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Controlling for Severity of Illness in Infectious Disease Outcome Studies:

Impact of Measurement at Different Time Points

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Abstract

Background—Severity of illness is an important confounder in infectious disease-outcome studies. However, it is unclear whether the time at which severity of illness is measured is important.

Methods—We used a retrospective cohort of adult patients with 328 episodes of Gram-negative bacteremia to assess the impact of the time of measurement of severity of illness on the association between empiric antimicrobial therapy and in-hospital mortality. Using a modified Acute Physiology Score (APS), severity of illness was measured at: 1) hospital admission and 2) 24 hours prior to collection of the first positive blood culture. Multivariate logistic regression was used to estimate the impact of adjusting for APS on the relationship between empiric therapy (the exposure) and in-hospital mortality (the outcome).

Results—The mean [standard deviation] APS increased during the hospital stay [19.2 (11.6) vs. 24.2 (13.6); $p < 0.01$]. When examining the association between empiric therapy and in-hospital mortality, there was a trend towards a decreased impact of appropriate therapy on in-hospital mortality controlling for APS. The unadjusted odds ratio (OR) for the association between appropriate therapy and in-hospital mortality was 0.83 (95% CI: 0.51-1.34). After controlling for APS at admission, this was attenuated (OR 0.94; 95% CI 0.57-1.55) and when change in APS was also included in the model the association was further attenuated (OR 0.99; 95% CI 0.58-1.69).

Conclusions—The magnitude of the association between appropriate antimicrobial therapy and in-hospital mortality among patients with Gram-negative bacteremia was sensitive to the timing of adjustment for severity of illness.

Underlying severity of illness is often an important confounder when studying outcomes of infectious diseases. Yet, it is not clear at which time point severity of illness should be measured in the course of the patient's infectious process. To illustrate this point, consider the example of a study which attempts to quantify the importance of appropriate antimicrobial therapy on mortality among patients with a bloodstream infection. In this example, patients with more severe illness at baseline (i.e. sicker patients) may be more likely to receive broad spectrum

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antimicrobial therapy and thus more likely to receive appropriate therapy. Alternatively, these patients may be more likely to be colonized with a resistant bacterium and thus less likely to receive appropriate therapy. Furthermore, patients with a higher underlying severity of illness may be more likely to die than those with a lower severity of illness. Therefore, severity of illness is an important confounder in that it may be associated with both the exposure (appropriate therapy) and the outcome (mortality) and thus should be controlled for when assessing the impact of appropriate therapy on mortality. However, depending on the time at which severity of illness is measured it may also be an intermediate variable in the causal pathway between exposure and outcome, and therefore not a confounder and thus should not be controlled for.[1,2] We believe that severity of illness is an important confounder in studies of infectious disease outcomes and that it should be measured as close to the onset of infection as possible in order to represent a true baseline severity of illness; but should not be measured after the exposure (in this case, empiric therapy) when it would be an intermediate variable in the causal pathway.

To our knowledge only two published studies have addressed the importance of measuring severity of illness at different time points and what quantitative impact measurement at a sub-optimal time point has on the results.[3,4] Both studies were limited by a small sample size. In addition, one study included all positive clinical cultures instead of focusing on infections at a particular site and mortality may have varied widely among this group based on site of infection.

In this study, we aimed to 1) compare severity of illness scores measured at admission and again 24 hours prior to the first positive blood culture to determine if the two scores were different and 2) assess whether differences in severity of illness measured at these two time points impact the effect of appropriate empiric antimicrobial therapy on in-hospital mortality among patients with *E. coli*, *Klebsiella* or *P. aeruginosa* blood stream infection.

METHODS

This study was performed at the University of Maryland Medical Center (UMMC), a 656-bed tertiary-care hospital located in Baltimore, Maryland. The UMMC Institutional Review Board approved this study. All adult patients with *E. coli*, *Klebsiella* or *P. aeruginosa* bacteria identified from a blood culture obtained at least 24 hours after admission to the hospital and during the time period of January 2001 and June 2005 were eligible for inclusion. Bacteremia caused by these three pathogens was chosen because these are the three most common causes of Gram-negative bacteremia in our institution. Patients were identified using the UMMC central data repository, a relational database that contains clinical and administrative data. Patients with multiple episodes of bacteremia during the study period were allowed to enter the cohort multiple times only if the episodes of bacteremia occurred during separate hospital admissions. Patients with a polymicrobial bacteremia were included; however, patients with positive blood cultures in which two or more of the organisms isolated included *E. coli*, *Klebsiella* and *Pseudomonas* species were counted only once.

Severity of illness was assessed by calculating a modified Acute Physiology Score (APS) based on the Acute Physiology and Chronic Health Evaluation (APACHE) III score, as done in other studies[5-7]. Severity of illness was measured at two time points: 1) at admission to the hospital and 2) 24 hours before the positive blood culture was obtained. This latter time point was used as a proxy to ensure severity of illness was measured before the receipt of empiric antimicrobial therapy and thus not in the causal pathway, i.e. not an intermediate variable. The components used to calculate the modified APS at admission were collected as close to the admission date/time as possible and were always within 24 hours of admission. The components used to calculate the modified APS at the second time period (24 hours before collection of the positive

blood culture) were collected prior to and as close to the culture collection date/time as possible (no value extended beyond 72 hours prior to culture collection date/time). The APACHE III score was designed for use among intensive care unit (ICU) patients. Since this study included participants who may not have been in an ICU at the time of bacteremia, we modified the score by excluding variables that were not applicable to our study population (e.g. pulmonary arterial gradient, urine output, neurologic status and acid-base data) as has been previously described [5-7]. In addition, if a patient had a missing value for any component, the modified APS was calculated as if that missing value was within the normal range.

Empiric antimicrobial therapy was defined as the receipt of an antimicrobial agent between 8 hours before and 24 hours after the first positive blood culture was drawn, as has been done in other studies[5,8,9]. We chose this early time period in attempt to exclude scenarios where preliminary microbiologic data were available (e.g. knowledge of whether the organism was a lactose-fermenter) since this may have influenced antimicrobial choice. Empiric therapy was considered appropriate if it included antimicrobials to which the specific isolate displayed *in vitro* susceptibility.

The UMMC central data repository was used to collect administrative, pharmacy, laboratory and outcome data. The data contained within the repository were validated against medical records for this and previous research studies and have positive and negative predictive values of greater than 98% [5,10]. Variables electronically collected included demographics, date/time the blood culture was obtained, time at risk (i.e. time from hospital admission to collection of the first positive blood culture), laboratory data included in the modified APS and patient disposition (i.e. whether the patient died in the hospital or was discharged). Patient vital signs, which were used to calculate the modified APS, were collected by review of patient medical records which was performed by two study investigators. All blood cultures and antimicrobial susceptibility tests were performed by the UMMC clinical microbiology laboratory as part of the patients' standard care and according to the recommendations of the Clinical and Laboratory Standards Institute[11].

All data were analyzed using SAS software version 9.1 (SAS Institute, Cary, NC). The modified APS was calculated systematically for all bacteremia episodes using a formula created in SAS. The paired Student's t-test was used to compare modified APS calculated at admission and 24 hours before culture collection within the same patient. The Student's t-test was used to compare the modified APS among survivors and non-survivors. Multivariate logistic regression was used to calculate odds ratios (OR) and 95% confidence intervals (CI) to estimate the impact of controlling for severity of illness on the association between receipt of appropriate empiric antimicrobial therapy and in-hospital mortality. The following associations were evaluated: Model 1) the effect of appropriate antimicrobial therapy on in-hospital mortality; Model 2) the effect of appropriate antimicrobial therapy on in-hospital mortality when controlling for severity of illness at admission; Model 3) the effect of appropriate antimicrobial therapy on in-hospital mortality when controlling for severity of illness at the second time point; and Model 4) the effect of appropriate antimicrobials on in-hospital mortality when controlling for severity of illness at admission and the change in severity of illness from admission to the second time point.

RESULTS

During the study period, 328 episodes of *E. coli*, *Klebsiella* or *P. aeruginosa* bacteremia were included. Among these, 98 (30%) were due to *E. coli*, 128 (39%) *Klebsiella* species (105 *K. pneumoniae* and 23 *K. oxytoca*) and 122 (37%) *P. aeruginosa*. Twenty-four percent (77/328) were polymicrobial. The mean age and standard deviation (SD) for the cohort was 57 years $\pm$

16 years and 62% (202/328) were men. Forty-eight percent of the bacteremia episodes were among patients who were in the intensive care unit at some point during their hospital stay.

Approximately one-half were among patients admitted to a medicine service (170/328, 51.8%), the remainder were among patients admitted to a surgical service (141/328, 43.0%), the emergency department (16/328, 4.9%) or a psychiatric service (1/328, 0.3%). At the time of the index blood culture, 54.0% (177/328) of bacteremia episodes occurred among patients on a medical service and 45.7% (150/328) among patients on a surgical service (the remaining 1 patient was on a psychiatric service). The median time (and inter-quartile range, IQR) from hospital admission to collection of the positive blood culture (time at risk) was 11.3 days (6.2 to 12.6 days). Table 1 summarizes the characteristics of the cohort.

The mean APS (SD) at admission was 19.2 (11.6) and the mean APS (SD) 24 hours before culture collection was 24.2 (13.6); $p < 0.01$. The median difference in time (and IQR) from the APS calculated at admission to the APS calculated 24 hours before culture collection was 10.3 days (5.2 to 20.5 days). For 8 of the 328 episodes of bacteremia, the variables used to calculate the modified APS at admission and the second time point were the same. Table 2 displays the APS data by organism type and demonstrates that the differences seen in APS at admission and APS 24 hours before culture collection existed for all organisms but was most pronounced for *P. aeruginosa*. Overall, 26% of the data needed to calculate the modified APS at admission and 12% at the second time period were missing, and thus assumed normal; 92% and 83% were due to missing albumin or bilirubin values for admission and the second time point, respectively.

The overall in-hospital mortality rate was 29%; 232 patients survived to discharge and 96 patients died in the hospital. The organism-specific mortality was 28% for *E. coli*, 20% for *Klebsiella* and 44% for *P. aeruginosa*, similar to what has been seen in previous studies [12-19]. Among survivors, the mean difference (SD) in modified APS calculated at admission and 24 hours before culture collection was 3.4 (12.7); and among non-survivors was 8.7 (16.1); $p < 0.01$.

For 185 (56.4%) episodes of bacteremia appropriate empiric therapy was received; for 133 (40.5%) episodes inappropriate empiric therapy (e.g. failure to receive antimicrobials, receipt of an antimicrobial to which the isolate did not display in vitro susceptibility or receipt of an antimicrobial outside of the defined time period) was received. For 10 episodes information regarding the receipt of empiric antimicrobial therapy was either missing from the chart or incomplete and therefore the multivariate regression analysis was performed on 318 episodes. The mean APS (SD) at admission was 17.9 (10.9) for the appropriate therapy group and 21.4 (12.2) for the inappropriate therapy group ($p < 0.01$). The mean APS (SD) 24 hours prior to culture collection was 23.3 (12.9) for the appropriate therapy group and 25.6 (14.6) for the inappropriate therapy group ($p=0.14$).

The results of the multivariate models used to measure the effect of appropriate empiric antimicrobial therapy on in-hospital mortality while controlling for severity of illness at different time points are presented in Table 3. The modified APS at admission (Model 2) and 24 hours before culture collection (Model 3) were both associated with in-hospital mortality (OR 1.04; 95% CI 1.01 to 1.06 and OR 1.06; 95% CI 1.04 to 1.08, respectively). Change in the modified APS (24 hours before culture collection — admission) was associated with in-hospital mortality (Model 4) when already controlling for the modified APS at admission (OR 1.06; 95% CI 1.04 to 1.08). Likewise, the modified APS at admission remained associated with in-hospital mortality (OR 1.07; 95% CI 1.05, 1.10) even after controlling for change in modified APS. The crude association, OR, between the receipt of appropriate antimicrobial therapy and the outcome, in-hospital mortality was 0.83 (95% CI 0.51 to 1.34) (Model 1). Controlling for

severity of illness either at admission (Model 2) or at the second time point (Model 3), altered the relationship between the receipt of appropriate antimicrobial therapy and in-hospital mortality (OR 0.94, 95% CI 0.57 to 1.55 and OR 0.95, 95% CI 0.56 to 1.60, respectively). Finally, there was an additional effect of appropriate antimicrobial therapy on in-hospital mortality by adding the change in modified APS to the model when already controlling for the modified APS at admission (OR 0.99; 95% CI 0.58 to 1.69).

DISCUSSION

We compared severity of illness scores measured at two separate time points and used multivariate analysis to assess whether a difference in severity of illness at these two time points had an impact on the association between appropriate antimicrobial therapy and in-hospital mortality among patients with *E. coli*, *Klebsiella* and *P. aeruginosa* bloodstream infection. We observed that the severity of illness scores measured 24 hours prior to culture were significantly higher than those measured at admission and that severity of illness, when measured at either time point, was an independent predictor of in-hospital mortality. In addition, we observed that controlling for the change in severity of illness was important even after controlling for severity of illness at admission.

In Model 4, we controlled for the change in severity of illness (from admission to 24 hours prior to the first positive culture) in addition to controlling for the severity of illness at admission. In doing this, we are asking what additional effect does controlling for severity of illness at the second time period (24 hours prior to the first positive blood culture) the association between our primary exposure (antimicrobial therapy) and the outcome (in-hospital mortality) when severity of illness at admission is already in the model. The data suggested that severity of illness 24 hours prior to the first positive blood culture independently predicts in-hospital mortality in addition to the effect of severity of illness at admission (OR 1.06; 95% CI 1.04 to 1.08).

When comparing the different models shown in Table 3 we noted a trend towards a decreased impact of appropriate empiric therapy on in-hospital mortality. In Model 1, in which severity of illness is not controlled for, the receipt of appropriate antimicrobial therapy appears to have a protective effect against in-hospital mortality (OR 0.83; 95% CI 0.51 to 1.34). In Model 2, in which severity of illness at admission is added as a potential confounder, this association between appropriate antimicrobial therapy and in-hospital mortality is attenuated (OR 0.94, 95% CI 0.57 to 1.55). Finally, in Model 4, in which the additional impact of severity of illness at the second time period is added, the association is even further attenuated so that the receipt of appropriate antimicrobial therapy is no longer protective against in-hospital mortality. These findings provide further support that severity of illness is a confounder in this example, and also suggest that the time at which severity of illness is measured is important.

In a recent study, Hamilton et al. used the APACHE II score to measure severity of illness on the date of the first positive culture and days 1 and 2 prior to the index culture among a cohort of 91 patients with clinical cultures positive for *E. coli* or *K. pneumoniae*. [3] The authors created multivariate logistic regression models to determine the impact of fluoroquinolone-resistant infection on mortality while controlling for severity of at each of the defined time points and concluded that adjusting for severity of illness did not differ substantially across models. However, a closer review of their results showed that the APACHE II score was an independent predictor of mortality in each of these models and a comparison of the three models showed a trend towards an increased risk of mortality among infections due to fluoroquinolone-resistant pathogens as the measurement of the APACHE II score approached the time of culture collection, similar to our results.

There are several limitations to our study. First, the modified APS used in this study was not developed or validated to assess the impact of infections on mortality. However, it has been used in a number of infectious disease studies and is the most studied and validated severity of illness measure.[5-7] Second, severity of illness was measured at only two time points and it possible that neither of these reflects ideal time to measure and control for severity of illness. Third, our study was subject to problems inherent with measuring severity of illness scores, such as intra-observer reliability and missing data. In addition, there was data missing regarding the receipt of empiric antimicrobial therapy on 10 patients and therefore these were not included in the multivariate analysis. Given the small number; we feel that this unlikely had an impact on the final results. Finally, this cohort was limited to patients who developed *E. coli*, *Klebsiella* or *P. aeruginosa* bacteremia while in the hospital and therefore these results may not be generalizable to patients with community-onset bacteremia or to those with bacteremia caused by other Gram-negative pathogens.

In conclusion, we observed that severity of illness scores were statistically different when measured at different time points. In addition, we demonstrated that controlling for these differences in severity of illness measurements altered the relationship between appropriate empiric antimicrobial therapy and mortality among patients with *E. coli*, *Klebsiella* and *P. aeruginosa* bloodstream infection. Based on these results, we conclude that the time at which severity of illness is measured is important when considering this variable as a confounder and we recommend that future studies should clearly outline the methods for measurement of severity of illness, including the time point at which it was measured, in order to make adequate comparisons between studies. In addition, we feel that for similar studies, the optimal time to measure severity of illness is 24 hours prior to culture collection since this time point is close to the onset of infection, representing the true baseline severity of illness, and since measurement at later times is likely to be in the causal pathway between exposure and mortality (i.e. an intermediate variable) and thus should not be controlled for.

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Table 1

Description of the Cohort

Descriptive Statistics	All Episodes of Bacteremia	<i>Escherichia coli</i>	<i>Klebsiella pneumoniae</i>	<i>Pseudomonas aeruginosa</i>
Number of Bacteremia Episodes	328	98	128	122
Age, in years (mean, SD)	57 (± 16)	55 (± 16)	58 (± 16)	57 (± 16)
Male Sex (%)	62%	61%	59%	63%
Polymicrobial (%)	24%	27%	28%	29%
Required Intensive Care during Hospitalization(%)	48%	50%	44%	53%
Time at risk *, in days (median, IQR)	11.3 (6.2,12.6)	8.8 (5.0,13.3)	10.9 (6.4,16.9)	15.5 (8.2,27.3)
In-hospital mortality	29%	28%	20%	44%

* Time at risk = Time from hospital admission to time of collection of the first positive blood culture

Table 2
Comparison of Modified Acute Physiology Score at Admission and 24 hours Prior to Culture Collection

	No. in Cohort	Admission APS mean(SD)	Culture APS* mean(SD)	Difference in APS** mean(SD)	P—value***
Complete Cohort	328	19.2 (11.6)	24.2 (13.6)	5.0 (13.0)	< 0.01
<i>Escherichia coli</i>	98	19.5 (12.8)	23.7 (13.1)	4.2 (10.6)	< 0.01
<i>Klebsiella species</i>	128	19.3 (12.7)	23.1 (13.4)	3.8 (13.7)	< 0.01
<i>Pseudomonas aeruginosa</i>	122	19.3 (8.9)	26.3 (13.8)	7.0 (16.0)	< 0.01

Abbreviations: APS = Acute Physiology Score; SD = Standard Deviation

* Modified Acute Physiology Score calculated at admission to hospital
** Modified Acute Physiology Score calculated 24 hours prior to collection of first positive blood culture
*** P-values were calculated using the paired Student's t-test

Table 3

Logistic Regression Models: Effect of Appropriate Empiric Antimicrobials on Mortality

Model	Odds Ratio (95% Confidence Interval)
Model 1: Without controlling for severity of illness Appropriate Antimicrobials	0.83 (0.51, 1.34)
Model 2: Controlling for severity of illness at admission Appropriate Antimicrobials Admission APS*	0.94 (0.57, 1.55) 1.04 (1.01, 1.06)
Model 3: Controlling for severity of illness 24 hours prior to first positive blood culture Appropriate Antimicrobials Culture APS**	0.95 (0.56, 1.60) 1.06 (1.04, 1.08)
Model 4: Controlling for severity of illness at admission and the change in severity of illness from admission to 24 hours prior to first positive blood culture. Appropriate Antimicrobials Admission APS* Change in Severity Scores***	0.99 (0.58, 1.69) 1.07 (1.05, 1.10) 1.06 (1.04, 1.08)

* Modified Acute Physiology Score calculated at admission to hospital

** Modified Acute Physiology Score calculated 24 hours prior to collection of first positive blood culture

*** Change in severity of illness from admission to 24 hours prior to the first positive culture