrone, Nelarabine, Nilotinib, Oxaliplatin, Pazopanib, Pegaspargase, Pralatrexate, Procarbazine, Romidepsin, Sorafenib, Sunitinib, Temozolomide, Temsirolimus, Topotecan, Tretinoin, Vorinostat
Immune-modulating agents	Abatacept, Adalimumab, Alefacept, Anakinra, Azathioprine, Basiliximab, Belatacept, Belimumab, Certolizumab pegol, Cyclosporine, Daclizumab, Denosumab, Eculizumab, Efalizumab, Etanercept, Fingolimod, Glatiramer, Golimumab, Infliximab, Interferon alfa-2a, Interferon alfa-2b, Interferon alfa-n3, Interferon alfacon-1, Interferon beta-1a, Interferon beta-1b, Interferon gamma-1b, Leflunomide, Lenalidomide, Muromonab-CD3, Mycophenolate acid, Mycophenolate mofetil, Natalizumab, Palifermin, Palivizumab, Pomalidomide, Pegademase bovine, Peginterferon alfa-2a, Peginterferon alfa-2b, Sirolimus, Tacrolimus, Tocilizumab, Ustekinumab

Systemic corticosteroids	Betamethasone, Budesonide, Dexamethasone, Methylprednisolone, Prednisolone, Triamcinolone

[a] Immunosuppressive medication use within the first 2 days of hospitalization were used to identify immunocompromised patients

Table 5.3. Hospitalization characteristics.

	2013 – 2014	2015 – 2017
Total hospitalizations, n	62,853	100,533
Unique patients, n	41,941	64,633
Female, n (%)	35,360 (56)	55,985 (56)
Age, median (IQR)	52 (34 – 66)	53 (35 – 66)
Race, n (%)		
White	37,766 (62)	60,089 (62)
Black	16,625 (27)	26,378 (27)
Asian	752 (1)	1,411 (1)
Hawaiian/Pacific Islander	31 (<1)	79 (<1)
Native American	533 (1)	908 (1)
Other race	5,159 (8)	8,166 (8)
Missing	1,987	3,502
Cause of admission[a], n (%)		
Circulatory disease	8,166 (13)	13,440 (14)
Injury or poisoning[b]	8,429 (13)	12,934 (13)
Childbirth/complications of pregnancy	7,938 (13)	12,408 (13)
Digestive disease	5,982 (10)	10,367 (11)
Neoplasms	6,094 (10)	9,882 (10)
Psychological disorders	4,485 (7)	6,738 (7)
Infectious/parasitic disease	3,651 (6)	5,789 (6)
Respiratory disease	2,977 (5)	4,674 (5)
Musculoskeletal disease	2,286 (4)	4,462 (5)
Endocrine/metabolic disease	1,959 (3)	3,233 (3)
Genitourinary disease	2,106 (3)	3,313 (3)
Nervous system disease	1,679 (3)	2,756 (3)
Skin disease	1,116 (2)	1,778 (2)
Blood disease	994 (2)	1,575 (2)
Other or ill-defined	4,862 (8)	4,972 (5)
LOS, days, median (IQR)	5 (3 – 8)	5 (3 – 8)

Abbreviations: IQR, interquartile range; LOS, length of stay

[a] Classified using primary diagnosis on each hospitalization; 2,341 hospitalizations (1%) were unable to be linked to their diagnosis codes

[b] A subset of these codes were used to identify trauma admissions

Table 5.4. Prevalence and effect of potential factors for ND-pneumonia, among adults hospitalized for >2 days between 2015 – 2017.

	Prevalence	Crude		Adjusted[a]	
	N (%)	HR (95% CI)	p-value	HR (95% CI)	p-value
Female	49,500 (56)	0.64 (0.50, 0.82)	**0.0003**	0.77 (0.59, 1.00)	**0.05**
Age, years					
18-39 years old	28,007 (32)	ref	–	ref	–
40-49 years old	11,018 (12)	2.41 (1.43, 4.08)	**0.001**	2.26 (1.28, 3.99)	**0.005**
50-59 years old	15,631 (18)	3.24 (2.05, 5.12)	**<0.0001**	2.58 (1.53, 4.36)	**0.004**
60-69 years old	16,400 (19)	3.92 (2.52, 6.12)	**<0.0001**	2.97 (1.78, 4.97)	**<0.0001**
≥70 years old	17,431 (20)	3.75 (2.39, 5.88)	**<0.0001**	2.57 (1.49, 4.49)	**0.0007**
Chronic pulmonary disease					
Bronchitis/emphysema	3,077 (4)	2.98 (2.14, 4.17)	**<0.0001**	2.07 (1.40, 3.06)	**0.0003**
Asthma	8,572 (10)	0.95 (0.63, 1.42)	0.79	1.17 (0.75, 1.81)	0.49
Bronchiectasis	1,121 (1)	0.33 (0.08, 1.31)	0.11	0.54 (0.14, 2.16)	0.38
Other COPD	6,923 (8)	1.14 (0.78, 1.67)	0.49	0.85 (0.56, 1.31)	0.47
Other comorbidities					
Prior MI	5,434 (6)	1.34 (0.90, 1.99)	0.15	0.91 (0.58, 1.41)	0.66
Heart failure	12,538 (14)	1.71 (1.32, 2.21)	**<0.0001**	1.48 (1.07, 2.05)	**0.02**
Cerebrovascular disease	1,923 (2)	1.29 (0.66, 2.51)	0.55	0.89 (0.41, 1.93)	0.77
Dementia	2,376 (3)	0.47 (0.21, 1.06)	0.07	0.41 (0.18, 0.95)	**0.04**
Rheumatoid arthritis	1,708 (2)	0.68 (0.26, 1.80)	0.44	0.52 (0.20, 1.38)	0.19
Peptic ulcer disease	441 (1)	1.21 (0.38, 3.82)	0.75	0.93 (0.28, 3.04)	0.90
Diabetes	20,821 (23)	1.06 (0.82, 1.37)	0.65	0.83 (0.61, 1.13)	0.24
Liver disease	3,320 (4)	1.96 (1.32, 2.89)	**0.0008**	1.49 (0.95, 2.33)	0.08
Renal disease	13,120 (15)	1.26 (0.96, 1.65)	0.09	0.94 (0.69, 1.28)	0.68
Paralysis	1,915 (2)	2.12 (1.39, 3.24)	**0.0005**	1.72 (1.09, 2.73)	**0.02**
Immunosuppression	35,810 (40)	1.51 (1.19, 1.91)	**0.0007**	1.50 (1.16, 1.95)	**0.002**
Body mass index					
Under/normal weight	24,535 (33)	ref	–	ref	–
Overweight	21,129 (29)	0.83 (0.62, 1.09)	0.18	1.33 (0.98, 1.82)	0.07
Obese	27,677 (38)	0.63 (0.48, 0.84)	**0.002**	0.80 (0.57, 1.14)	0.22
Trauma admission	9,683 (11)	1.02 (0.75, 1.39)	0.91	0.99 (0.70, 1.42)	0.97

Intensive care unit stay[b]	15,767 (20)	1.98 (1.53, 2.55)	**<0.0001**	1.49 (1.06, 2.09)	**0.02**
MEWS					
0-1	18,917 (27)	ref	–	ref	–
2	27,062 (39)	0.95 (0.69, 1.32)	0.77	1.07 (0.76, 1.49)	0.71
3	12,380 (18)	0.94 (0.65, 1.37)	0.74	0.95 (0.64, 1.40)	0.78
≥4	11,367 (16)	1.14 (0.82, 1.60)	0.44	1.07 (0.76, 1.52)	0.69
Morse fall risk					
0	4,626 (6)	ref	–	ref	–
1-24	19,862 (25)	0.91 (0.37, 2.24)	0.84	0.79 (0.32, 1.92)	0.60
25-45	33,833 (42)	1.87 (0.83, 4.24)	0.13	1.02 (0.44, 2.38)	0.95
>45	21,595 (27)	2.93 (1.30, 6.63)	**0.01**	1.59 (0.68, 3.71)	0.28
Inpatient medications[b]					
Anesthesia, local	23,820 (27)	1.06 (0.84, 1.34)	0.63	0.92 (0.69, 1.22)	0.54
Anesthesia, general	5,278 (6)	1.57 (1.21, 2.05)	**0.0008**	1.12 (0.68, 1.83)	0.66
Antibiotics	51,841 (59)	1.45 (1.06, 1.97)	**0.02**	1.15 (0.76, 1.74)	0.52
Antipsychotics	22,960 (26)	0.87 (0.69, 1.10)	0.25	1.03 (0.80, 1.33)	0.83
Benzodiazepines	28,293 (32)	0.94 (0.73, 1.21)	0.64	0.79 (0.58, 1.07)	0.13
H2 blockers	15,833 (18)	1.29 (1.02, 1.65)	**0.04**	0.97 (0.71, 1.31)	0.82
Proton-pump inhibitors	27,510 (31)	1.48 (1.18, 1.87)	**0.0009**	1.16 (0.90, 1.50)	0.25
Opioids	59,813 (68)	1.69 (1.17, 2.45)	**0.005**	1.27 (0.78, 2.06)	0.34
Total parenteral nutrition[b]	1,544 (2)	1.56 (1.09, 2.24)	**0.02**	1.37 (0.91, 2.08)	0.14
Prior ventilation[b]					
Endotracheal	13,939 (16)	1.42 (1.11, 1.82)	**0.005**	1.10 (0.78, 1.55)	0.59
Tracheostomy	4,348 (5)	1.05 (0.75, 1.47)	0.76	0.89 (0.61, 1.29)	0.53
Chlorhexidine mouthwash[b]	6,362 (7)	1.53 (1.18, 1.98)	**0.001**	0.90 (0.54, 1.52)	0.70

Abbreviations: HR, hazard ratio; CI, confidence interval; ref, reference; MI, myocardial infarction; MEWS, Modified Early Warning System; H2 blockers, histamine-type 2 receptor blockers

[a] Adjusted for all risk factors in the table above; correlation between repeat hospitalizations of the same patients were taken into account using a robust sandwich covariance matrix and inpatient mortality was treated as a competing risk using the Fine and Gray model; inverse-probability of missingness weights were used to account for missing data

[b] Treated as a time-varying exposure; patients were considered exposed for the remainder of the hospitalization

Figure 5.1. A) Quarterly rates of non-device associated pneumonia (ND-pneumonia), per 10,000 hospitalization days and B) Proportion of healthcare associated pneumonia that are device and non-device associated, stratified by year.

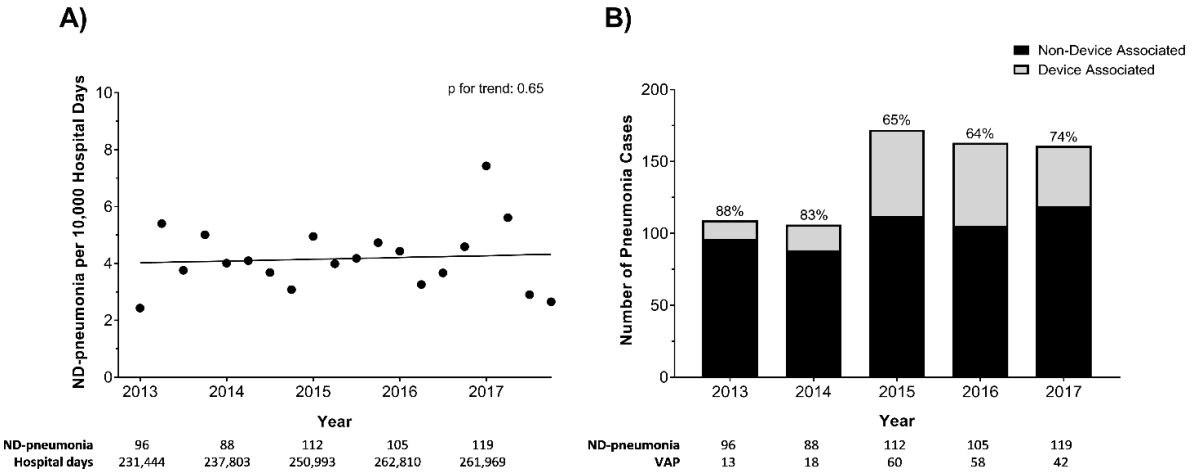
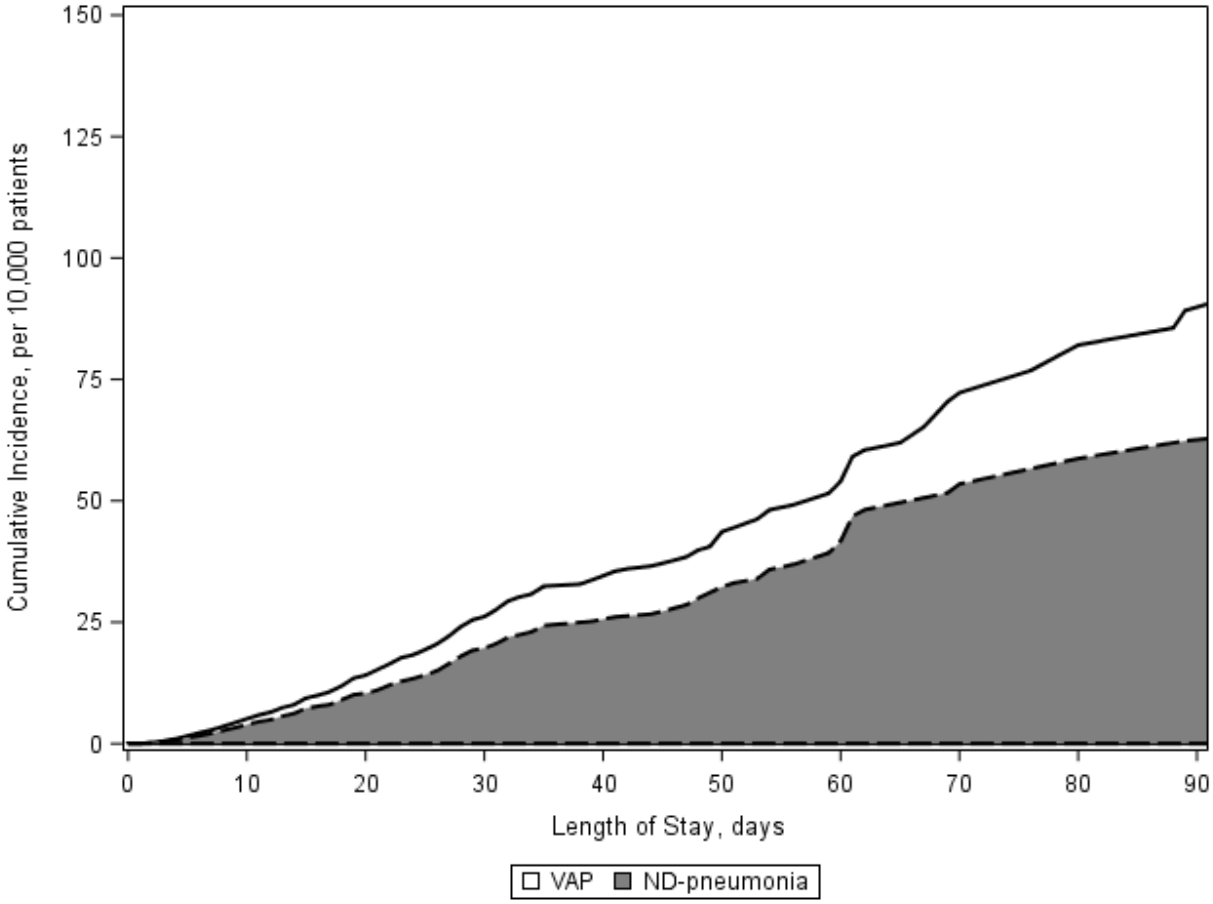


Figure 5.2. Stacked cumulative incidences of non-device (ND-pneumonia, gray) and ventilator associated (VAP, white) pneumonia.



CHAPTER 6: DISCUSSION

6.1 SUMMARY OF FINDINGS

The primary objective of the first aim was to describe the epidemiology of ND-UTIs, ND-pneumonia, and ND-BSIs, specifically, the rate of each infection, the relative frequency relative to device associated HAIs, and temporal trends in both. We found that between 2013 and 2017, the rates of ND-UTIs and ND-pneumonia have remained relatively stable, and the rate of ND-BSIs has increased. Additionally, ND-UTIs and ND-pneumonia cases represent the majority of infections, with almost 3 in 4 UTIs and pneumonia cases being non-device associated in 2017. One in three BSIs are non-device associated at UNC Hospitals.

The primary objective of the second aim was to identify modifiable and non-modifiable risk factors associated with ND-HAIs. Females, older adults, peptic ulcer disease, paralysis, immunosuppression, opioid use, TPN, and trauma patients all had a higher risk of ND-UTI. Urinary retention, suprapubic catheters and nephrostomy tubes may also increase patient risk of ND-UTI, although estimates were imprecise. Risk factors for ND-pneumonia included male sex, older age, ICU admission, and chronic bronchitis/emphysema, congestive heart failure, paralysis, and immunosuppression. Risk factors for ND-BSIs included male sex, peptic ulcer disease, paralysis, general anesthesia, opioids, and peripheral venous catheters; higher Morse Fall Risk score, beta-blockers, and UTIs (device or non-device associated) also appeared to increase patient risk.

6.2 PUBLIC HEALTH IMPLICATIONS

Incidence on ND-HAIs

Little is currently known about ND-HAIs and the majority of hospitals do not capture non-device infections as part of their surveillance practices. However, we found that the majority of UTIs and pneumonia cases are no longer device associated, and a substantial portion of BSIs are also non-device associated. These findings suggest that current targeted surveillance practices directed at patients with urinary catheters, on ventilators, and with central venous catheters alone are no longer sufficient to capture HAIs in acute care settings. This study is the most recent assessment of ND-HAIs and provides additional evidence that current targeted surveillance practices for HAIs needs to be updated to include ND-HAIs and evidence-based prevention strategies for these infections need to be developed and implemented in the United States.

Risk Factors for ND-UTIs

We found that patient demographics and comorbidities, specifically female sex, older age, peptic ulcer disease, paralysis, and immunosuppression, were associated with increased ND-UTI incidence. Female sex, older age, paraplegia, and immunosuppression have also been shown to increase the risk for CA-UTIs, indicating that certain subsets of patients may be at higher risk for all UTIs.[57-59] However, a recent study of CA-UTI found that after accounting for comorbidities and other severity measures age was no longer a predictor of infection, which likely means that age is a proxy for illness severity or frailty, and not an independent risk factor itself[59]. To the best of our knowledge, peptic ulcer disease has not been reported to be a risk factor for UTIs (or CA-UTIs), but treatments such as ranitidine, may cause drug-induced urinary

retention, particularly in new users, females, and those ≥60 years old.[60,61] However, peptic ulcer disease was associated with ND-UTI incidence even after adjusting for urinary retention, indicating that other factors may also be at play.

Inpatient medication use was also associated with ND-UTI incidence. Patients receiving antibiotics, local anesthetics, anticholinergics, and benzodiazepines were at reduced risk for infection, and patients receiving TPN and opioids were at increased risk. Opioids have also been found to cause drug-induced urinary retention[60], although opioid use may also be a proxy for acute pain and limited mobility (particularly after surgery), which may increase risk for UTIs, particularly in older adults[62]. Several studies have also found that TPN was associated with increased fungal infections, including UTIs, in hospitalized patients.[63,64] Interestingly, we found that antibiotic use was associated with reduced incidence of ND-UTIs although antibiotic prophylaxis has not been found to reduce risk of CA-UTIs.[8] And while local anesthetics, anticholinergics, and benzodiazepines are also known to cause urinary retention, anesthetics and benzodiazepines were associated with reduced risk of ND-UTIs, even in unadjusted analyses. It is possible that patients receiving these medications may represent an overall healthier patient population.

Finally, both suprapubic catheters and nephrostomy tubes were associated with increased incidence of ND-UTIs, but estimates were imprecise. A recent Cochrane review (2015) found that there was little or no difference in symptomatic UTI risk between short-term suprapubic versus indwelling catheters, but that patients with suprapubic catheters were catheterized for longer durations, which could explain the higher cumulative infection risk in this population.[65] Currently, neither suprapubic catheters nor nephrostomy tubes are included in the CDC CA-UTI

definition, and the CDC has no recommendations for preventing CA-UTI in these populations, although they do call for further research on the topic.[8]

Risk Factors for ND-pneumonia

Older age, pulmonary disease, and ICU stays have been associated with increased risk of VAP[69]. In our study, we found that these same risk factors extend to ND-pneumonia as well, albeit with some nuances. We noted increased risk in middle-aged adults (40-49 and 50-59 years old) were at higher risk compared to patients 18-39 years old, and only specific types of pulmonary disease (bronchitis and emphysema) were at increased risk (differences in ND-pneumonia risk among patients with asthma, bronchiectasis, and 'other' COPD were not detected). We also found that paralysis was associated with increased incidence of ND-pneumonia. Paralytic agents and coma/stupor have been associated with VAP[69,70], suggesting that limited mobility may increase a patient's risk. Patients with paralysis may also have other neurological issues, like impaired swallowed or decreased level of consciousness, that could also account for the increased pneumonia risk. Male sex, chronic pulmonary disease, and congestive heart failure have also been shown to increase the risk of community-acquired pneumonia in older adults.[71] Overall, these finding suggest that there are certain characteristics that may predispose some adults to pneumonia infections.

Interestingly, our study failed to detect an association between acid-suppressing medication (i.e. histamine-2 agonists and proton pump inhibitors [PPIs]), although they have been associated with increased risk of VAP.[69] However, the literature for VAP is mixed. Additionally, evidenced-based guidelines and awareness of potential adverse effects have narrowed indications for acid suppression therapies in the acute care setting and UNC Hospitals

implemented changes to the clinical guidelines for stress ulcer prophylaxis prior to the study period. Similarly, antipsychotics have also been associated with aspiration pneumonia in both the hospital[72] and community setting[73] but in our study failed to detect association between antipsychotic use and ND-pneumonia as well.

6.3 FUTURE RESEARCH

Future studies should attempt to develop prevention strategies that target these potential risk factors, as well as replicate the current results. For example, targeting opioid use, and other urinary devices may be potential avenues to reduce the rates of ND-UTIs. As mentioned above, a recent review found that there was little or no difference in symptomatic UTI risk between short-term suprapubic versus indwelling catheters[65], but there are currently no CDC guidelines for either suprapubic catheters or nephrostomy tubes.[8] And while we did find that antibiotics reduced the risk of ND-UTIs in our cohort, future research should assess whether prophylactic is a viable strategy, especially since it is not currently recommended for CA-UTI prevention.[8] There have been a few recent studies that have found the use of oral care prevented ND-pneumonia in high-risk patients (e.g. neurologic injury patients, older adults).[30,37,74] While we failed to detect an association between chlorhexidine mouthwash and ND-pneumonia rates, this discrepancy could be due to targeted use of oral care with chlorhexidine at UNC Hospitals. As opposed to the universal use in prior studies, only 8% of hospitalized patients included in this analysis received the treatment. It is possible that these individuals were selected to receive oral care with chlorhexidine specifically due to perceived higher risk for respiratory infections-(although indication for chlorhexidine could not be determined) which could explain our inconclusive finding. Chlorhexidine mouthwash has also been associated with increased

inpatient mortality.[75] Studies assessing the utility of chlorhexidine mouthwash and oral care with VAP are mixed[9], and future research is needed to provide additional evidence on whether chlorhexidine mouthwash is a viable prevention strategy for healthcare associated pneumonia.

6.4 CONCLUSIONS

ND-HAIs represent a substantial proportion of all HAIs, and rates of these infections have remained relatively unchanged over the past decade. This study, and similar findings by others suggest that hospital infection prevention programs should consider expanding the scope of surveillance and prevention programs to include ND-HAIs. Additionally, we identified several modifiable and non-modifiable risk factors for ND-UTIs and ND-pneumonia, including patient sex, age, comorbidities, opioid use, suprapubic catheters and nephrostomy tubes. Future research should continue to identify risk factors for ND-HAIs and develop potential prevention strategies for these infections.

REFERENCES

1. Magill SS, Edwards JR, Bamberg W, et al. Multistate point-prevalence survey of health care associated infections. *The New England journal of medicine.* 2014;370(13):1198-1208.

2. Magill SS, O'Leary E, Janelle SJ, et al. Changes in Prevalence of Health Care associated Infections in U.S. Hospitals. *The New England journal of medicine.* 2018;379(18):1732-1744.

3. Landrigan CP, Parry GJ, Bones CB, Hackbarth AD, Goldmann DA, Sharek PJ. Temporal trends in rates of patient harm resulting from medical care. *The New England journal of medicine.* 2010;363(22):2124-2134.

4. Umscheid CA, Mitchell MD, Doshi JA, Agarwal R, Williams K, Brennan PJ. Estimating the proportion of healthcare associated infections that are reasonably preventable and the related mortality and costs. *Infection control and hospital epidemiology.* 2011;32(2):101-114.

5. Zimlichman E, Henderson D, Tamir O, et al. Health care associated infections: a meta-analysis of costs and financial impact on the US health care system. *JAMA Intern Med.* 2013;173(22):2039-2046.

6. National Nosocomial Infections Surveillance (NNIS) System Report, data summary from January 1992 through June 2004, issued October 2004. *American journal of infection control.* 2004;32(8):470-485.

7. DiBiase LM, Weber DJ, Sickbert-Bennett EE, Anderson DJ, Rutala WA. The growing importance of non-device associated healthcare associated infections: a relative proportion and incidence study at an academic medical center, 2008-2012. *Infection control and hospital epidemiology.* 2014;35(2):200-202.

8. Gould CV, Umscheid CA, Agarwal RK, Kuntz G, Pegues DA. Guideline for prevention of catheter associated urinary tract infections 2009. *Infection control and hospital epidemiology.* 2010;31(4):319-326.

9. Klompas M, Branson R, Eichenwald EC, et al. Strategies to prevent ventilator associated pneumonia in acute care hospitals: 2014 update. *Infection control and hospital epidemiology.* 2014;35(8):915-936.

10. Tablan OC, Anderson LJ, Besser R, Bridges C, Hajjeh R. Guidelines for preventing health-care- associated pneumonia, 2003: recommendations of CDC and the Healthcare Infection Control Practices Advisory Committee. *MMWR Recommendations and reports : Morbidity and mortality weekly report Recommendations and reports.* 2004;53(Rr-3):1-36.

11. O'Grady NP, Alexander M, Burns LA, et al. Guidelines for the prevention of intravascular catheter-related infections. *American journal of infection control.* 2011;39(4 Suppl 1):S1-34.

12. Centers for Disease Control and Prevention. 2014 National and State Healthcare associated Infections Progress Report. Available at: https://www.cdc.gov/HAI/pdfs/progress-report/hai-progress-report.pdf. Accessed19 April 2019.

13. Weber DJ, Sickbert-Bennett EE, Brown V, Rutala WA. Completeness of surveillance data reported by the National Healthcare Safety Network: an analysis of healthcare associated infections ascertained in a tertiary care hospital, 2010. *Infection control and hospital epidemiology.* 2012;33(1):94-96.

14. Weber DJ, Sickbert-Bennett EE, Gould CV, Brown VM, Huslage K, Rutala WA. Incidence of catheter associated and non-catheter associated urinary tract infections in a healthcare system. *Infection control and hospital epidemiology.* 2011;32(8):822-823.

15. Davis J, Finley D. The breadth of hospital-acquired pneumonia: nonventilated versus ventilated patients in Pennsylvania. *Pennsylvania Patient Safety Advisory.* 2012;9(3):99-105.

16. Giuliano KK, Baker D, Quinn B. The epidemiology of nonventilator hospital-acquired pneumonia in the United States. *American journal of infection control.* 2017.

17. Baker D, Quinn B. Hospital Acquired Pneumonia Prevention Initiative-2: Incidence of nonventilator hospital-acquired pneumonia in the United States. *American journal of infection control.* 2018;46(1):2-7.

18. Centers for Disease Control and Prevention. National Healthcare Safety Network (NHSN): Patient Safety Component Manual. Available at: https://www.cdc.gov/nhsn/pdfs/pscmanual/pcsmanual_current.pdf. Accessed 19 April 2019.

19. Garrouste-Orgeas M, Timsit JF, Tafflet M, et al. Excess risk of death from intensive care unit-acquired nosocomial bloodstream infections: a reappraisal. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* 2006;42(8):1118-1126.

20. Chant C, Smith OM, Marshall JC, Friedrich JO. Relationship of catheter associated urinary tract infection to mortality and length of stay in critically ill patients: a systematic review and meta-analysis of observational studies. *Critical care medicine.* 2011;39(5):1167-1173.

21. Klevens RM, Edwards JR, Richards CL, Jr., et al. Estimating health care associated infections and deaths in U.S. hospitals, 2002. *Public health reports (Washington, DC : 1974).* 2007;122(2):160-166.

22. Glied S, Cohen B, Liu J, Neidell M, Larson E. Trends in mortality, length of stay, and hospital charges associated with health care associated infections, 2006-2012. *American journal of infection control.* 2016;44(9):983-989.

23. Roberts RR, Scott RD, 2nd, Hota B, et al. Costs attributable to healthcare-acquired infection in hospitalized adults and a comparison of economic methods. *Medical care.* 2010;48(11):1026-1035.

24. Manoukian S, Stewart S, Dancer S, et al. Estimating excess length of stay due to healthcare associated infections: a systematic review and meta-analysis of statistical methodology. *The Journal of hospital infection.* 2018;100(2):222-235.

25. De Angelis G, Murthy A, Beyersmann J, Harbarth S. Estimating the impact of healthcare associated infections on length of stay and costs. *Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases.* 2010;16(12):1729-1735.

26. Richards MJ, Edwards JR, Culver DH, Gaynes RP. Nosocomial infections in combined medical-surgical intensive care units in the United States. *Infection control and hospital epidemiology.* 2000;21(8):510-515.

27. Richards MJ, Edwards JR, Culver DH, Gaynes RP. Nosocomial infections in medical intensive care units in the United States. National Nosocomial Infections Surveillance System. *Critical care medicine.* 1999;27(5):887-892.

28. Calfee DP, Farr BM. Infection control and cost control in the era of managed care. *Infection control and hospital epidemiology.* 2002;23(7):407-410.

29. National Healthcare Safety Network (NHSN) Overview. In: Prevention CfDCa, ed2019.

30. Quinn B, Baker DL, Cohen S, Stewart JL, Lima CA, Parise C. Basic nursing care to prevent nonventilator hospital-acquired pneumonia. *Journal of nursing scholarship : an official publication of Sigma Theta Tau International Honor Society of Nursing.* 2014;46(1):11-19.

31. Kanamori H, Weber DJ, DiBiase LM, et al. Longitudinal trends in all healthcare associated infections through comprehensive hospital-wide surveillance and infection control measures over the past 12 years: substantial burden of healthcare associated infections outside of intensive care units and "other" types of infection. *Infection control and hospital epidemiology.* 2015;36(10):1139-1147.

32. Goto M, Ohl ME, Schweizer ML, Perencevich EN. Accuracy of administrative code data for the surveillance of healthcare associated infections: a systematic review and meta-analysis. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* 2014;58(5):688-696.

33. van Mourik MS, van Duijn PJ, Moons KG, Bonten MJ, Lee GM. Accuracy of administrative data for surveillance of healthcare associated infections: a systematic review. *BMJ open.* 2015;5(8):e008424.

34. Redondo-Gonzalez O, Tenias JM, Arias A, Lucendo AJ. Validity and Reliability of Administrative Coded Data for the Identification of Hospital-Acquired Infections: An Updated Systematic Review with Meta-Analysis and Meta-Regression Analysis. *Health services research.* 2018;53(3):1919-1956.

35. Tiwari S, Ukken J, Froehlich M, et al. Necessity for additional sensitivity analysis and the clinical implications of risk identification with nonventilator hospital-acquired pneumonia. *American journal of infection control.* 2018;46(7):846-847.

36. Baker D, Quinn B, Ewan V, Giuliano KK. Sustaining Quality Improvement: Long-Term Reduction of Nonventilator Hospital-Acquired Pneumonia. *Journal of nursing care quality.* 2018.

37. Munro S, Haile-Mariam A, Greenwell C, Demirci S, Farooqi O, Vasudeva S. Implementation and Dissemination of a Department of Veterans Affairs Oral Care Initiative to Prevent Hospital-Acquired Pneumonia Among Nonventilated Patients. *Nursing administration quarterly.* 2018;42(4):363-372.

38. Passaro L, Harbarth S, Landelle C. Prevention of hospital-acquired pneumonia in non-ventilated adult patients: a narrative review. *Antimicrobial resistance and infection control.* 2016;5:43.

39. Lee EW, Wei LJ, Amato DA, Leurgans S. Cox-Type Regression Analysis for Large Numbers of Small Groups of Correlated Failure Time Observations. In: Klein JP, Goel PK, eds. *Survival Analysis: State of the Art.* Dordrecht: Springer Netherlands; 1992:237-247.

40. Fine JP, Gray RJ. A Proportional Hazards Model for the Subdistribution of a Competing Risk. *Journal of the American Statistical Association.* 1999;94(446):496-509.

41. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *Journal of clinical epidemiology.* 1992;45(6):613-619.

42. Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Medical care.* 2005;43(11):1130-1139.

43. Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine for adults with immunocompromising conditions:

recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morbidity and mortality weekly report.* 2012;61(40):816-819.

44. Greenberg JA, Hohmann SF, Hall JB, Kress JP, David MZ. Validation of a Method to Identify Immunocompromised Patients with Severe Sepsis in Administrative Databases. *Annals of the American Thoracic Society.* 2016;13(2):253-258.

45. Subbe CP, Kruger M, Rutherford P, Gemmel L. Validation of a modified Early Warning Score in medical admissions. *QJM : monthly journal of the Association of Physicians.* 2001;94(10):521-526.

46. Morgan RJM, Williams F, Wright MM. An early warning scoring system for detecting developing critical illness. Clin Intensive Care, **1997**; 8(2): 100.

47. Morse JM, Morse RM, Tylko SJ. Development of a scale to identify the fall-prone patient. 1989;8(4):366-377.

48. Morse JM, Black C, Oberle K, Donahue P. A prospective study to identify the fall-prone patient. *Social science & medicine (1982).* 1989;28(1):81-86.

49. Institute for Healthcare Improvement. Early warning systems: Scorecards that save lives. Available at: http://www.ihi.org/resources/Pages/ImprovementStories/EarlyWarningSystemsScorecardsThatSaveLives.aspx. Accessed 5 April 2019.

50. Agency for Healthcare Research and Quality. Tool 3H: Morse fall scale for identifying fall risk factors. Available at: http://www.ahrq.gov/professionals/systems/hospital/fallpxtoolkit/fallpxtk-tool3h.html. Accessed 5 April 2019.

51. Seaman SR, White IR. Review of inverse probability weighting for dealing with missing data. *Statistical methods in medical research.* 2013;22(3):278-295.

52. Howe CJ, Cole SR, Westreich DJ, Greenland S, Napravnik S, Eron JJ, Jr. Splines for trend analysis and continuous confounder control. *Epidemiology (Cambridge, Mass).* 2011;22(6):874-875.

53. Tambyah PA, Knasinski V, Maki DG. The direct costs of nosocomial catheter associated urinary tract infection in the era of managed care. *Infection control and hospital epidemiology.* 2002;23(1):27-31.

54. Wasserstein RL, Lazar NA. The ASA's Statement on p-Values: Context, Process, and Purpose. *The American Statistician.* 2016;70(2):129-133.

55. Wasserstein RL, Schirm AL, Lazar NA. Moving to a World Beyond "$p < 0.05$". *The American Statistician.* 2019;73(sup1):1-19.

56. Hooton TM, Bradley SF, Cardenas DD, et al. Diagnosis, prevention, and treatment of catheter associated urinary tract infection in adults: 2009 International Clinical Practice Guidelines from the Infectious Diseases Society of America. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* 2010;50(5):625-663.

57. Foxman B. Epidemiology of urinary tract infections: incidence, morbidity, and economic costs. *The American Journal of Medicine.* 2002;113(1):5-13.

58. Letica-Kriegel AS, Salmasian H, Vawdrey DK, et al. Identifying the risk factors for catheter associated urinary tract infections: a large cross-sectional study of six hospitals. *BMJ open.* 2019;9(2):e022137.

59. Garibaldi RA, Burke JP, Dickman ML, Smith CB. Factors predisposing to bacteriuria during indwelling urethral catheterization. *The New England journal of medicine.* 1974;291(5):215-219.

60. Verhamme KM, Sturkenboom MC, Stricker BH, Bosch R. Drug-induced urinary retention: incidence, management and prevention. *Drug safety.* 2008;31(5):373-388.

61. Will you have Urinary retention with Ranitidine - from FDA reports. https://www.ehealthme.com/ds/ranitidine/urinary-retention/. Accessed 3/23/2019.

62. Rogers MA, Fries BE, Kaufman SR, Mody L, McMahon LF, Jr., Saint S. Mobility and other predictors of hospitalization for urinary tract infection: a retrospective cohort study. *BMC geriatrics.* 2008;8:31.

63. Muskett H, Shahin J, Eyres G, Harvey S, Rowan K, Harrison D. Risk factors for invasive fungal disease in critically ill adult patients: a systematic review. *Critical care (London, England).* 2011;15(6):R287.

64. Yang SP, Chen YY, Hsu HS, Wang FD, Chen LY, Fung CP. A risk factor analysis of healthcare associated fungal infections in an intensive care unit: a retrospective cohort study. *BMC infectious diseases.* 2013;13:10.

65. Kidd EA, Stewart F, Kassis NC, Hom E, Omar MI. Urethral (indwelling or intermittent) or suprapubic routes for short-term catheterisation in hospitalised adults. *The Cochrane database of systematic reviews.* 2015(12):Cd004203.

66. See I, Chang J, Gualandi N, et al. Clinical Correlates of Surveillance Events Detected by National Healthcare Safety Network Pneumonia and Lower Respiratory Infection Definitions-Pennsylvania, 2011-2012. *Infection control and hospital epidemiology.* 2016;37(7):818-824.

67. Klompas M. Hospital-Acquired Pneumonia in Nonventilated Patients: The Next Frontier. *Infection control and hospital epidemiology.* 2016;37(7):825-826.

68. Klompas M. Complications of mechanical ventilation--the CDC's new surveillance paradigm. *The New England journal of medicine.* 2013;368(16):1472-1475.

69. Chastre J, Fagon JY. Ventilator associated pneumonia. *American journal of respiratory and critical care medicine.* 2002;165(7):867-903.

70. Rello J, Ollendorf DA, Oster G, et al. Epidemiology and outcomes of ventilator associated pneumonia in a large US database. *Chest.* 2002;122(6):2115-2121.

71. Jackson ML, Neuzil KM, Thompson WW, et al. The burden of community-acquired pneumonia in seniors: results of a population-based study. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* 2004;39(11):1642-1650.

72. Herzig SJ, LaSalvia MT, Naidus E, et al. Antipsychotics and the Risk of Aspiration Pneumonia in Individuals Hospitalized for Nonpsychiatric Conditions: A Cohort Study. *Journal of the American Geriatrics Society.* 2017;65(12):2580-2586.

73. Dzahini O, Singh N, Taylor D, Haddad PM. Antipsychotic drug use and pneumonia: Systematic review and meta-analysis. *Journal of psychopharmacology (Oxford, England).* 2018;32(11):1167-1181.

74. Warren C, Medei MK, Wood B, Schutte D. A Nurse-Driven Oral Care Protocol to Reduce Hospital-Acquired Pneumonia. *The American journal of nursing.* 2019;119(2):44-51.

75. Deschepper M, Waegeman W, Eeckloo K, Vogelaers D, Blot S. Effects of chlorhexidine gluconate oral care on hospital mortality: a hospital-wide, observational cohort study. *Intensive care medicine.* 2018;44(7):1017-1026.