Sustained Reduction in Nosocomial Bloodstream Infections in the ICU Setting

A Major Qualifying Project

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Biology & Biotechnology

By

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TABLE OF CONTENTS:

PREFACE

The following document was completed as per requirement at Worcester Polytechnic Institute, submitted no later than April 30th, 2015.

The following manuscript satisfies the WPI Major Qualifying Project requirement for Biology/Biotechnology and is titled "Sustained Reduction in Nosocomial Bloodstream Infections in the ICU Setting." This project was advised by WPI faculty member Dr. Jill Rulfs and sponsored by the University of Massachusetts (UMASS) Medical School. This study was approved by the UMASS Medical School Institutional Review Board.

The following study was conducted over the course of eleven months spanning from June 2014 – April 2015; the study itself is a retrospective, data-based study examining bloodstream infections that occurred between October 1st 2004 and September 30th 2014 on the UMASS Medical Center campus. It was performed under the guidance of Dr. Richard T. Ellison III, Hospital Epidemiologist at UMASS Medical Center in Worcester, MA. Dr. Ellison has provided guidance, input, and many rounds of revision to this manuscript.

Other members of this study are as follows. Dr. Stephen O. Heard is a hospital anesthesiologist and intensivist who was instrumental in the execution of the study regarding primary infections that prompted the need for this study. Dr. Heard contributed knowledge of hospital history to this manuscript and helped fund portions of the work. Dr. J. Matthias Walz is a hospital anesthesiologist and intensivist and is the primary author on a previous study regarding primary infections. Dr. Walz contributed knowledge on hospital history to this manuscript. Deborah A. Mack is the lead Infection Control Preventionist in the UMass Medical Center's Infection Control Department. Debbie assisted with ascertaining missing data and patient information during the process of database curation. Dr. Eric Ruggieri is a statistician from Department of Mathematics and Computer Science at College of the Holy Cross in Worcester, MA. Dr. Ruggieri completed nearly all statistical analysis found within this manuscript and contributed to specific written portions of this paper. Dr. Michael Mitchell is the Microbiology Lab Manager at UMASS Medical School and provided information on the number of blood cultures performed at the hospital for analysis. Dr. Craig Lilly oversees the implementation of the electronic ICU monitoring system in use at the UMASS Medical Center, and assisted in the collection of patient acuity and outcome data for auxiliary analysis in this study. Karen E. Landry managed the database for the Critical Care Operations Committee (CCOC) from which the data for auxiliary analysis was obtained.

This study was inspired by a study published in 2013 which included Walz, Ellison, Heard, Mack, and Landry and examined the effects of a multidisciplinary intervention approach on trends in central line-associated bloodstream infections (CLABSIs). After witnessing large decreases in the number of CLABSIs, there was interest in determining if multimodal intervention strategies had impacted secondary bloodstream infections in a similar manner.

From June 2011 through August 2011, I was tasked with compiling a database of the patients which met the criteria outlined by Dr. Ellison for this study. First, the study examined only patients from FY05 through FY14, a decade-long study period. Next, patients were to be included if they were placed in an ICU unit and contracted a bloodstream infection during their stay that could directly be attributed to hospital stay (nosocomial). This process involved narrowing down over 7,000 potential patient entries to approximately 850 entries. This process proved to be painstaking and lengthy, as the information had previously been maintained in Excel spreadsheets which were not formatted in the same manner, and often had missing pieces of patient information that were required. The summer was spent combing through these entries and finding missing data to produce one, complete, final database which included information on date, ICU location, BSI source, and causative organism for all qualifying ICU admissions. Upon completion of this database, the de-identified information was send to Dr. Ruggieri for analysis. After the analysis was completed, an abstract for the project was completed, and a presentation was made of the preliminary findings to the CCOC.

In August, the abstract for this study was submitted for consideration to the Society of Critical Care Medicine for publishing in the journal *Critical Care Medicine*. (Note that the abstract in this report is longer than the abstract submitted with the e-CDR form, as this is the format in which it was submitted for publishing. In the interest of consistency, I chose to retain the full abstract for this report.)

We received word on September 22nd that the abstract was accepted for the 2015 Critical Care Conference in Phoenix, AZ. The abstract (#486) was published in a special supplement to *Critical Care Medicine*, and I was invited to attend the conference in Phoenix in January 2015 to do a poster presentation of the study. A poster was created and presented in the Infectious Disease category alongside top hospitals and institutions. A guided, moderated group of conference participants visited the poster and were able to ask questions and generate discussion regarding the study.

Following the acceptance of the abstract, the project progressed to the next phase of creating a complete manuscript in order to ultimately submit the manuscript for publishing in this same journal. During this time, more analysis was conducted – referred to as "auxiliary analysis" – to look deeper into some potentially confounding variables that may have affected the study, as well as to attempt to determine the causes of the trends seen in the initial results. It was at this point that the help of Dr. Mitchell, Dr. Lilly, and Karen Landry was enlisted to obtain the appropriate data sets. One data set consisted of in-depth patient information (ie. ICU length of stay, glucose levels, APACHE IV scores) (about 32,000 entries) while the other documented the blood cultures drawn during the entire study period (about 135,000 entries). I worked very closely with Dr. Ruggieri in order to outline what analyses were needed based on the information in these data sets. The process of outlining the analyses, executing the analyses, and interpreting the analyses took through the end of C-term; writing of this manuscript took

place over the course of latter three terms of the year. This project was presented on Project Presentation Day in the Campus Center Odeum on Thursday, April 23rd, 2015.

The manuscript below will likely continue to be modified as is necessary in order to submit it for publishing. However, for the purposes of this project, this paper can be considered complete. This paper's main and true goal is to provide information to the members of the CCOC so they may assess the efficacy of the interventions in place and proceed with this new knowledge in planning future interventions.

I am truly thankful for the opportunity to have worked with the Infection Control staff and other members of UMASS Medical Center/School on this project. Their knowledge, patience, encouragement, and support have made this project entirely possible. Enough cannot truly be said especially regarding the wonderful Infection Control Preventionists who exercised much patience with me on this project, constantly answering questions and clarifying information for me. Their kindness and willingness to assist removed much stress from the databasing portion of this project. Additionally, it has been a privilege to work alongside Dr. Ruggieri, who was always willing and able to answer questions and perform analysis, even while teaching classes at College of the Holy Cross. Finally, my sincerest thanks go to Dr. Richard Ellison, who initially provided me with the opportunity to work in Infection Control, then with motivation and guidance along the way to see this project through to its eventual submission for publication.

Primary authorship on a study such as this was something that I never would have expected to achieve during my time as an undergraduate. The knowledge and experience gained through this project will be invaluable to me as I continue on to pursue my Master of Public Health degree, and for that, I am eternally grateful.

Sustained reduction in nosocomial bloodstream infections in the ICU setting

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ABSTRACT

BACKGROUND: Central line–associated bloodstream infections (CLABSIs) have decreased significantly throughout the last decade within intensive care units (ICUs). A concurrent reduction in the total number of bloodstream infections (BSIs) in ICUs should also be expected. We report trends in nosocomial ICU-associated BSIs in a tertiary care academic medical center for a 10-year time period.

METHODS: This was a retrospective study of positive blood cultures from patients admitted to seven adult ICUs for the period FY2005 through FY2014. BSIs were evaluated and categorized according to Centers for Disease Control and Prevention (CDC) National Healthcare Safety Network (NHSN) definitions for primary BSIs and those secondary to another site. The rate of change for primary and secondary nosocomial BSIs was determined, as was the distribution of different organisms responsible for these BSIs.

RESULTS: Across all ICUs, the rate of primary BSIs progressively fell from 2.11/1000 patient days in FY05 to 0.32/1000 patient days in FY14; an 85.0% decrease (P<0.0001). Secondary BSIs also progressively decreased from 3.56/1000 patient days to 0.66/1000 patient days; an 81.4% decrease (P<0.0001). The total BSI rate per 1000 patient days decreased from 5.67 in FY05 to 0.98 FY14; an 82.8% decrease. The decrease in BSI rates remained significant after controlling for the number of blood cultures obtained and patient acuity. Both *S. aureus* and *S. not-aureus* infections exhibited notable changes, decreasing by 97.3% and 89.7% respectively; other species decreased 60-80% or remained constant.

CONCLUSION: An increased focus on reducing nosocomial infections at the academic medical center during the last 10 years, including multimodal multidisciplinary efforts to prevent CLABSIs, pneumonia, *Clostridium difficile* disease, surgical site infections, and

urinary tract infections as well as to reduce the number of blood transfusions, has led to a progressive and sustained decrease in both primary and secondary nosocomial BSIs.

KEYWORDS: bacteremia; nosocomial; blood stream infection

INTRODUCTION

Nosocomial bloodstream infections (BSIs) are a prominent category of hospital-acquired infections (HAIs), which are acquired after admission to the hospital for an unrelated reason. In 2008, bloodstream infections (BSIs) were ranked as the 11th major cause of death in the US (Goto & Al-Hasan, 2013). Based on a population-based study by Goto and Al-Hasan (2013), 100,000 of the estimated $536,000 - 628,000$ BSI episodes in the US annually are nosocomial with a 15-30% fatality rate. In this same study, based on a surveillance-based system, as many as 250,000 nosocomial BSIs occur annually with this same fatality rate (Goto & Al-Hasan, 2013). Nosocomial BSIs increase morbidity and mortality, as well as hospital costs – between $23,000 - $56,000 per episode – and can extend length of stay for as much as 32 days (Kaye, et al., 2011). Therefore, it is in the best interest to hospital staff to implement measures to greatly reduce the number of nosocomial BSIs occurring in their facilities.

The UMass Memorial Medical Center (UMMMC) is a 781-bed hospital located on two different campuses with seven adult ICUs. Beginning in 2004, the hospital implemented a major, coordinated, multidisciplinary quality improvement initiative to reduce the number of central-line associated bloodstream infections (CLABSIs) in these units which successfully led to a significant decrease in these infections (Walz, et al., 2013). We tested the hypothesis that this decrease in CLABSIs was also associated with a decrease in the total number of hospital-acquired BSIs in these ICUs, including those infections secondary to another site. To test this hypothesis we undertook a retrospective analysis of all hospital-acquired BSIs that occurred in patients receiving care in the adult

UMMMC ICUs between 10/01/2004 and 09/30/2014. The study was approved by the

University of Massachusetts Medical School Institutional Review Board.

METHODS

The UMMMC adult ICUs include two medical units, two surgical units, one combined medical/surgical unit (composed of two smaller units), a neurological critical care and trauma unit, and a cardiac surgery and coronary care unit. Community-acquired (CA) and healthcare-acquired (HCA) BSIs were excluded from the analysis.

All positive blood cultures were reviewed and categorized by UMMMC infection control practitioners in accordance with Centers for Disease Control and Prevention (CDC) National Healthcare Safety Network (NHSN) definitions for primary BSIs and those secondary to another site at the time of classification. This data had been maintained in spreadsheets until November 2010 (Microsoft Excel, Redmond, WA) and a dedicated infection control database thereafter (Theradoc, Premier, Charlotte, NC).

Infections were initially classified into two broad categories: primary infections and secondary infections. Primary infections included infections designated as CLABSIs or as non-specific types of primary infections. Secondary infections included all other infections, which were then broken down into six main categories: gastrointestinal (GI), respiratory (Resp), surgical site (SSI), skin and soft tissue (SST), urinary tract (UTI), and ultiple/other/unknown (Mult/Other/Unk). This last category included infections attributed to multiple sources, where the source listed did not fall into one of the five main categories, or if the site of the infection was unknown. Infections were then stratified by the organism indicated as causative to the infection, as well as by ICU.

The majority of the organisms identified were categorized into one of the following groups: *Staphylococcus aureus*, *Staphylococcus* not-*aureus,* Enteric Gram-Negative Bacteria, *Pseudomonas* species*, Candida* species, and *Enterococcus* species. The category "Staph not-aureus" included all *Staphylococcus* species that were not *S. aureus.* The category "Candida*"* contained all *Candida* species; "Pseudomonas" and "Enterococcus" were classified in the same manner. The category "Enteric Gram-Negative Bacteria" includes: *Citrobacter, Enterobacter, Escherichia, Klebsiella, Proteus,* and *Serratia* species. Additionally, many organisms were only responsible for a few infections throughout the time period. In order to avoid skewing of the data, these organisms were grouped into a category defined as "Other." This category contained the following organisms: *Acinetobacter, Bacteroides, Clostridium, Corynebacterium, Lecleria, Leuconostoc, Peptostreptococcus, Stenotrophomonas, Stomatococcus, alpha-hemolytic Streptococcus, Hafnia, Providencia, Cedecea, Cryptococcus, Haemophilus influenza, Peptoniphilus,* and *Morganella* species.

Additional information was obtained for further analysis. A custom report was used to extract relevant blood culture data from the Laboratory Information System (MEDITECH, Westwood, MA). Data was imported into Microsoft Excel (Redmond, WA) for analysis. Blood culture data was stored in a secure, restricted laboratory database. Auxiliary information regarding patient ICU stays was taken from the UMass Memorial ICU data repository using abstraction, privacy protection, data aggregation, and mapping techniques previously described (Lilly, Cody, & Zhao, 2011). Observations were entered by clinicians or transferred using a validated extract-transform-load process (Lilly, Landry, & Sood, 2014) from a clinical information

system and mapped to equivalent concepts in the ICU database. This database contained consistent physiological, laboratory, diagnosis, treatment, physical examination elements, microbiology, and nursing flow sheet data in the electronic record for every patient for the duration of their ICU stay; however, not all of this information was accessed for this study. Acuity was measured using the Acute Physiology and Chronic Health Evaluation (APACHE IV) software sublicensed from Cerner, Inc., (Kansas City, MO).

Statistical Analysis

Differences in infection rates over time by fiscal year (10/01 – 9/30) were evaluated with a Poisson test (Lehmann & Romano, 2005). Evaluation of the trend in infection rates was modeled by a Poisson regression model with a log link function (Dobson, 1990) (McCullagh & Nelder, 1990) using the R (R Core Team, 2014) package glm2 (Marschner, 2014). Fiscal year was modeled as a continuous fixed effect. A logistic regression model with fiscal year as the independent variable was used to compare the rate of decrease of primary BSIs relative to secondary BSIs. Additionally, linear mixed effects analysis was performed using the R (R Core Team, 2014) package lme4 (Bates, Maechler, Bolker, & Walker, 2014) using restricted estimation by maximum likelihood. The number of blood stream infections per year was modeled using general linear mixed models (Graybill, 1976) with fiscal year as a continuous fixed effect and ICU as a random effect. Indicator variables were added one at a time as fixed effects in order to evaluate the effect of interventions that were made in any given year. A likelihood ratio test was used to evaluate the improvement in the model by inclusion of the indicator variables. The final model contained only those terms found to be statistically significant. P-values were obtained by likelihood ratio tests of the full model with the effect in question against the model without the effect in question.

Trends in potential confounding variables such as the number of blood cultures obtained in the ICU, APACHE IV scores, and glucose levels were analyzed using linear regression models. Infection rates were adjusted for these variables where noted.

RESULTS

Overall, there was an 82.8% decrease in total BSIs (P<0.001). Primary BSIs exhibited a significant 85.0% reduction when comparing FY05 to FY14, with a progressive 0.245 fold reduction in the rate each year (P $\approx 10^{-16}$) (Table 1). In addition, there was a significant 81.4% reduction in secondary BSIs over the 10 year period with an annual rate fold reduction of 0.152 per year (P$\approx 10^{-11}$) (Table 1). It was concluded that both primary and secondary infections decreased in a similar manner, although primary infections decreased at an approximately 11% faster rate (Figure 1, Supplementary Table 1).

For secondary BSIs (Table 2), SSI-associated BSIs exhibited a 0.226-fold reduction (P <0.001), slightly larger than the 0.203-fold reduction (P $\approx 10^{-15}$) seen in respiratory infections. There was also a statistically significant decrease observed in GI-, UTI-, and SST-associated BSIs (P <0.001). The category encompassing all primary infections showed a 0.245-fold reduction (P $\approx 10^{-30}$). Overall, there was a decrease across all categories of primary and secondary infections (Table 2). A P-value was not calculated for the Mult/Unk/Other category, as it would not be meaningful to look for a trend in a group which does not have consistent characteristics.

In an analysis by pathogen (Figure 2, Table 3), *Staphylococcus* not-*aureus* exhibited the largest decrease with a 0.300-fold decrease per year in the annual BSI rate, 84.5% of which were primary BSIs. *Staphylococcus aureus* exhibited a 0.191-fold decrease per year with reductions in BSIs where 21.5% were primary BSIs. All other pathogen

classes, including the "Other" category, exhibited at least a 0.100-fold decrease per year; all P-values were significant. Over the study period, overall fold reductions were greater than 50%, with *Staphylococcus* species exhibiting a decrease >80% (Supplementary Table 2 - 4).

For each of these same categories, an overall percent reduction was calculated comparing the FY05 BSI rate to the FY14 rate (Supplementary Figure 4). In line with the annual fold reduction (Figure 2), *Staphylococcus aureus* exhibited a large overall reduction of 97.3%, while *Staphylococcus* non-*aureus* had a similar reduction of 89.7% overall. *Candida* species, *Enterococcus* species, Enteric Gram-Negative Bacteria¸ and *Pseudomonas* species had reductions of 67.1%, 68.0%, 78.7%, and 81.7%, respectively. The "Other" category decreased by 54.3%.

In an analysis by unit (Figure 3, Table 4), there was a statistically significant decrease in BSI rates in all units with the exception of the cardiac surgery and coronary care unit, which exhibited low baseline rates.

In order to address any potentially confounding trends, a regression model was used to analyze both the number of blood cultures obtained in the ICUs during the 10 year period as well as data on length of stay in the ICU, APACHE IV scores, glucose levels, vital status, and number of ICU stays. There was a significant decline in the number of blood cultures obtained over the 10 year period (Figure 4), however, the decrease in BSI rates remains highly significant after controlling for this reduction. The average

APACHE IV scores also decreased minimally (68 → 66) between FY07 and FY14, but again the decrease in BSI rates remains significant after controlling for this change (Supplementary Figure 1). The decreasing BSI rates were associated with a drop in mortality rates, although the association is not statistically significant. Median glucose levels dropped significantly from 123.7 to 122.0 across the study period but do not represent a clinically relevant difference. Finally, the total number of ICU stays per patient remained constant over time.

DISCUSSION

The initial purpose of this study was to confirm that infections had not remained stagnant or increased, and to determine by how much nosocomial BSI rates had decreased, if at all (Asgeirsson, Gudlaugsson, Kristinsson, Heiddal, & Kristjansson, 2011). The major finding of our study is that we observed a significant decrease in not only primary but also secondary BSIs during the study period. The rates of primary and secondary infections decreased over time; primary infections fell at a slightly faster rate.

The 85.0% decrease in primary infections was tightly temporally associated with the incorporation of a catheter bundle as well as education initiatives within the hospital system. The main features of these interventions have been previously reported by Walz et al. (2013).

The 81.4% decrease in secondary infections was associated with directed preventative measures to reduce secondary infections and the predispositions that cause them. In September of 2004, the Critical Care Operations Committee (CCOC) was formed (in part) at UMass Medical Center to generate a set of clinical practice guidelines (CPGs) which would help provide standardized medical care to ICU patients. In the three years following its creation, the CCOC generated nearly one dozen CPGs covering many aspects of care: central line-related BSIs, ventilator-associated pneumonia (VAP), sedation holidays, glycemic control, weaning from mechanical ventilation, transfusion criteria, sepsis, catheter-associated urinary tract infections (CAUTIs), and more. These CPGs, combined with general education initiatives regarding best practice, almost

certainly contributed to this large decline seen in secondary infections. Additionally, the creation and implementation of the e-ICU system described by Lilly, Cody, and Zhao (2011) resulted in an increased availability of intensivists in the hospital, which may have contributed as well.

It is possible to deduce potential associations between specific results and specific interventions. One example of this is the 0.203-fold decrease seen in respiratory infections. It is likely that this drop was associated with the implementation of specific CPGs (VAP, sedation holidays, weaning) as well as increased monitoring for head-of-bed elevation. Another example pertains to the large drop in *Staphylococcus* not-*aureus* (SNA) infections. Between 2005 and 2006, specific CPGs, in addition to the catheter bundle described by Walz et al. (2013), were deliberately targeted at reducing primary infections related to central line catheters. *Staphylococcus* not-*aureus* (SNA) is a common skin commensal that is often causative of primary BSIs due to inadequate maintenance of the line. Between FY06 and FY07, a large drop SNA was seen, and it is known that 84.5% of all SNA infections were primary infections. Therefore, the data suggests that the drop in SNA was associated with the implementation of direct intervention pertaining to central lines. These are just two examples of potential associations seen within this study.

During the study period, two changes were made to NHSN definitions that impacted our study, one regarding the definition of contaminants and the other regarding ICU length of stay requirements for nosocomial infections.

In January of 2008, the NHSN definition was altered to include contaminants as a category for blood culture results. Initially, blood cultures were classified as either true positives or false positives. In order for an infection to be considered a "laboratory confirmed" bloodstream infection (LCBI), there was to be no infection at another site in addition to one of the following criteria: at least one culture positive for a recognized pathogen; the same organism found in at least two positive blood cultures isolated from two separate sites; or an organism found in at least one positive blood culture and the doctor applies antimicrobial therapy. Beginning in January 2008, this third criteria was removed. In the NHSN manual, the definition for LCBIs subsequently changed to remove "common skin contaminant is cultured from at least one blood culture from a patient with an intravascular line, and the physician institutes appropriate antimicrobial therapy." This altered classifications to now account for a class of contaminants in which one culture was positive for a common skin commensal. This class includes many types of organisms seen in this study, including *Corynebacterium*, *Bacillus*, *Streptococcus*, and, most noteably, *Staphylococcus* non-*aureus* species.

A second definition change occurred in January of 2013. Previously, the NHSN manual stated that, in order for an infection to be attributable to a specific location, patients were required to remain in that location for at least 48 hours. As per this rule, prior to January 2013, exclusions were based on this 48-hour rule. Beginning in January 2013, the definition was changed so that patients were required to remain in the ICU for at least two midnights if they were admitted directly to the ICU from the Emergency Department; alternatively, if the patient was admitted to the hospital then transferred to

the ICU later, the 48-hour rule still applied and the patient must have been in the ICU

for at least 48 hours in order to have the infection attributed to that ICU stay.

STRENGTHS AND LIMITATIONS

The main strength of this study is that it encompasses seven different ICU locations which handled different types of patients including trauma, neurological, and cardiac populations over the course of a decade. Overall, P-values for the analysis performed were often extremely low, demonstrating very low probability of false attribution. Additionally, the auxiliary data analysis done examined over 32,000 separate ICU admissions, making the data very thorough. A large amount of care was put into assuring that all data involved in this study was complete, organized, and accurate.

There are limitations to the data used in this study. First and foremost, this study is a retrospective study, and therefore relied solely on the accuracy and completeness of previously maintained data. The main limitation is that multiple interventions were implemented during the study period, resulting in a multimodal intervention. Accordingly, it is not possible to identify which component parts of the intervention were most responsible for the outcome.

During the study period, two aforementioned major definition changes occurred which impacted this study. These definition changes had the potential to bias the study results in two ways: contributing to an artifactual reduction in BSIs, and reducing the acuity of the patients in the study. To address these potentially confounding factors, auxiliary analysis was performed that accommodated these changes. We were able to determine that these changes very likely did not affect the outcomes of our study.

The definition change regarding contaminants could have potentially contributed to the large drop in *Staphylococcus* non-*aureus* infections. However, the definition change occurred in January 2008 (in FY08), and the major drop occurred between October 2006 and March 2007, which are considered FY07. Therefore, it is unlikely that the definition change was causative of this large decrease. The definition change may have had a minor role in the small drop in BSI rates per 1000 patients seen between FY08 and FY09. However, there continued to be a steady, sustained decrease throughout the following six years after the definition change, which allowed us to deduce no major link between the results and the definition change.

The definition change regarding ICU length of stay in order to qualify an infection as nosocomial had the potential to confound the auxiliary analysis performed during this study.

After the definition change, the two midnights rule applying to direct admissions was also applied to this circumstance regarding those who were transferred to an ICU from the hospital ward, where the 48-rule should have been applied. This was due to an inability to exclude transfer patients based on the information available; however this ultimately included more patients as opposed to excluding too many patients. Since transfer patients were included who only remained in the ICU for two midnights and not 48 hours, there is potential that a small group of patients who were likely healthier (spending less time in the hospital) were included, which could have decreased the average APACHE IV score for this time period. Additionally, this general NHSN

change led to more – and also likely somewhat healthier – patients being included in the study post-January 2013 as they were required to remain in the hospital less time, and hospital length of stay often correlates with acuity of illness. Because of these new inclusions, it became important to determine if APACHE scores decreased over that time thereby requiring a re-analysis of the data using the correct 48 hour rule. However, APACHE scores for January 2013-September 2014 actually increased slightly, confirming that the inclusion of these patients did not skew the APACHE IV scores.

In summary, our study found that the rate of secondary nosocomial BSIs in the adult ICUs steadily decreased throughout the study period alongside primary nosocomial BSIs. Across all classification categories, causative organisms, and ICU locations (with the exception of one ICU location), rates of both secondary and primary nosocomial BSIs declined by over 80%. Our study demonstrates that the interventions, both technical and educational, direct and indirect, put into place during the study period were effective in greatly reducing hospital-acquired BSIs in the ICU setting.

REFERENCES

Asgeirsson, H., Gudlaugsson, O., Kristinsson, K., Heiddal, S., & Kristjansson, M. (2011). Staphylococcus aureus bacteraemia in Iceland, 1995–2008: changing incidence and mortality. Clin Microbiol Infect, 513-518.

Bates, D., Maechler, M., Bolker, B., & Walker, S. (2014). lme4: Linear mixed-effects models using Eigen and S4. Retrieved from R package Version 1.1-7: http://cran.r-project.org/package=lme4

Dobson, A. (1990). An Introduction to Generalized Linear Models. New York: Chapman & Hall.

Goto, M., & Al-Hasan, M. (2013). Overall burden of bloodstream infections and nosocomial bloodstream infections in North America and Europe. Clin Microbiol Infect, 501-509.

Graybill, F. (1976). Theory and Application of the Linear Model. Belmont: Wadsworth.

Kaye, K., Marchaim, D., Chen, T., Chopra, T., Anderson, D., Choi, Y.,…Schmader, K. (2011). Predictors of Nosocomial Bloodstream Infections in Older Adults. JAGS, 622-627.

Lehmann, E., & Romano, J. (2005). Testing Statistical Hypotheses. New York: Springer.

Lilly, C., Cody, S., & Zhao, H. (2011). Hospital mortality, length of stay, and preventable complications among critically ill patients before and after tele-ICU reengineering of critical care processes. JAMA, 2175-2183.

Lilly, C., Landry, K., & Sood, R. (2014). Prevalence and test characteristics of National Health and Safety Network ventilator-associated events. Critical Care Medicine, 2019-2028.

Marschner, I. (2014, May 7). Fitting Generalized Linear Models. Retrieved from glm2: Fitting Generalized Linear Models: http://cran.r-project.org/web/packages/glm2/index.html

McCullagh, P., & Nelder, J. (1990). Generalized Linear Models. New York: Chapman & Hall.

R Core Team. (2014). R: A Language and Environment for Statistical Computing. Retrieved from R Foundation for Statistical Computing: http://www.R-project.org

Walz, J., Ellison, R., Mack, D., Flaherty, H., McIlwaine, J., Whyte, K., . . . Heard, S. (2013). The Bundle "Plus": The Effect of a Multidiscilinary Team Approach to Eradicate Central Line-Associated Bloodstream Infections. Anesthesia and Analgesia.
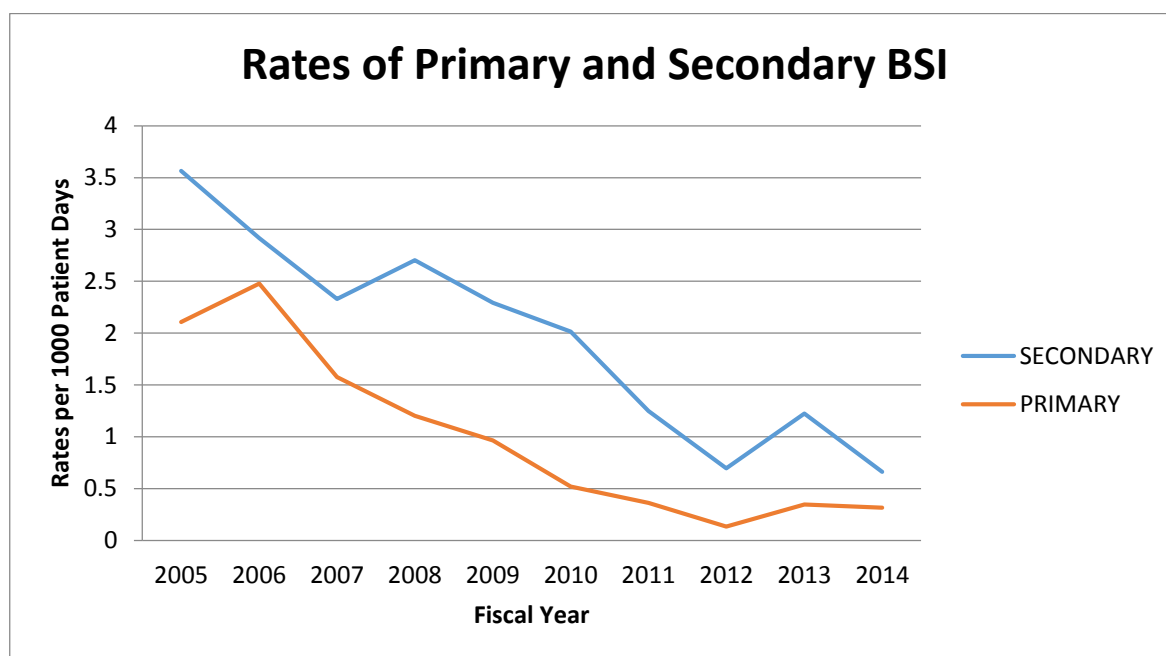
FIGURES & TABLES

Figure 1: Overall rates of primary and secondary BSIs for 10 year study period.

**Table 1: Total BSI rate fold reduction and percent reduction stratified by
primary/secondary classification.** Note the fold reduction and respective P-value followed
by percent reduction and respective P-value.

Infection Subclass	Fold Reduction	95% CI	95% Lower Bound	P-Value (FOLD RED)	% Reduction	P-Value (% RED)
Primary	.245	.201 - .287	.210	$\sim10^{-30}$	85.0	$\sim10^{-11}$
Secondary	.152	.121 - .182	.127	$\sim10^{-26}$	81.4	$\sim10^{-16}$

Table 2: Total BSI rate reduction stratified by source subclass. Note confidence intervals, lower bounds, and P-values for trends in each class.

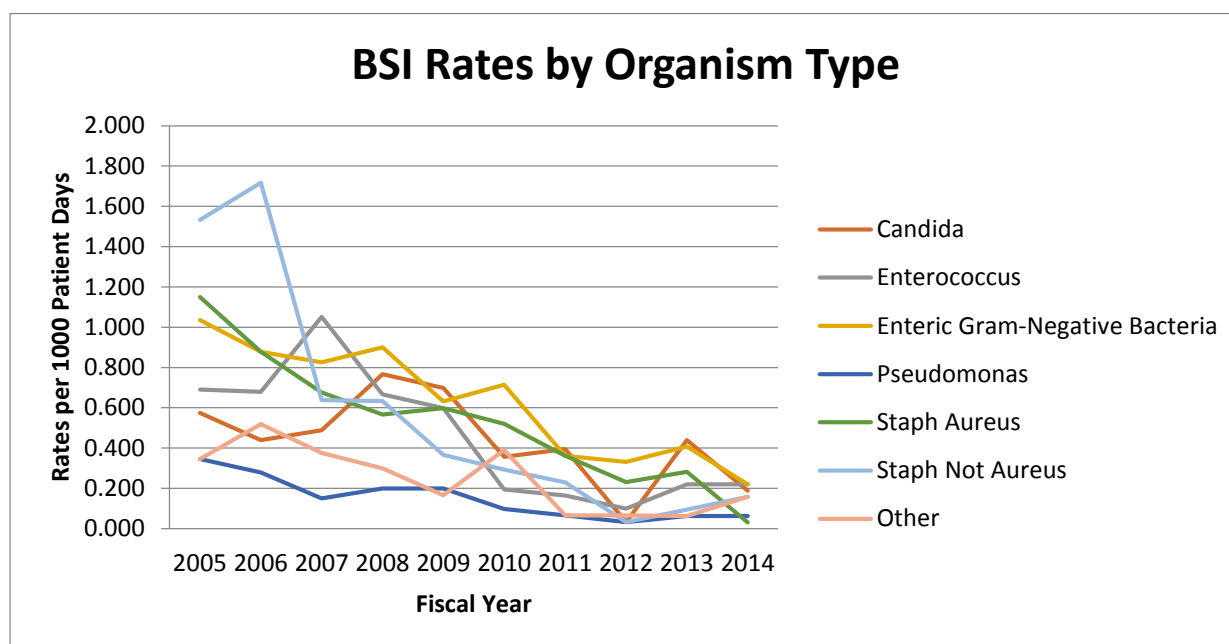| Infection Subclass	Fold Reduction	95% CI	95% Lower Bound	P-Value for Trend
Primary	.245	.201 - .287	.210	$\sim 10^{-30}$
GI	.131	.066 - .192	.079	.00001
Respiratory	.203	.150 - .254	.160	$\sim 10^{-15}$
SSI	.226	.112 - .326	.135	.00002
SST	.141	.030 - .239	.052	.0040
UTI	.124	.046 - .195	.062	.0003
Mult/Unk/Other				NS

Figure 2: Total BSI rate stratified by causative organism class.

Table 3: Total BSI fold reduction stratified by causative organism class. Note confidence intervals, lower bounds, and P-values for trends in each class.

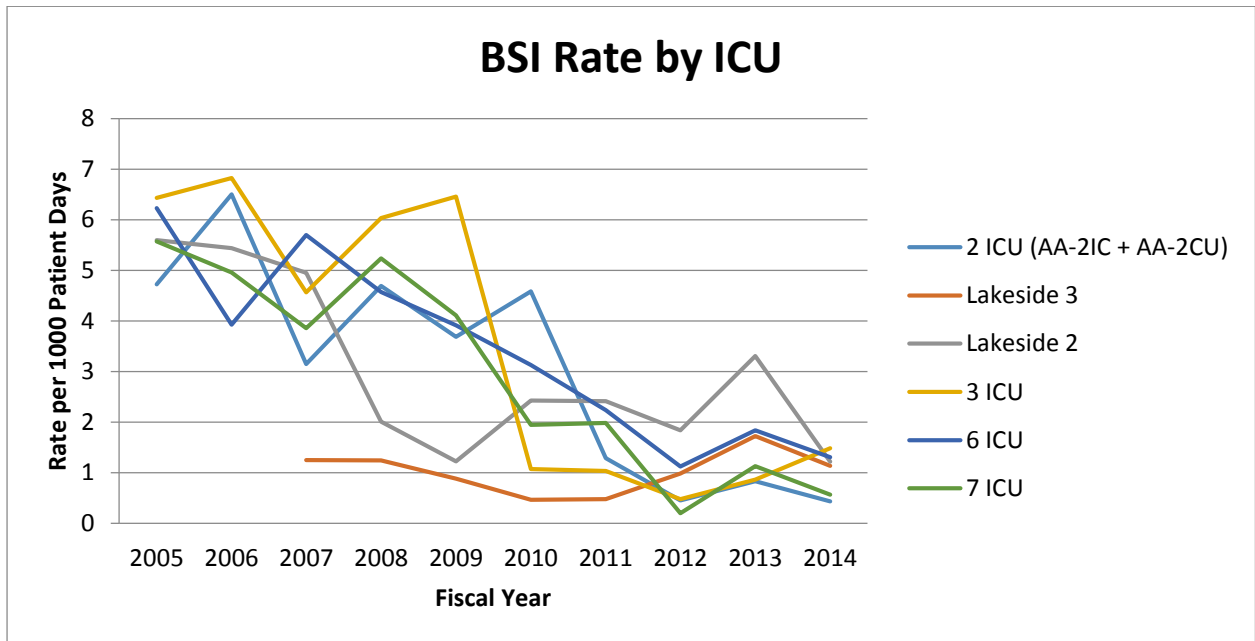| Organism	Fold Reduction	95% CI	95% Lower Bound	P-Value for Trend
Candida	.100	.032 - .163	.045	.0009
Enterococcus	.182	.117 - .243	.130	$\sim 10^{-9}$
Enteric Gram-Negative Bacteria	.137	.081 - .189	.092	$\sim 10^{-7}$
Pseudomonas	.202	.084 - .304	.108	.0002
Staph Aureus	.191	.131 - .247	.143	$\sim 10^{-11}$
Staph not-Aureus	.300	.240 - .354	.252	$\sim 10^{-23}$
Other	.165	.074 - .247	.093	.0001

Figure 3: Total BSI rate stratified by associated ICU location.

Table 4: Total BSI fold reduction stratified by ICU location. Note confidence intervals, lower bounds, and P-values for trends in each location.

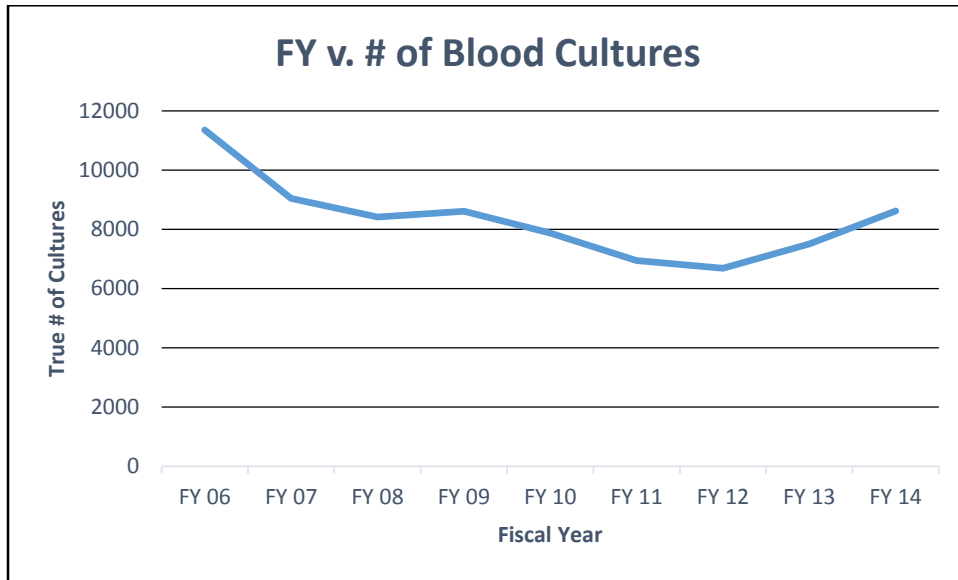| Organism	Fold Reduction	95% CI	95% Lower Bound	P-Value for Trend
2 ICU	.195	.143 - .243	.154	$\sim10^{-15}$
Lakeside 3	-0.026	-.237 to + .148	-.190	.7340
Lakeside 2	.128	.063 - .188	.076	.00001
3 ICU	.208	.146 - .265	.159	$\sim10^{-12}$
6 ICU	.153	.097 - .206	.108	$\sim10^{-9}$
7 ICU	.202	.142 - .258	.154	$\sim10^{-12}$

Figure 4: Comparison of annual number of blood cultures drawn and fiscal year.
Annual total is based on how many cultures were drawn (as opposed to how many bottles were cultured).

SUPPLEMENTARY FIGURES & TABLES

Supplementary Table 1: Comparison of primary and secondary nosocomial BSI rates over time. Rate is given in number of BSIs per 1000 patient days. Bottom row displays total percentage of annual nosocomial BSIs categorized as primary infections.

Type	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
Primary	2.108	2.477	1.577	1.201	0.964	0.520	0.361	0.132	0.345	0.315
Secondary	3.564	2.916	2.329	2.702	2.294	2.014	1.248	0.695	1.225	0.662
% Primary	37.2	45.9	40.4	30.8	29.6	20.5	22.4	16.0	22.0	31.5

Supplementary Table 2: Distribution of causative organisms by fiscal year.
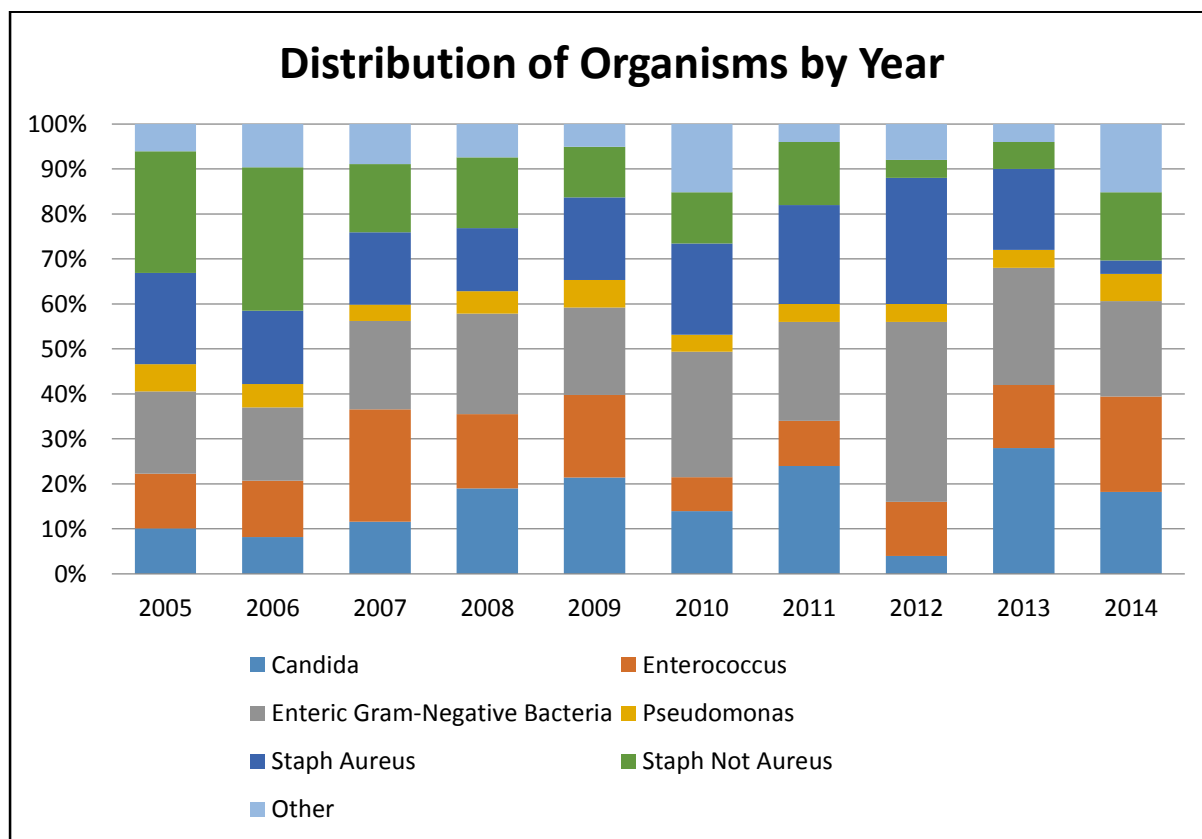
Supplementary Table 3: Total number of BSIs stratified by causative organism. Top half of table displays exact number of infections. Bottom half of table displays annual BSI rate per 1000 patient days for each organism class.

ORGANISM	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
Totals:										
Candida (Yeast)	15	11	13	23	21	11	12	1	14	6
Enterococcus	18	17	28	20	18	6	5	3	7	7
Enteric Gram-Negative Bacteria	27	22	22	27	19	22	11	10	13	7
Pseudomonas	9	7	4	6	6	3	2	1	2	2
Staph Aureus	30	22	18	17	18	16	11	7	9	1
Staph Not Aureus	40	43	17	19	11	9	7	1	3	5
Other	9	13	10	9	5	12	2	2	2	5
Rates:										
Candida (Yeast)	0.575	0.439	0.488	0.767	0.698	0.357	0.394	0.033	0.440	0.189
Enterococcus	0.690	0.679	1.052	0.667	0.598	0.195	0.164	0.099	0.220	0.221
Enteric Gram-Negative Bacteria	1.035	0.879	0.826	0.901	0.632	0.715	0.361	0.331	0.408	0.221
Pseudomonas	0.345	0.280	0.150	0.200	0.199	0.097	0.066	0.033	0.063	0.063
Staph Aureus	1.150	0.879	0.676	0.567	0.598	0.520	0.361	0.232	0.283	0.032
Staph Not Aureus	1.533	1.718	0.638	0.634	0.366	0.292	0.230	0.033	0.094	0.158
Other	0.345	0.519	0.376	0.300	0.166	0.390	0.066	0.066	0.063	0.158

Supplementary Table 4: Percent reduction in total nosocomial BSIs stratified by causative organism. Percent reduction directly compares FY05 and FY14.

Organism Subclass	% Reduction	P-Value
Candida	67.1	.0039
Enterococcus	68.0	.0017
Enteric Gram-Negative Bacteria	78.7	$\sim 10^{-5}$
Pseudomonas	81.7	.0023
Staph Aureus	97.3	$\sim 10^{-11}$
Staph not-Aureus	89.7	$\sim 10^{-10}$
Other	54.3	.0435

Supplementary Figure 1: Average APACHE IV scores by month.