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Inpatient Mortality Among Patients Prescribed Piperacillin/Tazobactam Comparing Intermittent and Extended-Infusion Dosing Strategies

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By

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Background: The emergence of antibiotic resistant infections is a major public health concern, and hospitals are assessing optimal dosing strategies of certain antibiotics to improve their effectiveness. Piperacillin/tazobactam is a commonly used broad-spectrum intravenous antibiotic in hospitalized patients, and has been associated with improved outcomes when using extended infusion (EI) compared to intermittent infusion (II) dosing in smaller studies in specific populations.
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Results: The study included 21,964 patients. Significant variables in the bivariate analysis were EI dosing compared to II, age ≥65 versus <65, Hospital B versus A , ICU versus ward, CCI ≥3 versus CCI <3, male sex versus female, African American versus Caucasian race, and sepsis versus no sepsis. Significant interactions included unit type and sepsis, sepsis and CCI, and CCI and unit type. In multivariate analysis, the odds of inpatient mortality among patients prescribed EI dosing compared to II was 0.70 (95% CI: 0.63, 0.78). Significant predictors included age ≥65 compared to <65, Hospital B versus A, ICU versus ward, and sepsis status, and interactions between unit type and sepsis, unit type and CCI, and sepsis and CCI. Sensitivity analyses did not change the observed OR when restricting the population to patients who had ≥3 days of therapy (OR 0.75, 95% CI: 0.65, 0.86) or patients without sepsis (OR 0.75, 95% CI: 0.65, 0.86). No significant difference was seen in patients who had a positive susceptible blood culture (OR 1.04, 95% CI: 0.56, 1.94).
Discussion: Inpatient mortality outcomes are similar when utilizing both EI and II, and EI may be associated with a lower mortality rate. Using EI as a dosing strategy may help decrease the incidence of antibiotic-resistant infections due to the misuse of antibiotics.

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Literature Review

Overview of Antibiotic Resistance

The emergence of antibiotic resistance (AR) continues to be a major public health concern (1-3). AR limits optimal treatment of infections with current antibiotics, threatening human and animal health worldwide(2, 4). In the United States, over 2 million people are infected with AR organisms annually, resulting in approximately 23,000 deaths, and the incidence is still increasing(5). AR often causes more severe disease, or occurs in patients with other comorbidities, resulting in longer illnesses, prolonged hospital stays, higher costs, and increased mortality(2). AR is estimated to cost the US up to $20 billion per year in excess healthcare costs, and an additional $35 billion due to lost productivity(6). Organizations and governments worldwide have designated combatting AR as a priority in public health(2, 3, 7).

Drivers of Antibiotic Resistance

AR occurs naturally through horizontal gene transfer or spontaneous mutations, but the misuse of antibiotics is accelerating the spread of AR bacteria (4, 8). In addition, many pathogens are becoming resistant to multiple classes of drugs, making them more difficult to treat(9). The major driver of AR is inappropriate antibiotic use in humans and animals (2, 6, 8). Inappropriate prescribing typically occurs from incorrect treatment indication, poor choice of agent, or improper duration of therapy, or in animals, as growth promoters (4, 7). Approximately 30% of antibiotics are estimated to be for patient use, while 70% is estimated for agricultural use(6, 7). However, up to half of antibiotic use across both of these sectors is inappropriate(6, 7).

The overuse of antibiotics is correlated with increases in AR bacterial strains(4). Nationally, the number of antibiotics prescribed for humans has decreased 5% from 2011 to 2014, but has shifted toward more broad spectrum antibiotics (7, 10). In the United States in 2014, approximately 269 million prescriptions were filled from outpatient pharmacies alone, corresponding to five out of every six people in the US receiving an antibiotic prescription per year (7). This estimate does not include hospitals, nursing homes, or the agricultural setting, which would likely increase the estimate markedly. In addition, rates of antibiotic use in hospitals stayed constant from 2006-2012, even though prescribing is estimated to be inappropriate in 30% of cases(4, 7).

Excessive agricultural use of antibiotics is also contributing to AR (2, 4, 6). Animals receive antibiotics and subsequently develop AR bacteria, and when improperly handled, the bacteria can remain on meat and be transmitted to humans (6). Additionally, antibiotics administered to animals are excreted through urine or stool, which is then used as fertilizer for various crops or runs off into the water, which may be used to irrigate fields. This increased antibiotic exposure ultimately results in possible human transmission through the food chain (4, 6).

The lack of antibiotics in the pipeline is a leading concern among medical and public health professionals today(4, 11). Regulatory burdens and economic factors have hindered the development of new antibiotics, which has led to fewer antibiotics available to combat AR organisms(4). This causes these pathogens to be more difficult to treat, resulting in increased spread of AR bacteria(4).

Combating Antibiotic Resistance

Organizations and governments around the world are declaring the fight against AR to be a priority in public health(2, 6, 8, 12, 13). These action plans typically aim to improve surveillance and testing, increase prevention efforts, and accelerate the development of new treatments(2, 13). In the United States, major efforts are being directed towards antibiotic stewardship, which aims to optimize antibiotic prescribing in hospitals. Core elements of stewardship programs include leadership commitment, accountability for program outcomes, drug expertise, action plans, tracking, reporting, and education (14). As of January 1, 2017, antibiotic stewardship programs are required in acute care hospitals (15). A primary focus of these antibiotic stewardship programs is to reduce inappropriate antibiotic prescribing. There are various interventions that programs have used to improve their prescribing practices. One of these practices is antibiotic "time outs". Antibiotics are often started in patients while diagnostic information is gathered(14). A "time out" is reassessing the continued need of antibiotics after all relevant information is obtained. Another intervention commonly used in antibiotic stewardship is the requirement of prior authorization of certain antibiotics from an expert before therapy has begun(14). Additional interventions are changing from intravenous (IV) to oral therapy, dose adjustments, dose optimization, and time-sensitive automatic stop orders for certain prescriptions(14). Antibiotic stewardship programs reduce antibiotic prescribing and cost (14, 16, 17).

Antibiotic Utilization

As part of this global effort to decrease the occurrence of AR infections, dosing antibiotics in alternative ways may increase their efficacy and therefore decrease the incidence of AR infections. β-lactams, commonly used antimicrobial agents including penicillins, cephalosporins, and carbapenems, are effective against gram-positive, gram-negative, and anaerobic organisms (18, 19). β-lactam antibiotics exhibit time-dependent killing; the bactericidal effect is dependent on the time that the free drug concentration (%*fT*) exceeds the minimum inhibitory concentration (MIC)(11). MICs are defined as "the lowest concentration of an antimicrobial that will inhibit the visible growth of a microorganism after overnight incubation(20)." Traditional dosing, referred to as intermittent infusion (II), consists of short infusions, such as 30 minutes, of antibiotics. However, pharmacodynamic studies have shown that extended infusion (EI, ≥3 hours) or continuous infusion (CI, 24 hours) of β-lactam antibiotics should be superior to II due to the time-dependent killing properties of the drug(21).

To determine whether these principles would theoretically be applicable within a healthcare setting, Monte Carlo simulations were conducted, which apply pharmacodynamic principles to clinical practice by mathematically modelling the probability that an antibiotic dosing regimen achieves the drug exposure target associated with maximum antimicrobial effect across various MICs in certain populations(21, 22). These studies have demonstrated that for β-lactam antibiotics, near maximal bactericidal activity is achieved when the %*fT*>MIC is 50% or more(21-23). The outcomes from various Monte Carlo simulations comparing EI and II regimens suggest that EI has the

highest probability of target attainment (50% fT>MIC) for increasing MIC values, due to drug concentrations remaining above the MIC for a longer period of time(22-26).

Based on the extensive pharmacokinetic and pharmacodynamic evidence suggesting EI is optimal to II dosing, the clinical efficacy of this research has been assessed with various β-lactam antibiotics. Piperacillin/tazobactam is a broad-spectrum β-lactam antibiotic that is commonly used for the treatment of hospital-acquired infections(27, 28). Most studies have determined that for piperacillin/tazobactam, EI is superior to II dosing for various clinical outcomes such as 14-day mortality, ventilator days, and hospital length of stay(23, 29-35). Other studies have found no difference between clinical outcomes when comparing the two modes of administration(36-38).

Overall, several studies demonstrated that clinical outcomes using EI was similar to, or potentially better than, using II . Most of these studies were observational quasi-experimental studies, which increases the likelihood that there is an uneven distribution of another parameter within the groups, known as Simpson's paradox(39). Additionally, many had a small sample size, which may have led to low power to detect small differences between the two dosing schemes. Generalizability is also limited because many of these studies were conducted within a certain subset of the hospital population or only on patients who tested positive for a certain pathogen. This demonstrates a need for a large-scale cohort study or additional clinical trials to be conducted to determine if there is a difference in clinical outcomes comparing EI versus II dosing in the overall hospital population.

Manuscript

Abstract

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Discussion: Inpatient mortality outcomes are similar when utilizing both EI and II, and EI may be associated with a lower mortality rate. Using EI as a dosing strategy may help decrease the incidence of antibiotic-resistant infections due to the misuse of antibiotics.

Introduction

Antibiotic resistance (AR) is a growing threat to public health, currently affecting at least 2 million people per year in the United States(1, 11). The Centers for Disease Control and Prevention has classified many AR pathogens as ‘urgent’, ‘serious’ and ‘concerning’ threats(3). In addition to increasing AR, the development of new antibiotics with Gram-negative activity has been slow, which may lead to a shortage in antibiotics that have the ability to treat AR organisms(40). New and innovative strategies to combat this growing concern are a priority in public health(3, 11).

One strategy to address AR is to modify current antibiotic dosing regimens to increase drug efficacy (11, 23). Piperacillin/tazobactam is a broad-spectrum β-lactam antibiotic prescribed for bacterial infections (33). Evidence from Monte Carlo simulations suggests that the optimal dosing of piperacillin/tazobactam to obtain the required MIC is extended-infusion (EI) dosing compared to intermittent infusion (II) (22-24). Optimized free drug concentrations resulting from EI have been shown in sub-populations within healthcare facilities(23, 30-35); however, further research is needed to generalize to more broad hospital populations. The objective of this study was to determine whether EI versus II dosing has an effect on inpatient mortality in the general hospital population.

Methods

Study design and population.

A retrospective cohort study was performed on all patients admitted to two 500-bed academic medical centers who were administered piperacillin/tazobactam between March 28, 2009 and March 27, 2015. II dosing (30 minutes) for piperacillin/tazobactam was used prior to March 28, 2012, but subsequently was switched to EI (240 minutes) based on a recommendation of the antibiotic stewardship team (Table 1). After August 18, 2014, a 4.5g loading dose over 30 minutes was given to all patients, while keeping all subsequent doses as EI.

Patients were included in the study if they were ≥18 years of age and had received at least one dose of intravenous piperacillin/tazobactam during their hospital stay. Only the first encounter during the study period was included. Patients were excluded if their hospital length of stay was 0 or 1 days to address survivor bias and increase validity.

Data

Data was extracted from Emory Healthcare's Clinical Data Warehouse (Microstrategy Inc, Tysons Corner, VA). Demographic data included age, sex, race, hospital (A vs. B), admission and discharge dates, hospital length of stay, date of death, and unit. Age was categorized as <65 and ≥65 years old. Unit type was defined as either 'Intensive Care Unit (ICU)' or 'Ward', based on where the first dose of piperacillin/tazobactam was given. Inpatient mortality, the primary outcome, was defined as patient death occurring within the admission and discharge dates.

Treatment data included date and time of administration to categorize as II or EI, and the administered dosage. A course of therapy was defined as receiving at least three consecutive days of piperacillin/tazobactam therapy, and was determined using dates and times of the administered doses. Additional diagnostic data included International Classification of Diseases, Ninth Revision (ICD9) codes, positive or negative microbiology culture, date and time of culture sample collection, type of organism cultured, organism susceptibility to piperacillin/tazobactam, and the first white blood cell (WBC) count taken during the patient's stay. Sepsis status was determined using ICD9 codes. ICD9 codes were also converted to Charlson comorbidity index (CCI) scores to obtain a measure of survival likelihood, by producing category indicators for specific diagnoses, then calculating an overall index score. CCI scores were then categorized into 2 groups: 0-2, and 3+.

Overall hospital mortality and the number of positive influenza tests in all of Emory Healthcare were also obtained to visualize possible confounders of the association between the intervention and mortality rate.

Data Analysis

Univariate analyses were conducted to determine normality and obtain medians and ranges for continuous variables, and to determine frequencies and proportions of categorical variables. The association between dosing regimen and continuous variables were compared using Student's t-test and the Mann-Whitney test, and categorical variables were compared using the X^2 test or the Fisher's exact test if appropriate.

Bivariate analysis was conducted to determine the relationship between the predictor variables and inpatient mortality using logistic regression.

Model selection was performed to determine the best model for multivariable logistic regression. Confounding variables were identified *a priori* based on clinical knowledge and included age, sex, hospital, unit (ICU vs ward), CCI, race, and presence of sepsis. Interactions were analyzed between some confounders, identified *a priori* based on clinical significance, including: type of therapy, hospital, unit type, CCI, and sepsis. Both two way and three way interactions were considered. Significant interactions were noted, and a full model was created including all significant interaction terms and all possible confounders. However, backwards, forwards, and stepwise assessment determined that three of these interactions were not necessary for inclusion in the final multivariate model. The models that were compared for confounding assessment to determine a final model were: the reduced model obtained from backwards, stepwise, and forward selection (Model 1), a modified version of the reduced model with the inclusion of sex and race (Model 2), a model without interaction (Model 3), and a simple model only using dosing regimen (Model 4). Due to the presence of three interaction terms in Model 1 and the unexpectedly low frequency of ICD9 codes for sepsis suggesting that this was not an accurate measure, a *post hoc* sensitivity analysis excluding patients with sepsis was also conducted to determine if the interactions remained significant to include in the model.

Logistic regression was performed to determine the association between treatment group and inpatient mortality while adjusting for confounding variables. Pre-specified sensitivity analyses were performed for 2 groups: patients who received ≥3 days of

therapy and those with a positive susceptible blood culture. Lastly, a sensitivity analysis among patients who did not have sepsis was conducted, removing the sepsis term and its corresponding interaction terms. For all of these groups, logistic regression was done for the both patients in the full time period and patients admitted after April 28, 2010, because of a severe 2009-2010 influenza season. Odds ratios (OR) and 95% confidence intervals (CI) were obtained for the primary predictor, the confounders, and the interaction terms.

An interrupted time-series analysis was conducted to view rates of inpatient mortality over time, specifically comparing the time periods before and after the change in dosing regimen. Data was aggregated by month. Model diagnostics were initially conducted by determining the model's stationarity. After stationarity was confirmed, an autoregressive model was used to obtain parameter estimates, including slopes, the change in slopes, and the immediate change in inpatient mortality after the intervention was implemented. A time series analysis including only patients admitted after April 28, 2010 was also conducted to account for the severe influenza season.

A *post hoc* power analysis using an unmatched case-control study design was conducted to determine what associations would be visible with the sample size. The power calculation was conducted with a two-sided 95% CI, and used the inpatient mortality proportions found in our analysis: 9.5% among II patients, compared to 7.3% among EI patients, leading to an OR of 0.75. All analyses were two-sided with a significance level of α=.05, and were conducted using SAS version 9.4 (Cary, NC). This study was approved by the Emory University institutional review board.

Results

Univariate and Bivariate Analyses

During the study period, 21,964 patients met the inclusion and exclusion criteria and were included in the final analysis, of whom 50.8% (n=11,168) were in the II group and 49.2% (n=10,796) in the EI group. The overall inpatient mortality was 8.4% (n=1,844). The inpatient mortality proportion among II patients was 9.47%, compared to 7.28% among EI patients. Most patients were male (53.9%), with a median age of 61 (range: 18-107) (Table 2). Most patients received piperacillin/tazobactam on wards (67.4%) and only a minority of patients (24.1%) had billing codes for sepsis (Table 2). The median CCI score was 3; 40.6% of patients had a CCI score of 0, 1, or 2 (Table 2). Comparing EI to II, significant differences included CCI score ($p<.0001$), race ($p<.0001$), and sepsis status ($p<.0001$).

In bivariate logistic regression, the crude ORs of the EI dosing compared to II (OR 0.75, 95% CI: 0.68, 0.83), age ≥65 compared to <65 (OR 1.45, 95% CI: 1.32, 1.60), Hospital B compared to Hospital A (OR 0.80, 95% CI 0.72, 0.88), ICU versus ward (OR 4.00, 95% CI: 3.63, 4.42), CCI ≥3 compared to CCI <3 (OR 1.72, 95% CI: 1.55, 1.90), male sex versus female (OR 0.91, 95% CI: 0.82, 1.00), African American versus Caucasian race (OR 0.83, 95% CI: 0.75, 0.92) and sepsis compared to no sepsis (OR 3.89, 95% CI: 3.53, 4.28) were found to be significant during both the full time period and among patients admitted after April 28, 2010 (Tables 3a and 3b).

Interaction and Confounding Assessment

Significant interactions included two way terms between dosing strategy and unit, dosing strategy and sepsis, hospital and unit type, unit type and CCI, unit type and sepsis, and sepsis and CCI (Table 4a). Three way interaction terms were not significant (Table 4b). A full model, containing all predictors and significant interaction terms was considered, however, this model had 6 interaction terms, including 2 terms that included the primary exposure variable. Due to the complexity of the model and the clinical insignificance of the type-of-therapy variable's interaction with any other predictors, this model was not tested as a final model. In addition, backward, stepwise, and forward selection determined that 3 of these interaction terms and 2 confounders were not necessary for inclusion in the final model; therefore, race, sex, and the interactions between dosing strategy and unit, dosing strategy and sepsis, and hospital and unit type were dropped.

The models tested and the outcomes of each of the models are detailed in Table 5. In Model 1, the OR for mortality using EI was 0.70 (95% CI: 0.63, 0.78) (Table 5). Model 2 was chosen for comparison to determine if the inclusion of sex and race improved the fit of the model, as they were significant in the bivariate analysis. The inclusion of race in any model decreased the sample size by 1,326 due to missing observations. The OR of Model 2 was 0.71 (95% CI: 0.64, 0.79) (Table 5). Model 3 was conducted to determine if the exclusion of the interaction terms and their corresponding variables had a negative impact on the fit of the model and the OR (OR 0.76, 95% CI: 0.69, 0.84) (Table 5). Lastly, a bivariate model was included to determine the effect of the predictors and interactions on the goodness of fit (OR 0.75, 95% CI: 0.68, 0.83)

(Table 5). Model 1 and Model 2 both had a goodness of fit statistic of 0.76. However, model fit was impacted by the exclusion of the interactions and other predictors, as in Model 3, c=.58, and Model 4, c=.54 (Table 5). Therefore, Model 1 was chosen as the final model for the logistic regression, as it maximizes goodness of fit while minimizing the number of predictors. The final model included the outcome of inpatient mortality, and the following predictors: therapy group, age ≥65, hospital, unit type, CCI, and sepsis score, and included interactions between unit type and CCI, unit type and sepsis, and CCI and sepsis. The interaction between unit type and CCI was not significant when excluding patients with sepsis from the analysis.

Logistic Regression

For the study population during the full time period (March 28, 2009 until March 27, 2015), the OR for inpatient mortality for EI was 0.70 (95% CI: 0.63, 0.78), suggesting a protective effect of EI compared to II (Table 6a). In limiting the population to only patients admitted on or after April 28, 2010, the OR increased to 0.83 (95% CI: 0.74, 0.93), but remained significant (Table 6b).

Each of the predictors in the models were significant except for CCI score in both study populations. The odds of inpatient mortality among those who were ≥65 years of age was 1.43 times the odds of inpatient mortality among those who were <65 years of age (95% CI: 1.29, 1.58) (Table 6a). Being admitted to Hospital B was protective against inpatient mortality (OR 0.70, 95% CI: 0.63, 0.78) (Table 6a). These results remained when excluding patients admitted prior to April 28, 2010 (Table 6b).

The three significant interactions in the model were between unit type and CCI, unit type and sepsis, and sepsis and CCI. ORs were obtained for each of the scenarios possible with these predictors, and are detailed in Table 6a. Among patients with a CCI ≥3, the OR varies greatly when stratified by unit type. In the ICU, patients with sepsis had a much higher odds of inpatient mortality (OR 12.23, 95% CI: 8.69, 17.23) than those without sepsis (OR 5.69, 95% CI: 4.71, 6.87) (Table 6b). With sepsis, those who were in the ICU had a higher OR (12.23, 95% CI: 8.69, 17.23) than those who were in the ward unit (OR 2.15, 95% CI: 1.66, 2.79) (Table 6b). Lastly, among those with a CCI ≥ 3, the odds of inpatient mortality was higher among those who have sepsis (OR 2.35, 95% CI: 1.67, 3.30) than those who do not (OR 1.09, 95% CI: 0.90, 1.33) (Table 6b). Results among those admitted on or after April 28, 2010 are consistent with these estimates (Table 6b). The inclusion of the interaction terms showed that the effect of certain variables is different based on the levels of other factors.

Sensitivity Analyses

Of the 21,964 patients, 10,453 (47.6%) had received ≥3 days of therapy, and 661 (3.0%) had a positive blood culture for an organism susceptible to piperacillin/tazobactam. Patients who received ≥3 days of therapy during the full time period had a similar OR for inpatient mortality, (OR 0.75, 95% CI: 0.65, 0.86) (Table 7a). The same predictors that were significant in the full study population were also significant in this population, and odds ratios were similar as well (Table 7a). Among those only admitted on or after April 28, 2010, the OR for patients who received ≥3 days of therapy was 0.90 (95% CI: 0.76, 1.06) (Table 7b). In this analysis, sepsis status was no

longer a significant predictor of inpatient mortality, and the unit type and CCI interaction also lost its significance (Table 7b).

The OR for patients who had a susceptible positive blood culture was null during the full time period (OR 1.04, 95% CI: 0.56, 1.94) and the subset time period (OR: 1.21, 95% CI: 0.60, 2.46) (Tables 8a and 8b). The only significant predictors were hospital and unit type, as well as the CCI and sepsis interaction (Table 8a). In the majority of OR estimates in this analysis, the confidence intervals were extremely wide due to the small sample size (Tables 8a and 8b).

When excluding patients with sepsis and the corresponding interaction terms from the analysis, the OR was 0.75 (95% CI: 0.65, 0.86) (Table 9a). All predictor variables, including age ≥ 65 compared to <65 (OR 1.69, 95% CI: 1.47, 1.94), Hospital B compared to Hospital A (OR 0.70, 95% CI: 0.61, 0.81), ICU versus Ward (OR 4.68, 95% CI: 4.06, 5.38), and CCI ≥3 compared to <3 (OR 0.87, 95% CI 0.75, 0.99) were significant. Among patients admitted on or after April 28, 2010 without sepsis, the OR was no longer significant at 0.87 (95% CI 0.74, 1.02). In this analysis, age ≥ 65 compared to <65 (OR 1.68, 95% CI: 1.44, 1.97), Hospital B compared to Hospital A (OR 0.69, 95% CI: 0.59, 0.82), and ICU versus Ward (OR 4.35, 95% CI: 3.71, 5.12) were significant predictors (Table 9b).

Interrupted Time Series Analysis

Over the full time period, the overall slope of the inpatient mortality rate was trending slightly, but significantly, downwards (slope=-0.08, p<.0001). The slope before the intervention was also decreasing significantly (-.20, p<.0001), while the slope after

the intervention was flat, and was not significant (slope 0.01, p=.85) (Table 10a, Figure 1). When analyzing these time periods using an autoregressive model, the change in slope from pre- to post-intervention was significant (p<.0001), and there was a non-significant increase in mortality rate of 0.93 deaths per 100 patients (p=.34).

Based on visualization of the data, the decreasing slope was due to high mortality observed in the first few months of the study. Because this was during influenza season, we assessed the number of influenza tests performed (Figure 2). There was a higher proportion of tests during the 2009-2010 influenza season than during the rest of the study period, and therefore, patients admitted prior to April 28, 2010 were excluded for a post-hoc sensitivity analysis of the time series. The overall slope for this analysis was trending slightly downward, but no longer significant (slope=-0.02, p=.10) (Figure 3). The pre-intervention slope was -0.06 (p=.30), and the post-intervention slope remained the same (0.01, p=.85) (Table 10b, Figure 3). When analyzing these slopes using an autoregressive model, the change in slopes was not significant (p=.31), and there was an immediate non-significant decrease in the mortality rate of -0.31 deaths per 100 patients (p=.74).

Power Analysis

The post-hoc power analysis demonstrated that we would have >99.9% power to detect the observed OR of 0.75 with the sample size of 21,964 in this study.

Discussion

EI was associated with improved mortality in multivariate analysis using a long follow-up period in two academic medical centers, which is consistent with previous studies on dosing strategies for piperacillin/tazobactam. These findings should be interpreted cautiously, and the main finding is that EI is a safe alternative to II. Based on prior studies, we expected to see no difference in inpatient mortality rates between EI and II dosing. However, when analyzing both the overall time period and a time period limited to patients admitted after April 10, 2010, logistic regression suggested that inpatient mortality was improved with the EI protocol. This remained significant with a very small confidence interval in both the full time period and the post-April 2010 time period to account for the severity of the influenza season at the beginning of the study period.

In contrast, adoption of EI appeared to have a negative effect on inpatient mortality in the time series analysis of the full time period. However, excluding patients from the severe influenza season in 2009 showed no difference in the slopes before and after the switch to EI, which supports our findings in multivariate analysis. Due to the quasi-experimental nature of this analysis, it is difficult to determine what factors were different pre- and post-intervention, though no major new interventions were undertaken during the study period. However, the ability to account for time allows us to see the trend throughout the study period. In this case, as determined in the analysis, EI appeared to have similar inpatient mortality outcomes as II.

The sensitivity analyses including those who received a full course of therapy did not demonstrate a marked difference from the entire hospital population. Though this

may have been partially due to the exclusion criteria that eliminated patients who were in the hospital for ≤1 day, our initial hypothesis was that the population who received a full course of therapy would have a more valid result, as the full effect of the drug would be able to be observed. The lack of a marked difference when comparing the full population to those who received a full course of therapy suggests that the demonstrated relationship between the type of therapy and inpatient mortality may either be unaffected by the duration of therapy, or that the results may be confounded by additional factors that were not controlled for, such as influenza mortality rates or other interventions in the hospitals. The small proportion of patients with sepsis may indicate that ICD9 codes may not fully capture clinical suspicion of sepsis given its much higher clinical frequency, and therefore a sensitivity analysis was used to assess patients without an known ICD9 code for sepsis. In this analysis, EI remained significantly superior to II, and the most important predictors were age, hospital, unit type, and CCI. However, in the analysis excluding patients admitted before April 27, 2010, the dosing regimen and CCI were no longer significant. In assessing only patients with positive susceptible blood cultures, the association between EI and mortality was also not significant. While this may be due to the smaller sample size, it also supports our overall finding that EI is not associated with worse outcomes compared to the standard of care II approach.

Univariate analysis indicated that the presence of sepsis, race, and CCI were significantly associated with the dosing regimen. However, there is no clinical basis to readily explain this observation. Admission to Hospital A versus Hospital B predicted mortality in both the crude bivariate analysis and the logistic regression outcomes, as admission to Hospital B was associated with lower mortality compared to Hospital A.

This suggests that the patient populations may be different in the two hospitals, including unmeasured confounders, and may warrant further investigation.

Unit type, CCI, and sepsis status were all significantly associated with inpatient mortality in the bivariate analysis, and had significant interactions in most of the logistic regression analyses. However, when excluding patients with sepsis from the analysis, the interaction between unit type and CCI was no longer significant. This indicates that the ICD9 codes may not be an accurate representation of the sepsis population.

The adoption of EI initially appeared to have a negative effect on inpatient mortality according to the time series analysis of the full time period, however, these results are likely due to various other occurrences that were present during the II period and not during the EI period. After excluding patients from the severe influenza season in 2009, there were no longer significant changes in slope. Due to the quasi-experimental nature of this analysis, it is difficult to determine what factors were different pre- and post-intervention. However, the ability to account for time allows us to see the trend throughout the study period. In this case, as determined in the analysis, EI appeared to have similar outcomes as II.

The results from this study and prior studies indicate that hospitals should consider implementing EI protocol. Antibiotic stewardship programs have been implemented to improve prescribing practices with the appropriate selection, dosing, route of administration, and duration of antibiotic therapy(11). Another goal of antibiotic stewardship is to decrease the cost of healthcare while maintaining the quality of care(11). The implementation of an EI protocol would assist stewardship programs with both of these goals by decreasing the number of AR infections that are caused by

inappropriate prescribing practices as well as leading to lower costs(16, 17). Implementing EI as a standard protocol could be beneficial for the individual and the public, since antibiotic sensitivity can be preserved in the general population, and the cost of care can decrease while the quality of care is maintained.

To our knowledge, this is the largest-scale cohort study to date assessing EI versus II protocol, as most of the literature was conducted on smaller populations within the hospital setting. Therefore, our study was able to detect smaller associations between the two groups, as was demonstrated in the post-hoc power calculation. The inclusion of the entire hospital population in this study also allows the results to be more generalizable to all groups within a hospital. A third strength of our study is the use of a time series analysis. Time series analyses are able to account for changes in the population over time, leading to stronger results. Finally, we assessed mortality, a more direct and important measure than length of stay or costs.

There are several limitations to this study. First, this study only included two hospitals within one healthcare system and may not be generalizable to all hospitals. Additionally, the two groups that we compared had some significantly different measures at baseline, leading to possible bias if these groups were incomparable. However, the large sample size likely led to statistical significance, though the differences may not be clinically significant. A third limitation is that during the study period, unmeasured population characteristics may have changed, which may have caused bias. However, there were no major interventions undertaken in the hospitals during this time period, reducing the likelihood for bias due to unmeasured population characteristics. In the time series analysis, the outcomes may be attributable to third-party factors that differed

between the intervention periods, leading to Simpson's paradox. One factor that could possibly account for the results is the seasonality of influenza, with regard to both prevalence and mortality. We attempted to account for this by excluding patients admitted prior to April 27, 2010 to reduce bias from the severe flu season, but additional adjustment for seasonality was beyond the scope of this thesis. Finally, we relied on administrative data for CCI and sepsis, which may have underestimated the prevalence of these confounders.

In conclusion, EI leads to similar inpatient mortality outcomes as II, and may have improved outcomes in the overall hospital population. Consistent with prior smaller studies, our study suggests that adoption of EI dosing is safe in hospitals. Further large-scale cohort, prospective, and experimental studies would validate our findings and lead to increased adoption of an EI protocol.

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Tables

Table 1. Standard dosing regimens for piperacillin/tazobactam used at two academic medical centers during the study period. Intermittent infusion (II) dosing used 30 minute doses and was used from the start of the study until March 28, 2012. Extended infusion (EI) was used after this date. A 4.5 g loading dose over 30 minutes was given to all patients after August 18, 2014.

Creatinine clearance (mL/hour)	II Dosing	EI Dosing
>50	4.5 g q6h	4.5 g q8
30-50	3.375 g q8h	4.5 g q12
10-30	3.375 g q12h	4.5 g q24
<10	2.25 g q 12h	4.5 g q24

Table 2. Comparison of study population characteristics for patients who received piperacillin/tazobactam stratified by dosing strategy.

Characteristic	Full Population	Intermittent Infusion	Extended Infusion	P-Value
	N (%)	N (%)	N (%)	
Age				
<65 years	13,032 (59.3)	6,680 (30.4)	6,352 (28.9)	-
≥65 years	8,932 (40.7)	4,488 (20.4)	4,444 (20.2)	0.14
Sex				
Male	11,829 (53.9)	5,957 (27.1)	5,872 (26.7)	-
Female	10,137 (46.2)	5,211 (23.7)	4,926 (22.4)	0.12
Race				
African American	10,539 (48.0)	5,366 (24.4)	5,173 (23.6)	-
Caucasian	9,735 (44.3)	4,956 (22.6)	4,779 (21.8)	-
Other	364 (1.7)	112 (3.9)	252 (3.8)	<.0001
Hospital LOS, median days (IQR)	9 (11)	9 (11)	9 (11)	0.75
Sepsis	5,304 (24.1)	2,515 (11.5)	2,789 (12.7)	<0.0001
Unit				
Ward	14,801 (67.4)	7,574 (34.5)	7,227 (32.9)	-
Intensive Care Unit	7,165 (32.6)	3,594 (16.4)	3,571 (16.3)	0.16
Hospital				
A	12,931 (58.9)	6,590 (30.0)	6,341 (28.9)	-
B	9,035 (41.1)	4,578 (20.8)	4,457 (20.3)	0.67
Charlson Comorbidity Index				
0, 1, 2	8,909 (40.6)	4,748 (21.6)	4,161 (18.9)	-
3+	13,055 (59.4)	6,420 (29.23)	6,635 (30.21)	<.0001
First WBC count, median (IQR)	10 (7.5)	10 (7.4)	10 (7.5)	0.19
Positive Microbiology	3,761 (17.1)	1,952 (8.9)	1,809 (8.24)	0.15

LOS length of stay; IQR interquartile range; WBC white blood cell

Table 3a. Crude relationship between predictor variables and inpatient mortality, March 28, 2009 to March 27, 2015.

Characteristic	Estimate	Pr>ChiSq	Odds Ratio	Wald 95% Confidence Limits
Type of Therapy				
Extended Infusion	-0.29	<.0001	0.75	0.68, 0.83
Intermittent Infusion	--	--	1	--
Age				
≥65	0.37	<.0001	1.45	1.32, 1.60
<65	--	--	1	--
Sex				
Male	-0.05	.05	0.91	0.82, 1.00
Female	--	--	1	--
Hospital				
B	-0.23	<.0001	0.80	0.72, 0.88
A	--	--	1	--
Unit Type				
ICU	1.39	<.0001	4.00	3.63, 4.42
Ward	--	--	1	--
Charlson Comorbidity Index				
3+	0.54	<.0001	1.72	1.55, 1.90
0-2	--	--	1	--
Sepsis				
Present	1.36	<.0001	3.89	3.53, 4.28
Absent	--	--	1	--
Race				
African American	-0.18	<.001	0.83	0.75, 0.92
Other	-0.35	.11	0.71	0.46, 1.09
Caucasian	--	--	1	--

ICU intensive care unit

Table 3b. Crude relationship between predictor variables and inpatient mortality, April 28, 2009 to March 27, 2015.

Characteristic	Estimate	Pr>ChiSq	Odds Ratio	Wald 95% Confidence Limits
Type of Therapy				
Extended Infusion	-0.12	.04	0.89	0.80, 0.99
Intermittent Infusion	--	--	1	--
Age				
≥65	0.36	<0.0001	1.44	1.29, 1.61
<65	--	--	1	--
Sex				
Male	0.12	.04	1.12	1.01, 1.25
Female	--	--	1	--
Hospital				
B	-0.26	<0.0001	0.77	0.69, 0.87
A	--	--	1	--
Unit Type				
ICU	1.32	<0.0001	3.74	3.34, 4.19
Ward	--	--	1	--
Charlson Comorbidity Index				
3+	0.55	<.0001	1.73	1.53, 1.95
0-2	--	--	1	--
Sepsis				
Present	1.32	<0.0001	3.76	3.36, 4.20
Absent	--	--	1	--
Race				
African American	-0.17	<.01	0.84	0.75, 0.95
Other	-0.18	.42	0.84	0.54, 1.29
Caucasian	--	--	1	--

ICU Intensive Care Unit

Table 4a. Interaction between predictor variables and their association with inpatient mortality, March 28, 2009 to March 27, 2015.

	Variable X		Variable Y		Variable X*Variable Y	
	Odds Ratio	P Value	Odds Ratio	P Value	Odds Ratio	P Value
Type of Therapy *Hospital	0.75	<.0001	0.80	<.01	0.60	.96
Type of Therapy * Unit Type	0.86	.03	4.48	<.0001	3.79	.02
Type of Therapy * CCI	0.74	<.0001	0.75	<.0001	0.56	.68
Type of Therapy * Sepsis	0.78	<.01	4.35	<.0001	3.38	.03
Hospital *CCI	0.69	<.0001	4.02	<.0001	2.76	.54
Hospital *Unit Type	0.75	<.0001	0.81	<.0001	0.61	<.01
Hospital * Sepsis	0.76	<.01	3.67	<.0001	2.79	.16
Unit Type * CCI	5.16	<.0001	1.98	<.0001	10.24	<.001
Unit Type * Sepsis	4.58	<.0001	4.74	<.0001	21.75	<.0001
Sepsis * CCI	1.04	<.0001	2.89	0.21	3.01	<.0001

CCI Charlson Comorbidity Index

Table 4b. Test for significance of three-way interaction between unit type, Charlson Comorbidity Index (CCI), and sepsis status, March 28, 2009 to March 27, 2015.

	Odds Ratio	P Value
Unit Type, CCI, and Sepsis Status Interaction	--	0.09
ICU, CCI=0-2, No Sepsis	4.62	<.0001
Ward, CCI=3+, No Sepsis	0.99	.84
Ward, CCI=0-2, Sepsis	3.20	<.0001
ICU, CCI=3+, No Sepsis	4.57	<.0001
ICU, CCI=0-2, Sepsis	14.81	.07
Ward, CCI=3+, Sepsis	3.17	<.01
ICU, CCI=3+, Sepsis	14.65	.09

ICU Intensive Care Unit; CCI Charlson Morbidity Index

Table 5. Confounding and interaction assessment of possible models.

Model	OR	CI	Difference	c-statistic
Model 1[1]	0.70	0.63, 0.78	ref	0.76
Model 2[2]	0.71	0.64, 0.79	1.4%	0.76
Model 3[3]	0.76	0.69, 0.84	8.6%	0.58
Model 4[4]	0.75	0.68, 0.83	7.1%	0.54

[1]Model 1 predictors: Type of therapy, age, hospital, unit type, CCI, sepsis status, and interactions between unit type and CCI, unit type and sepsis, and CCI and sepsis
[2]Model 2 predictors: Type of therapy, age, race, sex, hospital, unit type, CCI, sepsis status, and interactions between unit type and CCI, unit type and sepsis, and CCI and sepsis
[3]Model 3 predictors: Type of therapy, age, race, sex
[4]Model 4 predictors: Type of therapy

Table 6a. Parameter estimates obtained from multivariable logistic regression assessing the effect of predictors on inpatient mortality, March 28, 2009 to March 27, 2015.

Parameter	Estimate	Pr>ChiSq	Odds Ratio	Wald 95% Confidence Limits
Type of Therapy				
Extended Infusion	-0.36	<.0001	0.70	0.63, 0.78
Intermittent Infusion	--	--	1	--
Age				
≥65	.36	<.0001	1.43	1.29, 1.58
<65	--	--	1	--
Hospital				
B	-.35	<.0001	0.70	0.63, 0.78
A	--	--	1	--
Unit Type	1.74	<.0001	--	--
CCI	0.09	.39	--	--
Sepsis	0.77	<.0001	--	--
Unit Type and CCI Interaction	-0.37	<.01	--	--
ICU, CCI=0-2	--	--	5.69	4.71, 6.87
Ward, CCI=3+	--	--	1.09	0.90, 1.33
ICU, CCI=3+	--	--	6.21	4.44, 8.68
Unit Type and Sepsis Interaction	-0.52	<.0001		
ICU, No Sepsis	--	--	5.69	4.71, 6.87
Ward, Sepsis	--	--	2.15	1.66, 2.79
ICU, Sepsis	--	--	12.23	8.69, 17.23
CCI and Sepsis Interaction	0.93	<.0001		
Sepsis, CCI=0-2	--	--	2.15	1.66, 2.79
No Sepsis, CCI=3+	--	--	1.09	0.90, 1.33
Sepsis, CCI=3+	--	--	2.35	1.67, 3.30

CCI Charlson Comorbidity Index; ICU Intensive Care Unit

Table 6b. Parameter estimates obtained from multivariable logistic regression assessing the effect of predictors on inpatient mortality, April 28, 2010 to March 27, 2015.

Parameter	Estimate	Pr>ChiSq	Odds Ratio	Wald 95% Confidence Limits
Type of Therapy				
Extended Infusion	-0.19	<.01	0.83	0.74, 0.93
Intermittent Infusion	--	--	1	--
Age				
≥65	0.35	<.0001	1.42	1.27, 1.60
<65	--	--	1	--
Hospital				
B	-0.38	<.0001	0.69	0.61, 0.77
A	--	--	1	--
Unit Type	1.66	<.0001	--	--
CCI	0.11	.36	--	--
Sepsis	0.75	<.0001	--	--
Unit Type and CCI Interaction	-0.35	.01		
ICU, CCI=0-2	--	--	5.26	4.23, 6.54
Ward, CCI=3+	--	--	1.11	0.89, 1.39
ICU, CCI=3+	--		5.84	3.98, 8.57
Unit Type and Sepsis Interaction	-0.49	<.001		
ICU, No Sepsis	--	--	5.26	4.23, 6.54
Ward, Sepsis	--	--	2.11	1.57, 2.83
ICU, Sepsis	--	--	11.09	7.52, 16.38
CCI and Sepsis Interaction	0.88	<.0001		
Sepsis, CCI=0-2	--	--	2.11	1.57, 2.83
No Sepsis, CCI=3+	--	--	1.11	0.89, 1.39
Sepsis, CCI=3+	--	--	2.34	1.59, 3.46

CCI Charlson Comorbidity Index; ICU Intensive Care Unit

Table 7a. Parameter estimates obtained from multivariable logistic regression assessing the effect of predictors on inpatient mortality among patients who had at least three days of therapy, March 28, 2009 to March 27, 2015.

Parameter	Estimate	Pr>ChiSq	Odds Ratio	Wald 95% Confidence Limits
Type of Therapy				
Extended Infusion	-0.29	<.0001	0.75	0.65, 0.86
Intermittent Infusion	--	--	1	--
Age				
≥65	0.19	.01	1.20	1.04, 1.39
<65	--	--	1	--
Hospital				
B	-0.24	<.01	0.78	0.68, 0.91
A	--	--	1	--
Unit Type	1.57	<.0001	--	--
CCI	0.02	.92	--	--
Sepsis	0.42	.05	--	--
Unit Type and CCI Interaction	-0.39	.03		
ICU, CCI=0-2	--	--	4.78	3.61, 6.34
Ward, CCI=3+	--	--	1.02	0.75, 1.37
ICU, CCI=3+	--	--	4.86	2.93, 8.05
Unit Type and Sepsis Interaction	-0.50	<.01		
ICU, No Sepsis	--	--	4.78	3.61, 6.34
Ward, Sepsis	--	--	1.53	1.00, 2.32
ICU, Sepsis	--	--	7.30	4.31, 12.38
CCI and Sepsis Interaction	1.29	<.0001		
Sepsis, CCI=0-2	--	--	1.53	1.00, 2.32
No Sepsis, CCI=3+	--	--	1.02	0.75, 1.37
Sepsis, CCI=3+	--	--	1.55	0.92, 2.62

CCI Charlson Comorbidity Index; ICU Intensive Care Unit

Table 7b. Parameter estimates obtained from multivariable logistic regression assessing the effect of predictors on inpatient mortality among patients who had at least three days of therapy, April 28, 2010 to March 27, 2015.

Parameter	Estimate	Pr>ChiSq	Odds Ratio	Wald 95% Confidence Limits
Type of Therapy				
Extended Infusion	-0.11	.20	0.90	0.76, 1.06
Intermittent Infusion	--	--	1	--
Age				
≥65	0.21	.01	1.24	1.05, 1.46
<65	--	--	1	--
Hospital				
B	-0.24	<.01	0.78	0.66, 0.93
A	--	--	1	--
Unit Type	1.48	<.01	--	--
CCI	-0.05	.76	--	--
Sepsis	.42	.09	--	--
Unit Type and CCI Interaction	-0.25	.25		
ICU, CCI=0-2	--	--	4.40	3.17, 6.10
Ward, CCI=3+	--	--	0.95	0.67, 1.34
ICU, CCI=3+	--	--	4.17	2.33, 7.46
Unit Type and Sepsis Interaction	-0.57	<.01		
ICU, No Sepsis	--	--	4.40	3.17, 6.10
Ward, Sepsis	--	--	1.52	0.94, 2.47
ICU, Sepsis	--	--	6.70	3.64, 12.33
CCI and Sepsis Interaction	1.25	<.0001		
Sepsis, CCI=0-2	--	--	1.52	0.94, 2.47
No Sepsis, CCI=3+	--	--	0.95	0.67, 1.34
Sepsis, CCI=3+	--	--	1.44	0.79, 2.65

CCI Charlson Comorbidity Index; ICU Intensive Care Unit

Table 8a. Parameter estimates obtained from multivariable logistic regression assessing the effect of predictors on inpatient mortality among patients who had a positive susceptible blood culture, March 28, 2010 to March 27, 2015.

Parameter	Estimate	Pr>ChiSq	Odds Ratio	Wald 95% Confidence Limits
Type of Therapy				
Extended Infusion	0.04	.90	1.04	0.56, 1.94
Intermittent Infusion	--	--	1	--
Age				
≥65	0.05	.86	1.06	0.58, 1.91
<65	--	--	1	--
Hospital				
B	-0.70	.04	0.50	0.26, 0.96
A	--	--	1	--
Unit Type	2.36	<.01	--	--
CCI	-1.30	.19	--	--
Sepsis	-0.28	.78	--	--
Unit Type and CCI Interaction	-0.27	.79		
ICU, CCI=0-2	--	--	10.56	2.87, 38.80
Ward, CCI=3+	--	--	0.27	0.04, 1.92
ICU, CCI=3+	--	--	2.88	0.22, 38.63
Unit Type and Sepsis Interaction	-0.79	.45		
ICU, No Sepsis	--	--	10.56	2.87, 38.80
Ward, Sepsis	--	--	0.76	0.11, 5.35
ICU, Sepsis	--	--	7.99	0.60, 107.30
CCI and Sepsis Interaction	2.89	<.01		
Sepsis, CCI=0-2	--	--	0.76	0.11, 5.35
No Sepsis, CCI=3+	--	--	0.27	0.04, 1.92
Sepsis, CCI=3+	--	--	0.21	0.02, 2.50

CCI Charlson Comorbidity Index; ICU Intensive Care Unit

Table 8b. Parameter estimates obtained from multivariable logistic regression assessing the effect of predictors on inpatient mortality among patients who had a positive susceptible blood culture, April 28, 2010 to March 27, 2015.

Parameter	Estimate	Pr>ChiSq	Odds Ratio	Wald 95% Confidence Limits
Type of Therapy				
Extended Infusion	0.19	.60	1.21	0.60, 2.46
Intermittent Infusion	--	--	1	--
Age				
≥65	0.23	.52	1.26	0.62, 2.57
<65	--	--	1	--
Hospital				
B	-0.63	.11	0.53	0.25, 1.15
A	--	--	1	--
Unit Type	2.27	<.01	--	--
CCI	-3.16	.05	--	--
Sepsis	0.09	.93	--	--
Unit Type and CCI Interaction	1.35	.33		
ICU, CCI=0-2	--	--	9.66	2.23, 41.88
Ward, CCI=3+	--	--	0.04	0.00, 1.01
ICU, CCI=3+	--	--	0.41	0.01, 12.72
Unit Type and Sepsis Interaction	-2.07	.15		
ICU, No Sepsis	--	--	9.66	2.23, 41.88
Ward, Sepsis	--	--	1.10	0.13, 9.00
ICU, Sepsis	--	--	10.60	0.54, 209.10
CCI and Sepsis Interaction	3.94	.01		
Sepsis, CCI=0-2	--	--	1.10	0.13, 9.00
No Sepsis, CCI=3+	--	--	0.04	0.00, 1.01
Sepsis, CCI=3+	--	--	0.05	0.00, 1.15

CCI Charlson Comorbidity Index; ICU Intensive Care Unit

Table 9a. Parameter estimates obtained from multivariable logistic regression assessing the effect of predictors on inpatient mortality among patients without sepsis, March 28, 2010 to March 27, 2015.

Parameter	Estimate	Pr>ChiSq	Odds Ratio	Wald 95% Confidence Limits
Type of Therapy				
Extended Infusion	-0.29	<.0001	0.75	0.65, 0.86
Intermittent Infusion	--	--	1	--
Age				
≥65	0.53	<.0001	1.69	1.47, 1.94
<65	--	--	1	--
Hospital				
B	-0.36	<.0001	0.70	0.61, 0.81
A	--	--	1	--
Unit Type				
ICU	1.54	<.0001	4.68	4.06, 5.38
Ward	--	--	1	--
CCI				
3+	-0.14	.04	0.87	0.75, 0.99
0-2	--	--	1	--

CCI Charlson Comorbidity Index

Table 9b. Parameter estimates obtained from multivariable logistic regression assessing the effect of predictors on inpatient mortality among patients without sepsis, April 28, 2010 to March 27, 2015.

Parameter	Estimate	Pr>ChiSq	Odds Ratio	Wald 95% Confidence Limits
Type of Therapy				
Extended Infusion	-0.14	.09	0.87	0.74, 1.02
Intermittent Infusion	--	--	1	--
Age				
≥65	0.52	<.0001	1.68	1.44, 1.97
<65	--	--	1	--
Hospital				
B	-0.37	<.0001	0.69	0.59, 0.82
A	--	--	1	--
Unit Type				
ICU	1.47	<.0001	4.35	3.71, 5.12
Ward	--	--	1	--
CCI				
3+	-0.10	.20	0.90	0.77, 1.06
0-2	--	--	1	--

ICU Intensive Care Unit; CCI Charlson Comorbidity Index

Table 10a. Time series analysis autoregressive model parameter estimates, March 28, 2009 to March 17, 2015.

Parameter	Estimate	t Value	Pr>t
Intermittent Infusion Slope	-0.20	-6.04	<.0001
Change in Rate Immediately After Intervention	0.93	0.96	.34
Change in Slope from Pre to Post Intervention	0.21	4.39	<.0001

Table 10b. Time series analysis autoregressive model parameter estimates, April 28, 2009 to March 17, 2015.

Parameter	Estimate	t Value	Pr>t
Intermittent Infusion Slope	-0.06	-1.04	.30
Change in Rate Immediately After Intervention	-0.31	-0.34	.74
Change in Slope from Pre to Post Intervention	0.06	1.02	.31

Figures

Figure 1. Rate of inpatient mortality before and after dosing regimen change in general hospital population, March 28, 2009 to April 27, 2015.

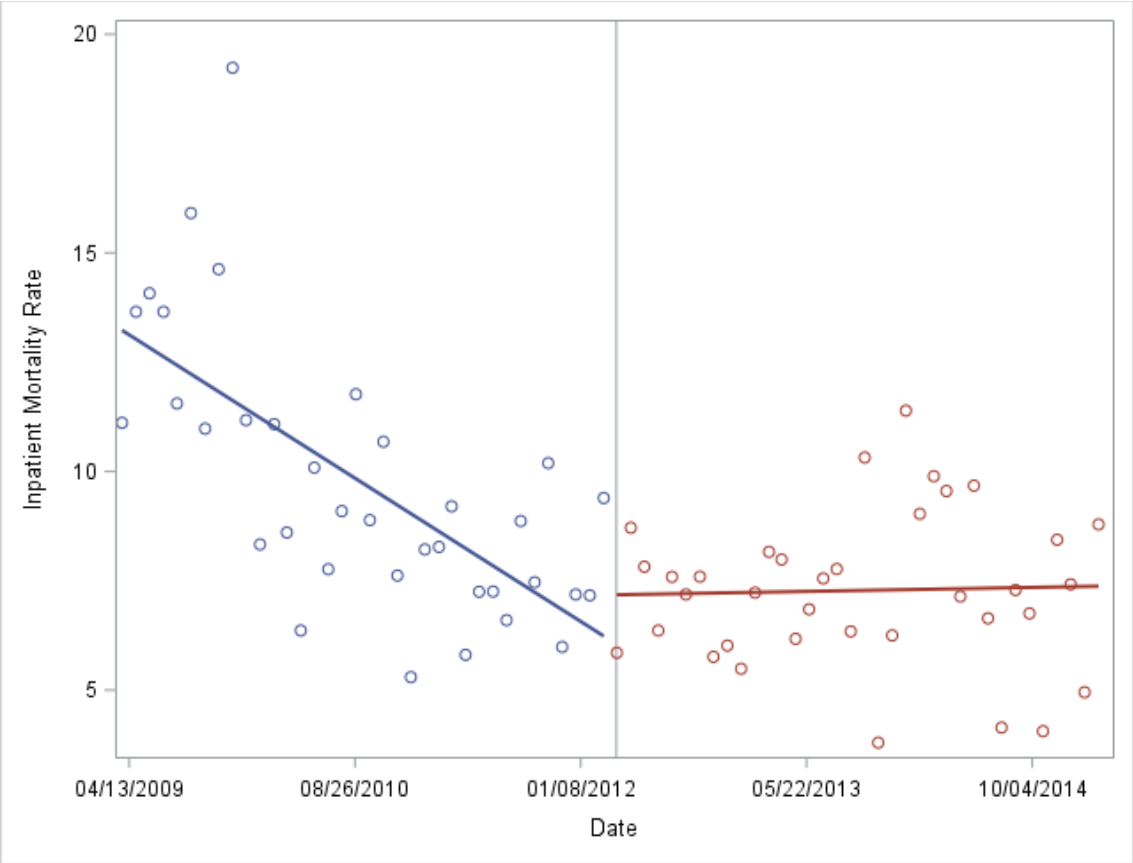


Figure 2. Number of positive influenza tests from March 2009 until March 2015.

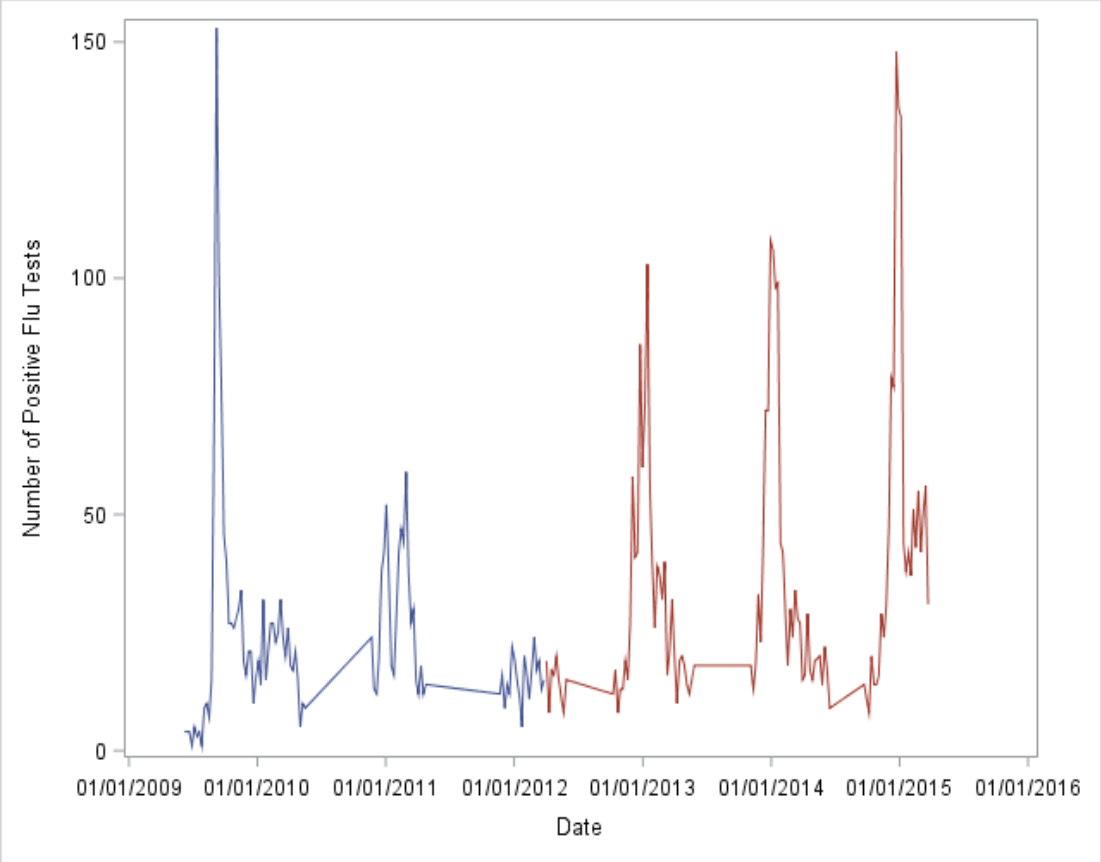
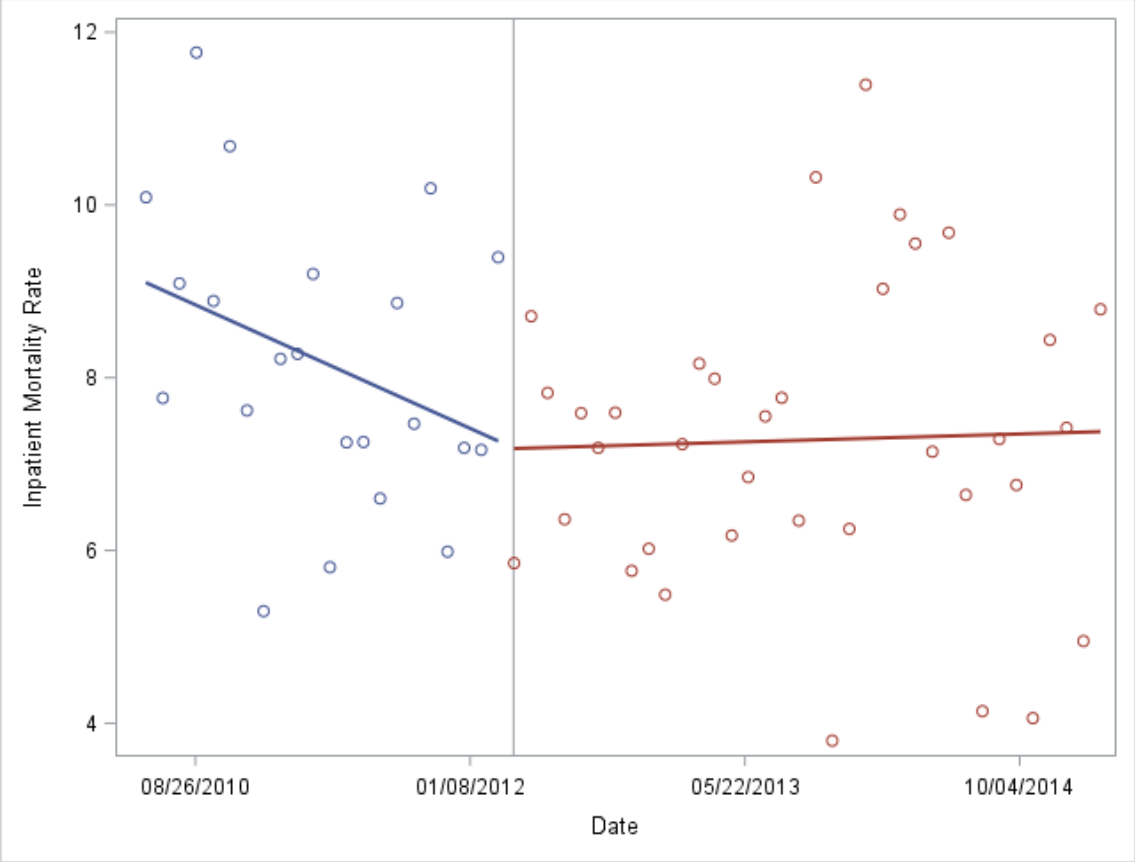


Figure 3. Rate of inpatient mortality before and after dosing regimen change in general hospital population, April 28, 2010 to April 27, 2015.



Public Health Importance and Future Directions

The primary importance of this study is to add to the existing literature, with the ultimate goal of determining whether EI will improve patient outcomes compared to II. The existing literature, as well as our study, has largely determined that EI is no worse than II, and in some cases may improve patient outcomes. Our analysis, based on a large, more generalizable cohort strengthens the case for EI compared to II dosing, ultimately driving additional hospitals to adopt an EI dosing strategy for piperacillin/tazobactam.

In the future, additional large-scale cohort studies can support an EI dosing strategy for piperacillin/tazobactam. In addition, this research may inform future research on the dosing strategies of additional antibiotics.