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Delay of Active Antimicrobial Therapy and Mortality among Patients with Bacteremia: Impact of Severe Neutropenia▽

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Increasing bacterial antimicrobial resistance has prompted physicians to choose broad-spectrum antimicrobials in order to reduce the likelihood of inactive empirical therapy. However, for bacteremic patients already receiving supportive care, it is unclear whether delay of active antimicrobial therapy significantly impacts patient outcomes. We performed a retrospective cohort study of patients with monomicrobial bloodstream infections at a large urban hospital in the United States from 2001 to 2006. We assessed the impact of delay of active antimicrobial therapy on mortality by using multivariable logistic regression modeling with and without propensity score methodology. We evaluated 1,523 episodes of monomicrobial bacterial bloodstream infections at our institution. Nine hundred eighty-three bacteremic episodes (64.5%) were treated with an active antimicrobial agent within 24 h of the index blood culture; the remaining 540 episodes (35.5%) were considered to have delay of active antimicrobial therapy. In adjusted analysis, among patients in the non-intensive-care-unit setting with an absolute neutrophil count (ANC) of <100 cells/μl, delay was associated with increased mortality (odds ratio [OR], 18.0; 95% confidence interval [CI], 2.84 to 114.5; $P < 0.01$); among intensive-care-unit patients with an ANC of <100 cells/μl, the effect of delay on mortality was nearly significant (OR, 5.56; 95% CI, 0.85 to 36.3; $P = 0.07$). However, for patients who were nonneutropenic (ANC, >500 cells/μl) or had ANCs of 100 to 500 cells/μl, delay was not associated with increased mortality. While the delay of active antimicrobial therapy was not significantly associated with higher mortality for most patients in this cohort, patients with severe neutropenia appeared to be vulnerable.

In an era of rising antimicrobial resistance rates, choosing appropriate empirical antimicrobial therapy is an increasing challenge. For serious infections such as bacterial bloodstream infections, inadequate empirical antimicrobial therapy has been associated with worse clinical outcomes in some patient groups (16). Such consequences have led physicians to treat "more broadly," sometimes using combination therapy, to decrease the probability of inadequate empirical regimens. Use of unnecessarily broad-spectrum antimicrobials, however, has potential consequences such as emergence of further antimicrobial resistance, greater cost, and more side effects.

While inadequate antimicrobial treatment of bloodstream infections has been associated with worse outcomes in specific populations of patients, such as those in the intensive care unit (ICU) (11, 15, 19), those with septic shock (22), and those infected with *Staphylococcus aureus* (25), *Pseudomonas aeruginosa* (24, 27), extended-spectrum β-lactamase-producing organisms (1, 18), or *Candida* spp. (28), not all studies have shown these associations (5, 21, 29, 32).

The heterogeneity of the results can be explained partly by methodological challenges inherent in studying the impact of inadequate antimicrobial therapy. First, the definitions of inadequate therapy are inherently arbitrary and vary among studies. Second, local antimicrobial resistance patterns and cultures of prescribing empirical antimicrobial therapy differ between institutions and over time, thus creating differences in the types and virulences of organisms that are likely to be inadequately treated. Third, because such studies are observational, removing confounding factors is a challenge.

In observational studies, significant differences that exist between treatment groups (in this study, nondelayed active antimicrobial therapy versus delayed active antimicrobial therapy) may not be adjusted sufficiently using commonly used multivariable techniques (16, 31, 35). In particular, multivariable models that include confounders based only on statistical significance with respect to the outcome (which is often encountered with automated variable selection methods) may inappropriately exclude important confounders that adjust for differences between treatment groups (14).

In this study, we used a manual model-building approach that evaluated potential confounders based on their impact on the point estimate and confidence interval (CI) of the main exposure-mortality relationship. Second, we assessed whether further inclusion of a propensity score in the multivariable model had an impact on residual confounding. The propensity score is a composite variable defined as the subject's probability, between 0 and 1, of receiving a particular treatment, derived from a separate logistic regression model incorporating variables that are associated with treatment. Two patients with the same propensity score have equal estimated probabilities of receiving treatment; if one receives treatment while another does not, then the treatment allocation can be considered random, conditional on the observed confounders. Such an approach has been proposed as a useful adjunct to traditional multivariable logistic regression models for observational studies of antimicrobial therapy (16, 30).

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We report a retrospective study of a large cohort of patients with monomicrobial bloodstream infections over a 5-year period at our institution. We hypothesized that patients with a delay of active antimicrobial therapy for bloodstream infections would have a higher mortality risk than patients who did not have a delay.

MATERIALS AND METHODS

Study setting, study design, and patient enrollment. We performed a retrospective cohort study comparing the outcomes of bacteremic patients receiving antimicrobial therapy at John H. Stroger, Jr. (Cook County) Hospital, a 464-bed public hospital in Chicago, IL. Enrolled patients were those aged 18 years or older who developed monomicrobial bacterial bloodstream infections during the study period, 1 August 2001 to 28 February 2006, and received at least one antimicrobial, active or inactive.

The following patients were excluded: those with blood isolates of common skin commensals (coagulase-negative *Staphylococcus* spp., *Micrococcus* spp., *Bacillus* spp., or *Corynebacterium* spp.), to avoid misclassification of blood culture contaminants as true infections; those with anaerobes, because susceptibility testing was not routinely performed; those already receiving active antimicrobial therapy prior to index blood culture; those who were discharged within one hospital day after the index blood culture; those who died within one hospital day of index blood culture, as differences in antimicrobial therapy likely would not have changed their outcome (2, 7, 16); and those with bacteremia due to a second organism within 30 days of index bacteremia. Patients could be entered more than once in the study if episodes of monomicrobial bloodstream infections were separated by more than 30 days.

All clinical, microbiological, and pharmacy records were obtained using an electronic research database, developed as a part of the Chicago Antimicrobial Resistance Project (37). Data are prospectively collected in an event-driven fashion and systematically validated against the main hospital electronic record in an ongoing basis. Antimicrobial administration times were derived from electronic pharmacy records, based on the time of prescribed administration. Manual comparisons of electronic pharmacy dispensing records with a sample of bedside medication administration records showed excellent concordance (>95%) with respect to timing.

The study was reviewed by the hospital's institutional review board, and the need for informed consent was waived.

Data collection and variables of interest. (i) Outcome. Mortality was defined as in-hospital death due to any cause within 30 days of index blood culture.

(ii) Adequate antimicrobial therapy. To be categorized as adequate, initial antimicrobial therapy had to meet three criteria: (i) administration by intravenous route was initiated within 24 h of index blood draw, (ii) the bacterial blood isolate should be susceptible to the antimicrobial by subsequent in vitro testing, and (iii) the antimicrobial should be considered clinically effective or moderately effective against the isolate, as determined by the Sanford Guide to Antimicrobial Therapy (12). Patients who did not meet these criteria were considered to have delay of active antimicrobial therapy.

(iii) Covariates. For all patients in the cohort, the following covariates were considered: age, number of hospital days prior to index blood culture, gender, human immunodeficiency virus (HIV) status, absolute neutrophil count (ANC; the lowest value measured 0 to 2 days prior to index blood culture, categorized as nonneutropenic [ANC, >500 cells/μl], moderately neutropenic [ANC, 100 to 500 cells/μl], or severely neutropenic [ANC, <100 cells/μl]), receipt of any inpatient antibacterial in the prior 30 days, blood culture time and date, location of patient at midnight prior to the time of blood culture draw (dichotomized as ICU versus non-ICU), and all medications, including antimicrobials, administered to the patient up to 14 days after index blood culture draw. Vasopressor use (defined as receipt of epinephrine, norepinephrine, phenylephrine, or vasopressin) was ascertained 0 to 2 days prior to index blood culture; for sensitivity analysis, vasopressor use ascertained 1 to 2 days prior to index blood culture was used. A modified Charlson comorbidity index was calculated using International Classification of Diseases (ICD-9) diagnosis codes (9); because we found the variable to be nonlinear with respect to mortality, we dichotomized the Charlson score (≤1 versus ≥2). Specific bacterial groups considered covariates of interest included gram-positive and gram-negative organisms, *Enterobacteriaceae*, *S. aureus* (categorized as methicillin sensitive or resistant), *Enterococcus* spp. (categorized as vancomycin sensitive or resistant), *E. coli* and *Klebsiella* spp. (categorized as ceftazidime sensitive or resistant), *Pseudomonas aeruginosa* (categorized as imipenem sensitive or resistant), and *Acinetobacter* spp. (categorized as imipenem sensitive or resistant).

To allow adjustment for the level of antimicrobial resistance across different organisms as a factor for delayed antimicrobial therapy, we constructed a continuous variable called the pathogen resistance index (PRI). Using the in vitro susceptibility data for each bacterial isolate, a PRI was calculated by the formula (number of classes of resistant antimicrobials/number of total classes of antimicrobials tested) × 100 to create a score between 0 and 100. A completely resistant organism would have a score of 100, while a completely susceptible organism would have a score of 0.

Similarly, to allow adjustment for the spectrum of empirical antimicrobial therapy received as a factor for delayed antimicrobial therapy, we constructed a continuous variable called the antimicrobial spectrum index (ASI). Using the Sanford Guide to Antimicrobial Therapy, ASI was defined by the formula (number of susceptible bacteria/number of total bacteria listed) × 100 to create a score between 0 and 100 (see Table 4 in reference 12). Broad-spectrum antimicrobials had higher ASI scores than narrow-spectrum antimicrobials did. When patients were given multiple active drugs as empirical therapy, the antimicrobial with the highest ASI score was used for analysis.

Statistical analysis. This study was predicated on at least 80% power to detect a difference between a 15% death rate in the delayed-treatment group of 540 subjects versus a 10% death rate in the nondelayed-treatment group of 983 subjects (and a power of 99% to detect a difference between a death rate of 20% versus a 10% death rate for the treatment groups, respectively), with an alpha level of 0.05 in a two-sided chi-square test of proportions.

Bivariable analyses were performed using Fisher's exact and chi-square tests to compare categorical variables, and Student's *t* tests were performed to compare continuous variables.

To calculate a propensity score for the probability of delay in active antimicrobial therapy, we constructed a multivariable logistic regression model with treatment delay dichotomized as the dependent variable. For propensity score calculation, we evaluated baseline patient and organism covariates by using backward selection at a prespecified significance level ($P < 0.05$) for retaining terms.

Multivariable logistic regression was used to obtain an adjusted estimate of the association between delay of active antimicrobial therapy and mortality. First, all two-way interaction terms with antimicrobial therapy delay were analyzed in a model saturated with all covariates considered in this study. Significant interaction terms (*P* value, below or near 0.05) were retained in the model, along with their lower-order covariates. Next, covariates were manually assessed as confounders by determining whether their removal substantially changed the effect estimates of delayed antimicrobial therapy stratified by interaction terms. We assessed the fit of the logistic regression model to observed data by using the Hosmer-Lemeshow goodness-of-fit test (17). For sensitivity analysis, the propensity score was added as an additional covariate to determine whether measured differences between the delay and nondelay groups contributed to residual confounding. For interpretation of final model results, tests of significance were two tailed, and *P* values of <0.05 were considered significant. All data were analyzed using SAS software, version 9.1 (SAS Institute, Cary, NC).

RESULTS

Characteristics of cohort. During the study period, 2,692 bloodstream episodes were potentially eligible based on organism and study period criteria. The following subgroups of episodes were excluded: 82 that were associated with death or discharge within 24 h, 837 that were polymicrobial, and 250 that were associated with active antimicrobial therapy already present. The final cohort consisted of 1,523 episodes of bloodstream infections. There were 1,448 unique patients represented; 57 patients had two qualifying episodes of bacteremia, 6 patients had three episodes, and 2 patients had four episodes. The mean age of the final cohort was 49.6 (range, 18 to 102) years. Three hundred eighty-six (25.3%) index blood cultures were drawn in the ICU. A total of 1,110 (72.9%) index blood cultures were obtained within 3 days of hospital admission. The overall mortality rate of the final cohort was 8.5%.

In the overall cohort, 938 (61.6%) episodes were caused by gram-positive organisms. Four hundred eighty episodes were caused by *Staphylococcus aureus*, of which 169 were methicillin

TABLE 1. Characteristics of patients with nondelay or delay of active antimicrobial therapy

Covariate	Value for indicated cohort		*P* value
	Nondelay (n = 983)	Delay (n = 540)	
Patient baseline measures			
Mean age (yr)	49.7	49.3	0.64
Female gender (%)	42.6	39.8	0.29
Charlson score of ≥2 (%)	40.8	43.2	0.37
Patients in ICU (%)	24.7	26.5	0.45
Vasopressor, on day of culture (%)	10.7	7.2	0.03
Nosocomial (%)	18.2	43.3	<0.01
Length of hospital stay prior to positive culture (days)	1.9	6.4	<0.01
Neutropenia			
Severe neutropenia (ANC, <100 cells/μl) (%)	3.5	1.9	0.07
Moderate neutropenia (ANC, 100–500 cells/μl) (%)	2.0	0.75	0.08
HIV infection (%)	13.4	11.1	0.19
Organism and treatment characteristics			
Gram-positive organisms (%)	62.4	60.2	0.40
Enterobacteriaceae (%)	33.8	32.0	0.49
Methicillin-resistant *Staphylococcus aureus* (%)	8.0	16.7	<0.01
Vancomycin-resistant *Enterococcus* spp. (%)	0.2	8.2	<0.01
Ceftazidime-resistant *E. coli* or *Klebsiella* spp. (%)	0.3	0.7	0.46
Pseudomonas aeruginosa (%)	2.9	4.3	0.14
Acinetobacter spp. (%)	0.9	3.5	<0.01
PRI			
Mean	17.1	35.1	<0.01
Median	8	33	
ASI			
Mean	68.2	62.6	<0.01
Median	72	70	
Patient outcome			
Inpatient 30-day mortality (%)	8.0	9.3	0.41

TABLE 2. Independent predictors of delay of active antimicrobial therapy in a multivariable logistic regression model (used to derive a propensity score for delay)

Predictor	OR	95% CI	*P* value
ICU stay	0.70	0.51–0.96	0.03
Vasopressor use	0.37	0.20–0.67	<0.01
Neutropenia level (ANC [cells/μl])			
Severe neutropenia (<100 [vs >500])	0.27	0.10–0.72	0.01
Moderate neutropenia (100–500 [vs >500])	0.18	0.05–0.67	0.01
Receipt of antibacterials in prior 30 days	2.08	1.35–3.20	<0.01
PRI	1.02	1.02–1.03	<0.01
ASI	0.992	0.987–0.997	<0.01
Length of hospital stay prior to culture (days)	1.03	1.01–1.06	0.01
Enterococcus spp. (reference, non-*Enterococcus* spp.)			
Vancomycin sensitive *Enterococcus*	2.16	1.35–3.44	<0.01
Vancomycin resistant *Enterococcus*	8.49	1.92–37.5	<0.01

resistant. One hundred thirty-six episodes were caused by *Enterococcus* spp., of which 46 were vancomycin resistant. Of the 535 (38.4%) episodes caused by gram-negative organisms, highly resistant gram-negative organisms were rare (ceftazidime-resistant *E. coli* or *Klebsiella* spp., $n = 8$; imipenem-resistant *Pseudomonas aeruginosa*, $n = 11$; and imipenem-resistant *Acinetobacter* spp., $n = 1$).

Antimicrobial therapy delay. Overall, there were 540 (35.5%) episodes of delay of active antimicrobial therapy, while 983 (64.5%) had nondelayed therapy. The mortality rate in the delay group was 9.3%, while the mortality rate in the nondelay group was 8.0%. A total of 89 (5.8%) episodes of bacteremia were treated only with inactive antimicrobials; 15 of these were associated with death (mortality rate, 17%). Compared to the nondelay group, bacteremias leading to delay of active antimicrobial therapy were more likely to be caused by methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus* spp., or *Acinetobacter* spp. (all *P* values, <0.05). The mean PRI of organisms in the delay group was significantly higher than that of the nondelay group (35 versus 17; $P < 0.01$). Table 1 compares baseline and outcome characteristics of the nondelay group with those of the delay group.

Predictors of delayed active antimicrobial therapy (derivation of propensity score). All covariates significantly associated with delay of active antimicrobial therapy were used to derive a propensity score for delay for each subject (Table 2). Significant independent predictors of delay of active antimicrobial therapy included the following: length of hospital stay prior to index blood culture (OR, 1.03; 95% CI, 1.01 to 1.06); receipt of any antibacterial in the prior 30 days (OR, 2.08; 95% CI, 1.35 to 3.20); *Enterococcus* spp. categorized as vancomycin sensitive (OR, 2.16; 95% CI, 1.35 to 3.44) or vancomycin resistant (OR, 8.49; 95% CI, 1.92 to 37.51); and greater antimicrobial resistance of the bloodstream isolate, measured by the PRI (OR, 1.02; 95% CI, 1.02 to 1.03). Independent covariates that were protective of delay of active antimicrobial therapy included the following: ICU stay (OR, 0.64; 95% CI, 0.46 to 0.88); vasopressor use (OR, 0.49; 95% CI, 0.30 to 0.78); neutropenia level, both moderate (OR, 0.18; 95% CI, 0.05 to 0.67) and severe (OR, 0.27; 95% CI, 0.10 to 0.72); and a wider antimicrobial spectrum, as measured by the ASI (OR, 0.992; 95% CI, 0.987 to 0.997).

Modeling the effect of delay of active antimicrobial therapy on mortality. In bivariate analysis, delay of active antimicrobial therapy was not a significant predictor of mortality (OR, 1.17; 95% CI, 0.81 to 1.69). The unadjusted bivariate ORs and 95% CIs of other covariates are listed in Table 3.

Next, delay of active antimicrobial therapy was modeled using multivariable logistic regression, with mortality as the outcome. Two-way interaction terms between delay and ICU stay, as well as those between delay and level of neutropenia, were significant; these interaction terms as well as lower-order covariates were retained in the final model. Of note, no interactions between delay and organism class were significant, indicating that the effects of delay on mortality varied by ICU stay (versus non-ICU stay) and by level of neutropenia, but not by organism class. Important confounders included age,

TABLE 3. Bivariate analysis of covariates with mortality as the outcome

Covariate	OR	95% CI	*P* value
Delay of active antimicrobial therapy	1.17	0.81–1.69	0.41
Age (yr)	1.03	1.02–1.04	<0.01
Female gender	0.76	0.52–1.11	0.15
Charlson score of ≥2 (vs ≤1)	3.09	2.11–4.52	<0.01
ICU stay	6.67	4.54–9.81	<0.01
Vasopressor use	10.96	6.89–17.5	<0.01
Neutropenia level (ANC, cells/μl)			
Severe neutropenia (<100 [vs >500])	6.00	3.09–11.67	<0.01
Moderate neutropenia (100–500 [vs >500])	9.89	4.24–23.1	<0.01
HIV infection	1.30	0.79–2.16	0.30
Receipt of antibacterials in prior 30 days	3.45	2.36–5.05	<0.01
Length of hospital stay prior to positive culture (day)	1.06	1.04–1.08	<0.01
Nosocomial infection	3.27	2.27–4.72	<0.01
PRI (1 unit change)	1.02	1.01–1.03	<0.01
ASI (1 unit change)	0.99	0.99–1.00	0.17
Gram-positive organism (vs gram-negative organism)	1.14	0.78–1.66	0.50
Enterobacteriaceae (vs non-*Enterobacteriaceae*)	0.67	0.45–1.01	0.06
Acinetobacter spp. (vs non-*Acinetobacter* spp.)	0.83	0.19–3.53	0.80
Staphylococcus aureus (refererence, non-*S. aureus*)			
Methicillin-sensitive *S. aureus*	0.92	0.56–1.50	0.73
Methicillin-resistant *S. aureus*	2.29	1.43–3.66	<0.01
Enterococcus spp. (reference, non-*Enterococcus* spp.)			
Vancomycin-sensitive *Enterococcus*	1.62	0.83–3.13	0.15
Vancomycin-resistant *Enterococcus*	2.45	1.11–5.37	0.03
Pseudomonas aeruginosa (reference, non-*P. aeruginosa*)			
Imipenem-sensitive *P. aeruginosa*	1.62	0.63–4.22	0.32
Imipenem-resistant *P. aeruginosa*	9.48	2.85–31.5	<0.01

Charlson score, vasopressor use, length of hospital stay prior to positive culture (in days), HIV infection, and *S. aureus* bacteremia; all were retained in the final model.

In the final model (Table 4), among non-ICU patients, delay was not associated with significantly increased mortality among patients with ANCs of >500 cells/μl (OR, 1.78; 95% CI, 0.91 to 3.45; $P = 0.09$) or patients with ANCs of 100 to 500 cells/μl (OR, 1.92; 95% CI, 0.17 to 21.6; $P = 0.60$). However, non-ICU patients who were severely neutropenic with ANCs of <100 cells/μl had significantly higher odds of mortality when comparing delay versus nondelay of active antimicrobial therapy (OR, 18.0; 95% CI, 2.84 to 114.5; $P < 0.01$).

Among ICU patients, delay of active antimicrobial therapy was not associated with increased mortality for patients with ANCs of >500 cells/μl (OR, 0.55; 95% CI, 0.29 to 1.02; $P = 0.06$) or for patients with ANCs of 100 to 500 cells/μl (OR 0.59, 95% CI 0.06 to 6.22, $P = 0.66$). There was a trend toward higher odds of mortality for severely neutropenic patients in the ICU experiencing delays of active antimicrobial therapy, although the estimate was not statistically significant (OR, 5.56; 95% CI, 0.85 to 36.3; $P = 0.07$).

In the final model, methicillin-resistant *S. aureus* bacteremia conferred a twofold-increased odd of mortality, even after adjusting for antimicrobial therapy delay and other confounders (OR, 2.04; 95% CI, 1.17 to 3.53; $P = 0.02$). In contrast, methicillin-sensitive *S. aureus* bacteremia trended toward increased mortality but was not statistically significant (OR, 1.57; 95% CI, 0.90 to 2.75; $P = 0.11$). The final model also suggested that among bacteremic patients, HIV infection conferred a nearly twofold increase in odds of death (OR, 1.87; 95% CI, 1.03 to 3.38; $P = 0.04$), even after adjusting for patient and treatment characteristics.

Sensitivity analysis. To adjust for residual confounding due to measured differences between the delay and nondelay groups, the propensity score was added to the final regression model. Addition of the propensity score did not substantially change the effect estimates or CIs of the final model (Table 4). Furthermore, removal of the covariate controlling for sepsis (vasopressor use) or redefining the timing of sepsis determination (measuring vasopressor use 1 and 2 days prior to the index blood culture) did not substantially change the final-model results (data not shown). Finally, changing the definition of delay to a more restrictive time cutoff (12 h) in the final model did not substantially change the results of the final model.

The Hosmer-Lemeshow goodness-of-fit test did not reject the null hypothesis of good fit ($P = 0.75$), indicating that the final logistic regression model fit the observed data well.

DISCUSSION

In this study of 1,523 monomicrobial bacteremia episodes in hospitalized patients, the impact of delay of active antimicrobial therapy on mortality was found to vary by level of neutropenia. In adjusted analysis, delay was not significantly associated with increased mortality among patients who either were nonneutropenic or had ANCs of 100 to 500 cells/μl. However, for non-ICU patients with ANCs of <100 cells/μl, delay was associated with statistically significant 18-fold-increased odds of death, while for ICU patients with ANCs of <100 cells/μl, delay was associated with nearly significant fivefold-increased odds of death.

Neutrophils are the predominant leukocytes in the blood and are the first line of defense in controlling bacteria invading the bloodstream (6). The risk for developing infection increases significantly as the ANC falls below 500 cells/μl and is the highest when the ANC falls below 100 cells/μl (4). Among neutropenic patients who develop bacteremia, studies have been inconclusive about the effect of the ANC level on mortality. González-Barca et al. studied 438 consecutive neutropenic cancer patients with bacteremia and found that patients with ANCs of <100 cells/μl at the onset of bacteremia had approximately 40%-increased unadjusted odds of death relative to those with ANCs of 100 to 500 cells/μl (13). In contrast, Elting et al. analyzed 909 episodes of neutropenic bacteremia and found that there was no substantial difference in mortality between patients with ANCs of <100 cells/μl and those with ANCs of 100 to 1,000 cells/μl, particularly for uncomplicated bacteremia (10). In both studies, neither ANC level nor inadequate empirical antimicrobial therapy predicted increased mortality in adjusted analyses; rather, other factors, such as

TABLE 4. Adjusted effects of delay of active antimicrobial therapy on mortality, stratified by ICU stay and level of neutropenia[a]

Variable	Values for indicated model[b]					
	Without propensity score			With propensity score		
	OR	95% CI	*P* value	OR	95% CI	*P* value
Delay vs nondelay among non-ICU patients with ANCs (cells/μl) of:						
<100	18.0	2.84–114.5	<0.01	17.3	2.65–113.5	<0.01
100 to 500	1.92	0.17–21.6	0.60	1.90	0.17–21.3	0.60
>500	1.78	0.91–3.45	0.09	1.75	0.89–3.44	0.10
Delay vs nondelay among ICU patients with ANCs (cells/μl) of:						
<100	5.56	0.85–36.3	0.07	5.32	0.78–36.1	0.09
100–500	0.59	0.06–6.22	0.66	0.58	0.06–6.11	0.65
>500	0.55	0.29–1.02	0.06	0.54	0.28–1.03	0.06
Age (yr)	1.03	1.01–1.04	<0.01	1.03	1.01–1.04	<0.01
Charlson score ≥ 2 (vs ≤1)	1.90	1.23–2.93	<0.01	1.90	1.23–2.93	<0.01
Vasopressor use	3.93	2.25–6.86	<0.01	4.01	2.23–7.20	<0.01
Length of hospital stay prior to positive culture (day)	1.04	1.02–1.06	<0.01	1.04	1.00–1.07	0.03
HIV infection	1.87	1.03–3.38	0.04	1.86	1.03–3.37	0.04
Staphylococcus aureus bacteremia (reference, non-*S. aureus*)						
Methicillin-sensitive *S. aureus*	1.57	0.90–2.75	0.11	1.59	0.90–2.82	0.11
Methicillin-resistant *S. aureus*	2.04	1.17–3.53	0.01	1.98	1.10–3.59	0.02
Propensity score				1.18	0.28–4.96	0.82

[a] Multivariable logistic regression models are shown with and without the propensity score for delay. The propensity score is derived from the following covariates: ICU stay, vasopressor use, level of neutropenia, length of hospital stay prior to positive culture, receipt of antibacterials in prior 30 days, PRI, ASI, and *Enterococcus* spp.

[b] Model without propensity score is the final model; model with propensity score is the sensitivity analysis.

shock at the time of bacteremia, appeared to be the most important predictors. Nevertheless, there is biological plausibility that severe neutropenia at the onset of bacteremia could impair the ability of the patient to survive the infection in the face of inadequate antimicrobial therapy. Our study suggests that there is a threshold ANC level (100 cells/μl) below which delay of active antimicrobial therapy has an important effect on mortality.

For bacteremic patients without severe neutropenia, delay of active antimicrobial therapy did not appear to significantly impact mortality. Although it is reasonable to expect inadequate antimicrobial therapy to worsen mortality, this relationship is complex and not consistently supported in the literature. While several studies have shown an association between inappropriate antimicrobial therapy and mortality (1, 19, 23, 25, 27, 33, 36), other studies have not found a significant association (3, 5, 8, 20, 21, 29, 32, 38).

Much of the conflicting findings may be due to differences in methodology, making generalizations difficult (26). Our study was unique in the following ways. First, we focused on monomicrobial bacterial infections, and we excluded common skin commensals and nonbacterial pathogens, such as fungi. Second, the majority of our subjects (73%) had community-acquired bacteremia; in this population, the true duration of bacteremia is unclear, and initial inappropriate antimicrobial therapy may not have significant impact. Third, because our electronic database lacked the necessary data to calculate common severity-of-illness variables, such as the APACHE score, we relied on other markers of acuity, such as vasopressor use and ICU stay. While we controlled for measured differences between the treatment groups by using multivariable regression models and testing the inclusion of a propensity score, there likely remained residual confounding by indication, as demonstrated by the nearly protective effect that delay had on mortality among nonneutropenic ICU patients.

Several studies have highlighted specific populations with bacteremia that may be vulnerable to inappropriate antimicrobial therapy. Ibrahim et al. found a relationship between inappropriate antimicrobial therapy and mortality among bacteremic patients in the ICU setting (19). Kumar et al. further identified inappropriate antimicrobial therapy as an important risk factor for death among bacteremic patients with septic shock. In contrast, other studies that included more heterogeneous patient populations have found a lack of association (5, 32). Our study focused on a heterogeneous patient population as well, but our experience suggests that including interaction terms and stratifying specific subgroups of bacteremic patients may reveal important associations between antimicrobial therapy and mortality.

Several publications have highlighted the importance of

proper assessment of time-dependent covariates, such as severity of illness (26, 34). At issue is whether a covariate such as septic shock might be considered an intermediate variable in studies of bacteremia treatment and death. In our study, the main exposure of interest was whether a bacteremic patient received active antimicrobial therapy in the first 24 h after index blood culture draw. The main outcome, mortality, was assessed at a time point beyond the initial 24-hour window. Any patient characteristic known to physicians during the initial 24 h could influence choice of antimicrobials (e.g., septic shock developing in the first 24 h may influence physicians to broaden antimicrobial coverage) and would thus represent a potential confounder. We did not measure vasopressor use or other covariates beyond 24 h of the index blood culture, as those measurements clearly would be in the intermediate pathway to death.

Several limitations remain in this study. First, we did not examine primary versus secondary sources of bacteremia. It is possible that certain sources of bacteremia, such as the lung or abdomen, might be more susceptible to delayed antimicrobial therapy. Second, the study was retrospective, with data gathered through an electronic hospital database. Our medication administration data, like that of many retrospective studies of antimicrobial use, was based on the electronic pharmacy dispensing record rather than information at the point of care. Nondifferential misclassification may exist in categorizing patients as delayed versus nondelayed, which may bias results toward the null. Third, mortality was assessed only in the hospital setting; we did not assess for deaths occurring outside the hospital. It is possible that informative censoring could lead to bias in effect estimation. Finally, although we assessed for level of neutropenia at the time of index blood culture, we did not measure duration of neutropenia, which may be an important consideration in identifying patients who are the most immunocompromised and therefore vulnerable to inappropriate antimicrobial therapy.

In summary, our study found that patients with severe neutropenia, particularly in the non-ICU setting, were at increased risk of death when exposed to delay of active antimicrobial therapy. The mortality risk of inappropriate antimicrobial therapy was not significant for patients who were nonneutropenic or moderately neutropenic. In light of the evolution of the types of bloodstream pathogens and of available antimicrobials over the last 10 years, an updated assessment of appropriate empirical antimicrobial therapy focused on neutropenic patients may be warranted.

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REFERENCES

1. **Anderson, D. J., J. J. Engemann, L. J. Harrell, Y. Carmeli, L. B. Reller, and K. S. Kaye.** 2006. Predictors of mortality in patients with bloodstream infection due to ceftazidime-resistant *Klebsiella pneumoniae*. Antimicrob. Agents Chemother. **50:**1715–1720.
2. **Austrian, R., and J. Gold.** 1964. Pneumococcal bacteremia with special reference to bacteremic pneumococcal pneumonia. Ann. Intern. Med. **60:** 759–776.
3. **Bates, D. W., K. E. Pruess, and T. H. Lee.** 1995. How bad are bacteremia and sepsis? Outcomes in a cohort with suspected bacteremia. Arch. Intern. Med. **155:**593–598.
4. **Bodey, G. P., M. Buckley, Y. S. Sathe, and E. J. Freireich.** 1966. Quantitative relationships between circulating leukocytes and infection in patients with acute leukemia. Ann. Intern. Med. **64:**328–340.
5. **Bryan, C. S., K. L. Reynolds, and E. R. Brenner.** 1983. Analysis of 1,186 episodes of gram-negative bacteremia in non-university hospitals: the effects of antimicrobial therapy. Rev. Infect. Dis. **5:**629–638.
6. **Burg, N. D., and M. H. Pillinger.** 2001. The neutrophil: function and regulation in innate and humoral immunity. Clin. Immunol. **99:**7–17.
7. **Clec'h, C., J. F. Timsit, A. De Lassence, E. Azoulay, C. Alberti, M. Garrouste-Orgeas, B. Mourvilier, G. Troche, M. Tafflet, O. Tuil, and Y. Cohen.** 2004. Efficacy of adequate early antibiotic therapy in ventilator-associated pneumonia: influence of disease severity. Intensive Care Med. **30:**1327–1333.
8. **Deal, E. N., S. T. Micek, D. J. Ritchie, R. M. Reichley, W. M. Dunne, Jr., and M. H. Kollef.** 2007. Predictors of in-hospital mortality for bloodstream infections caused by *Enterobacter* species or *Citrobacter freundii*. Pharmacotherapy **27:**191–199.
9. **Deyo, R. A., D. C. Cherkin, and M. A. Ciol.** 1992. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. J. Clin. Epidemiol. **45:**613–619.
10. **Elting, L. S., E. B. Rubenstein, K. V. Rolston, and G. P. Bodey.** 1997. Outcomes of bacteremia in patients with cancer and neutropenia: observations from two decades of epidemiological and clinical trials. Clin. Infect. Dis. **25:**247–259.
11. **Garrouste-Orgeas, M., J. F. Timsit, M. Tafflet, B. Misset, J. R. Zahar, L. Soufir, T. Lazard, S. Jamali, B. Mourvillier, Y. Cohen, A. De Lassence, E. Azoulay, C. Cheval, A. Descorps-Declere, C. Adrie, M. A. Costa de Beauregard, and J. Carlet.** 2006. Excess risk of death from intensive care unit-acquired nosocomial bloodstream infections: a reappraisal. Clin. Infect. Dis. **42:**1118–1126.
12. **Gilbert, D. N., R. C. Moellering, G. M. Eliopoulos, and M. A. Sande.** 2007. The Sanford guide to antimicrobial therapy 2007, 37th ed. Antimicrobial Therapy, Inc., Sperryville, VA.
13. **González-Barca, E., A. Fernandez-Sevilla, J. Carratala, A. Salar, J. Peris, A. Granena, and F. Gudiol.** 1999. Prognostic factors influencing mortality in cancer patients with neutropenia and bacteremia. Eur. J. Clin. Microbiol. Infect. Dis. **18:**539–544.
14. **Greenland, S., and K. J. Rothman.** 1998. Introduction to stratified analysis, p. 256–257. Modern epidemiology, 2nd ed. Lippincott-Raven Publishers, Philadelphia, PA.
15. **Harbarth, S., J. Garbino, J. Pugin, J. A. Romand, D. Lew, and D. Pittet.** 2003. Inappropriate initial antimicrobial therapy and its effect on survival in a clinical trial of immunomodulating therapy for severe sepsis. Am. J. Med. **115:**529–535.
16. **Harbarth, S., V. Nobre, and D. Pittet.** 2007. Does antibiotic selection impact patient outcome? Clin. Infect. Dis. **44:**87–93.
17. **Hosmer, D. W., S. Taber, and S. Lemeshow.** 1991. The importance of assessing the fit of logistic regression models: a case study. Am. J. Public Health **81:**1630–1635.
18. **Hyle, E. P., A. D. Lipworth, T. E. Zaoutis, I. Nachamkin, W. B. Bilker, and E. Lautenbach.** 2005. Impact of inadequate initial antimicrobial therapy on mortality in infections due to extended-spectrum beta-lactamase-producing Enterobacteriaceae: variability by site of infection. Arch. Intern. Med. **165:** 1375–1380.
19. **Ibrahim, E. H., G. Sherman, S. Ward, V. J. Fraser, and M. H. Kollef.** 2000. The influence of inadequate antimicrobial treatment of bloodstream infections on patient outcomes in the ICU setting. Chest **118:**146–155.
20. **Kang, C. I., S. H. Kim, W. B. Park, K. D. Lee, H. B. Kim, E. C. Kim, M. D. Oh, and K. W. Choe.** 2004. Bloodstream infections due to extended-spectrum beta-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae*: risk factors for mortality and treatment outcome, with special emphasis on antimicrobial therapy. Antimicrob. Agents Chemother. **48:**4574–4581.
21. **Kim, S. H., W. B. Park, K. D. Lee, C. I. Kang, J. W. Bang, H. B. Kim, E. C. Kim, M. D. Oh, and K. W. Choe.** 2004. Outcome of inappropriate initial antimicrobial treatment in patients with methicillin-resistant *Staphylococcus aureus* bacteraemia. J. Antimicrob. Chemother. **54:**489–497.
22. **Kumar, A., D. Roberts, K. E. Wood, B. Light, J. E. Parrillo, S. Sharma, R. Suppes, D. Feinstein, S. Zanotti, L. Taiberg, D. Gurka, A. Kumar, and M. Cheang.** 2006. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit. Care Med. **34:**1589–1596.
23. **Lautenbach, E., J. P. Metlay, W. B. Bilker, P. H. Edelstein, and N. O. Fishman.** 2005. Association between fluoroquinolone resistance and mortality in *Escherichia coli* and *Klebsiella pneumoniae* infections: the role of inadequate empirical antimicrobial therapy. Clin. Infect. Dis. **41:**923–929.
24. **Lodise, T. P., Jr., N. Patel, A. Kwa, J. Graves, J. P. Furuno, E. Graffunder, B. Lomaestro, and J. C. McGregor.** 2007. Predictors of 30-day mortality among patients with *Pseudomonas aeruginosa* bloodstream infections: impact of delayed appropriate antibiotic selection. Antimicrob. Agents Chemother. **51:**3510–3515.
25. **Lodise, T. P., P. S. McKinnon, L. Swiderski, and M. J. Rybak.** 2003. Outcomes analysis of delayed antibiotic treatment for hospital-acquired *Staphylococcus aureus* bacteremia. Clin. Infect. Dis. **36:**1418–1423.

26. **McGregor, J. C., S. E. Rich, A. D. Harris, E. N. Perencevich, R. Osih, T. P. Lodise, Jr., R. R. Miller, and J. P. Furuno.** 2007. A systematic review of the methods used to assess the association between appropriate antibiotic therapy and mortality in bacteremic patients. Clin. Infect. Dis. **45:**329–337.
27. **Micek, S. T., A. E. Lloyd, D. J. Ritchie, R. M. Reichley, V. J. Fraser, and M. H. Kollef.** 2005. *Pseudomonas aeruginosa* bloodstream infection: importance of appropriate initial antimicrobial treatment. Antimicrob. Agents Chemother. **49:**1306–1311.
28. **Morrell, M., V. J. Fraser, and M. H. Kollef.** 2005. Delaying the empiric treatment of *Candida* bloodstream infection until positive blood culture results are obtained: a potential risk factor for hospital mortality. Antimicrob. Agents Chemother. **49:**3640–3645.
29. **Osih, R. B., J. C. McGregor, S. E. Rich, A. C. Moore, J. P. Furuno, E. N. Perencevich, and A. D. Harris.** 2007. Impact of empiric antibiotic therapy on outcomes in patients with *Pseudomonas aeruginosa* bacteremia. Antimicrob. Agents Chemother. **51:**839–844.
30. **Paul, M., A. Fraser, and L. Leibovici.** 2007. Propensity-matched analysis of appropriate empirical antibiotic treatment. Clin. Infect. Dis. **44:**1251–1252.
31. **Rubin, D. B.** 1997. Estimating causal effects from large data sets using propensity scores. Ann. Intern. Med. **127:**757–763.
32. **Scarsi, K. K., J. M. Feinglass, M. H. Scheetz, M. J. Postelnick, M. K. Bolon, and G. A. Noskin.** 2006. Impact of inactive empiric antimicrobial therapy on inpatient mortality and length of stay. Antimicrob. Agents Chemother. **50:**3355–3360.
33. **Schramm, G. E., J. A. Johnson, J. A. Doherty, S. T. Micek, and M. H. Kollef.** 2006. Methicillin-resistant *Staphylococcus aureus* sterile-site infection: the importance of appropriate initial antimicrobial treatment. Crit. Care Med. **34:**2069–2074.
34. **Soriano, A., J. A. Martinez, and J. Mensa.** 2008. Reply to Lustberg and to Porath and Brooks. Clin. Infect. Dis. **46:**1484–1485.
35. **Sun, G. W., T. L. Shook, and G. L. Kay.** 1996. Inappropriate use of bivariable analysis to screen risk factors for use in multivariable analysis. J. Clin. Epidemiol. **49:**907–916.
36. **Weinstein, M. P., M. L. Towns, S. M. Quartey, S. Mirrett, L. G. Reimer, G. Parmigiani, and L. B. Reller.** 1997. The clinical significance of positive blood cultures in the 1990s: a prospective comprehensive evaluation of the microbiology, epidemiology, and outcome of bacteremia and fungemia in adults. Clin. Infect. Dis. **24:**584–602.
37. **Wisniewski, M. F., P. Kieszkowski, B. M. Zagorski, W. E. Trick, M. Sommers, and R. A. Weinstein.** 2003. Development of a clinical data warehouse for hospital infection control. J. Am. Med. Inform. Assoc. **10:**454–462.
38. **Zaragoza, R., A. Artero, J. J. Camarena, S. Sancho, R. Gonzalez, and J. M. Nogueira.** 2003. The influence of inadequate empirical antimicrobial treatment on patients with bloodstream infections in an intensive care unit. Clin. Microbiol. Infect. **9:**412–418.