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Association Between the Sequence of β-Lactam and Vancomycin Administration and Mortality in Patients With Suspected Sepsis

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Background. Timely antibiotic initiation is critical to sepsis management, but there are limited data on the impact of giving β-lactams first versus vancomycin first among patients prescribed both agents.

Methods. We retrospectively analyzed all adults admitted to 5 US hospitals from 2015–2022 with suspected sepsis (blood culture collected, antibiotics administered, and organ dysfunction) treated with vancomycin and a broad-spectrum β-lactam within 24 hours of arrival. We estimated associations between β-lactam- versus vancomycin-first strategies and in-hospital mortality using inverse probability weighting (IPW) to adjust for potential confounders.

Results. Among 25 391 patients with suspected sepsis, 21 449 (84.4%) received β-lactams first and 3942 (15.6%) received vancomycin first. Compared with the β-lactam-first group, patients administered vancomycin first tended to be less severely ill, had more skin/musculoskeletal infections (20.0% vs 7.8%), and received β-lactams a median of 3.5 hours later relative to emergency department arrival. On IPW analysis, the β-lactam-first strategy was associated with lower mortality (adjusted odds ratio [aOR]: .89; 95% CI: .80–.99). Point estimates were directionally similar but nonsignificant in a sensitivity analysis using propensity score matching rather than IPW (aOR: .94; 95% CI: .82–1.07) and in subgroups of patients with positive blood cultures, methicillin-resistant *Staphylococcus aureus* cultures, and those administered antipseudomonal β-lactams.

Conclusions. Among patients with suspected sepsis prescribed vancomycin and β-lactam therapy, β-lactam administration before vancomycin was associated with a modest reduction in in-hospital mortality. These findings support prioritizing β-lactam therapy in most patients with sepsis but merit confirmation in randomized trials given the risk of residual confounding in observational analyses.

Keywords. sepsis; antibiotics; antibacterial agents; β-lactam; antibiotic sequence.

Sepsis is a leading cause of morbidity and mortality globally [1]. Early administration of effective antibiotic therapy is the intervention most consistently associated with improvements in sepsis mortality [2, 3]. Clinical practice guidelines and regulatory measures therefore heavily emphasize time-to-antibiotic administration as a key sepsis process metric [4–6].

There are fewer data, however, on whether the sequence of antibiotic administration in patients prescribed combination empiric therapy impacts patient outcomes. Many patients with suspected sepsis are initially treated with a broad-spectrum β-lactam as well as vancomycin to cover methicillin-resistant *Staphylococcus aureus* (MRSA) [7]. However, MRSA coverage is unnecessary in retrospect in most cases, and administering vancomycin first (which typically infuses over 60 minutes, or longer when there are concerns about infusion reactions) can potentially delay administration of effective β-lactam therapy when intravenous access is limited [7–9].

Underscoring the potential importance of antibiotic sequence, a recent retrospective study reported that prioritizing β-lactam administration over vancomycin was associated with a 52% reduction in the odds of short-term mortality [10]. This study, however, focused only on patients with confirmed bloodstream infections in a single healthcare system; it is unclear whether these findings are generalizable to other settings and to the broader population of patients with sepsis, of whom only 15%–20% have positive blood cultures [11]. We therefore investigated the association of a β-lactam- versus vancomycin-first strategy with mortality in a large multihospital cohort of patients with suspected sepsis.

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METHODS

Study Design, Setting, and Data Source

This was a retrospective cohort study of adults (≥18 years old) admitted from the emergency department (ED) at 5 hospitals within the Mass General Brigham (MGB) healthcare system, including 2 academic and 3 community hospitals, between June 2015 and August 2022. Data were obtained from the MGB Enterprise Data Warehouse, which contains detailed administrative and electronic health record (EHR) data for all MGB encounters [12–14]. The study was approved by the MGB institutional review board.

Inclusion/Exclusion Criteria

We included adults with suspected sepsis on admission, defined as suspected infection (blood culture draw and intravenous antibiotic administration) within 24 hours of ED arrival plus acute organ dysfunction within 12 hours of arrival [12]. Organ dysfunction definitions were adapted from the Centers for Medicare and Medicaid Services (CMS) SEP-1 definition and included hypotension (systolic blood pressure <90 mmHg), lactate greater than 2.0 mmol/L, noninvasive or invasive mechanical ventilation, creatinine greater than 2.0 mg/dL and a 50% or more increase from baseline, total bilirubin greater than 2.0 mg/dL and a 50% or more increase from baseline, or platelets less than 100 000/μL and a 50% or more decrease from baseline [12]. Within this group, we focused on patients who received both a broad-spectrum β-lactam (ceftriaxone, ampicillin-sulbactam, cefepime, ceftazidime, piperacillin-tazobactam, meropenem, or imipenem-cilastin) and vancomycin within 24 hours. Exclusion criteria included transfer from a non-MGB hospital, comfort measures or death within 6 hours of arrival, admission to psychiatry or obstetric services, antibiotic receipt prior to arrival, incomplete vital signs or missing key labs (creatinine, platelet count, anion gap, hematocrit, or white blood cell count) within 12 hours, and simultaneous infusion (start times of the first β-lactam and vancomycin dose within 1 minute).

Exposure, Outcomes, and Covariates

The exposure of interest was a β-lactam-first (vs vancomycin-first) antibiotic strategy. The outcome was in-hospital mortality. Covariates included demographics (age, sex, race/ethnicity), encounter characteristics (calendar year, arrival by ambulance, academic vs community hospital, insurance type, arrival from a healthcare facility, hospital discharge within the preceding 90 days), Elixhauser comorbidities (leukemia, lymphoma, solid tumor with and without metastases, chronic lung disease, diabetes, heart failure, liver disease, renal failure, and the composite Agency for Healthcare Research and Quality [AHRQ] Elixhauser mortality index [15]), physiologic severity-of-illness markers (vital signs, laboratory results, and highest respiratory support and vasopressors), body mass index, infection site (derived from present-on-admission International Classification of Diseases, Tenth Revision [ICD-10], discharge diagnosis codes), and time-to-first antibiotic infusion (in minutes, relative to ED arrival).

Statistical Analysis

We used inverse probability weighting (IPW) with propensity scores to compare in-hospital mortality rates between groups receiving β-lactam versus vancomycin as initial treatment [16]. To test the balance of covariate distribution between the groups, the standardized mean difference (SMD) for each covariate was calculated before and after applying IPW. After applying IPW, an SMD greater than 10% was defined as unbalanced. This approach targets an estimate of the average treatment effect: specifically, here the effect of treating everyone in the population first with β-lactams versus instead treating everyone first with vancomycin on the odds of in-hospital mortality. We calculated these estimates using generalized linear models, which were estimated with logit link using robust sandwich variance estimation [17]. Given that β-lactams are more likely to constitute effective antimicrobial therapy than vancomycin, we also assessed whether effect estimates for the β-lactam-first strategy changed when replacing the time-to-first antibiotic covariate with time-to-first β-lactam.

We performed several subgroup analyses focusing on patients who (1) had positive blood cultures (excluding common skin contaminants) from samples taken within 24 hours of arrival, (2) had positive clinical cultures for MRSA (excluding nasal swabs) within 24 hours, (3) received antipseudomonal β-lactams (ie, excluding ceftriaxone and ampicillin-sulbactam from the β-lactam definition), and (4) had shock (defined as hypotension or lactate ≥4.0 mmol/L, similar to CMS SEP-1 criteria [18]) versus no shock within 12 hours. We also conducted sensitivity analyses using stricter criteria for shock (≥2 hypotension readings ≥15 minutes apart plus lactate >2.0 mmol/L, similar to Sepsis-3 criteria [19]), as well as stricter time windows for blood cultures and receipt of both vancomycin and β-lactam (within 12 hours and 6 hours of arrival, rather than 24 hours) and organ dysfunction (within 6 hours and 3 hours of arrival, rather than 12 hours). Finally, to assess the consistency of our results under a different causal inference method, we conducted a sensitivity analysis using propensity score matching (PSM). We modeled the likelihood of receiving vancomycin as the initial treatment and matched these patients with similar individuals who received β-lactams first. One-to-one nearest-neighbor matching without replacement was performed using the propensity score with a caliper width of 0.2 SDs.

Continuous variables are presented as medians and interquartile ranges (IQRs). Categorical variables are presented as counts and percentages. The 2-sided significance level for all tests was set at a P value <.05. Baseline characteristics, treatments, and

crude outcomes were compared using the Mann–Whitney test for continuous variables and using the chi-square test or Fisher's exact test for categorical variables. The IPW estimates of odds ratios (ORs) were obtained by the exponentiated coefficient on treatment group in a weighted generalized linear model with logit link, weighted by the inverse probability weights, with the dependent variable an indicator of mortality and independent variable the treatment group indicator. Conservative 95% confidence intervals (CIs) for IPW estimates were obtained via the commonly used robust sandwich variance estimator [20]. Odds ratios from the PSM estimates were obtained by the exponentiated coefficient on the treatment group from a similar generalized linear model applied to the matched sample. All analyses were performed using R version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Study Cohort

The final analytic cohort included 25 391 patients admitted with suspected sepsis between June 2015 and August 2022 who received both β-lactam and vancomycin therapy within 24 hours; 21 449 (84.4%) received the β-lactam first and 3942 (15.6%) received vancomycin first (Supplementary Figure 1). The most commonly initially prescribed β-lactams were cefepime (n = 12 549, 58.5%), piperacillin-tazobactam (n = 4110, 19.2%), and ceftriaxone (n = 3571, 16.6%).

Baseline Characteristics

Compared with the β-lactam-first group, patients in the vancomycin-first group were younger (median age: 65 vs 67 years), arrived less often by ambulance (59.9% vs 63.7%), were more frequently admitted to academic versus community hospitals (73.0% vs 70.6%), more commonly had Medicaid or private insurance, had more hospitalizations within the past 90 days (46.3% vs 43.5%), had a lower comorbidity burden (median AHRQ Elixhauser mortality score: 14 vs 15), had fewer abnormalities in most initial vital signs (heart rate, respiratory rate, temperature) and laboratory values (albumin, anion gap, glucose, hematocrit, lactate, white blood cell count), and required less oxygen support (43.6% vs 40.3% on room air) and vasopressors within 12 hours (21.4% vs 24.1%) ($P < .05$ for all comparisons) (Table 1). More patients in the vancomycin-first group were also admitted in earlier years of the study (ie, the β-lactam-first strategy became more common over time). There were no significant differences in sex, race/ethnicity, admission from a facility, median body mass index, most individual comorbidities, initial systolic blood pressure, and other laboratory tests.

Infectious Diagnoses and Microbiologic Results

The vancomycin-first group had more skin and musculoskeletal infections (20.0% vs 7.8%; $P < .001$) and miscellaneous infections (10.5% vs 7.3%; $P < .01$), while the β-lactam-first group had more septicemia (51.7% vs 46.4%; $P < .001$), urinary infections (10.3% vs 7.5%; $P < .001$), and intra-abdominal infections (9.2% vs 7.7%; $P = .004$); there was no difference in pulmonary or central nervous system infections (Figure 1). Rates of documented bloodstream infections (from blood cultures drawn within 24 hours) were similar in the 2 groups (16.3% vs 15.5%; $P = .261$), but there were more positive MRSA clinical cultures (4.5% vs 3.2%; $P < .001$) and MRSA bloodstream infections (1.8% vs 1.2%; $P < .001$) in the vancomycin-first group.

Time-to-Antibiotics

Initial antibiotics were administered later in the vancomycin-first group (median: 175 minutes from ED arrival; IQR: 99–324) compared with the β-lactam-first group (median: 133 minutes; IQR: 77–231) (difference in median time: 42 minutes; $P < .001$) (Figure 2). In the vancomycin-first group, β-lactams were administered a median of 339 minutes from arrival (IQR: 198–574 minutes), for a difference in median time of 164 minutes (almost 3 hours) between the initial vancomycin infusion and subsequent β-lactam infusion and a difference of 206 minutes (~ 3.5 hours) for time from ED arrival to first β-lactam compared with the β-lactam-first group. In the β-lactam-first group, the median time to vancomycin was 242 minutes (IQR: 146–452), for a difference of 109 minutes between the initial β-lactam and subsequent vancomycin infusion.

Covariate Balance and Outcomes

Following IPW, characteristics became well balanced between the 2 groups, with no SMDs greater than 10% (Figure 3). Crude in-hospital mortality was similar between the groups (2874/21 449 [13.4%] in the β-lactam-first group and 538/3942 [13.6%] in the vancomycin-first group; OR: .98; 95% CI: .89–1.08; $P = .67$). In the primary IPW analysis, the β-lactam-first strategy was associated with significantly lower in-hospital mortality (adjusted OR [aOR]: .89; 95% CI: .80–.99; $P = .046$). When the time-to-first antibiotic covariate was replaced with time-to-first β-lactam, this association was attenuated and no longer significant (aOR: .93; 95% CI: .82–1.05; $P = .25$).

Subgroup and Sensitivity Analyses

Results for the IPW subgroup and sensitivity analyses are shown in Figure 4. There were trends towards lower mortality with the β-lactam-first strategy that did not reach statistical significance for most subgroups examined, including patients with positive blood cultures (n = 4099; 16.1% of the cohort; aOR: .80; 95% CI: .62–1.04) or positive MRSA clinical cultures (n = 868; 3.4% of the cohort; aOR: .91; 95% CI: .55–1.51), and patients who received antipseudomonal

Table 1. Characteristics of Patients With Suspected Sepsis in the β-Lactam-First Versus Vancomycin-First Groups

Characteristic	β-Lactam First (n = 21 449)	Vancomycin First (n = 3942)	*P*
Median (IQR) age, y	67 (56–78)	65 (53–73)	<.001
Male sex, n (%)	12 323 (57.5%)	2275 (57.7%)	.776
Race/ethnicity, n (%)			.052
White	15 932 (74.3%)	2904 (73.7%)	
Black	2011 (9.4%)	416 (10.6%)	
Hispanic	1242 (5.8%)	218 (5.5%)	
Other	1868 (8.7%)	330 (8.4%)	
Year of ED arrival, n (%)			<.001
2015–2016	2167 (10.1%)	833 (21.1%)	
2017–2018	5889 (27.5%)	1432 (36.3%)	
2019–2020	7476 (34.9%)	914 (23.2%)	
2021–2022	5914 (27.6%)	763 (19.4%)	
Arrival via ambulance, n (%)	13 662 (63.7%)	2360 (59.9%)	<.001
Academic (vs community) hospital, n (%)	15 153 (70.6%)	2877 (73.0%)	.003
Primary insurance type, n (%)			.031
Medicaid	2305 (10.7%)	449 (11.4%)	
Medicare	10 454 (48.7%)	1810 (45.9%)	
Private	8259 (38.5%)	1599 (40.6%)	
Other	168 (0.8%)	33 (0.8%)	
Admission from facility, n (%)	2191 (10.2%)	376 (9.5%)	.205
Hospitalization within past 90 d, n (%)	9320 (43.5%)	1827 (46.3%)	.001
Median (IQR) body mass index, kg/m^2	26.0 (22.3–31.0)	25.9 (22–3.30.5)	.173
Select comorbidities, n (%)			
Lymphoma	933 (4.3%)	174 (4.4%)	.89
Solid tumor without metastases	3736 (17.4%)	615 (15.6%)	.006
Solid tumor with metastases	2719 (12.7%)	481 (12.2%)	.424
Chronic pulmonary disease	1312 (6.1%)	242 (6.1%)	.986
Diabetes with complications	5419 (25.3%)	961 (24.4%)	.247
Heart failure	6781 (31.6%)	1265 (32.1)	.568
Renal failure (severe)	1894 (8.8%)	411 (10.4%)	.001
Median (IQR) AHRQ Elixhauser mortality score	15 (1–30)	14 (1–28)	.048
Initial vital signs, median (IQR)			
Heart rate, beats/min	102 (85–119)	100 (83–115)	<.001
Respiratory rate, breaths/min	20 (18–24)	20 (18–22)	<.001
Systolic blood pressure, mmHg	118 (94–140)	118 (99–138)	.688
Temperature, °F	98.2 (97.4–99.6)	98.3 (97.6–99.6)	.01
Initial lab values, median (IQR)			
Albumin, g/dL	3.5 (3.0–3.9)	3.5 (3.0–3.9)	.008[a]
Anion gap, mEq/L	15 (13–19)	16 (13–19)	.015
Aspartate transferase, U/L	31 (20–59)	31 (20–59)	.913
Creatinine, mg/L	1.2 (0.9–2.0)	1.2 (0.9–2.1)	.759
Glucose, mg/L	134 (109–185)	130 (104–182)	<.001
Hematocrit, %	35.5 (30.1–40.5)	34.7 (29.2–39.6)	<.001
Lactate, mmol/L	2.5 (1.6–3.7)	2.3 (1.6–3.4)	<.001
Platelets, 10^9/L	218 (149–302)	219 (146–301)	.315
Sodium, mEq/L	136 (133–140)	137 (133–140)	.431
Total bilirubin, mg/dL	0.6 (0.4–1.0)	0.6 (0.4–1.0)	.1
White blood cell count, 10^9/L	11.9 (7.7–17.1)	11.8 (7.6–16.6)	.083
Highest oxygen support (within 12 h), n (%)			<.001
Room air	8648 (40.3%)	1717 (43.6%)	
Simple nasal cannula	6095 (28.4%)	1050 (26.6%)	
Mask/high-flow nasal cannula	888 (4.1%)	118 (3.0%)	
Noninvasive ventilation	1040 (4.8%)	191 (4.8%)	
Invasive ventilation	3607 (16.8%)	675 (17.1%)	
Vasopressor support (within 12 h)	5168 (24.1%)	843 (21.4%)	<.001

Abbreviations: AHRQ, Agency for Healthcare Research and Quality; ED, emergency department; IQR, interquartile range.

[a]Albumin levels were statistically higher in the β-lactam group.

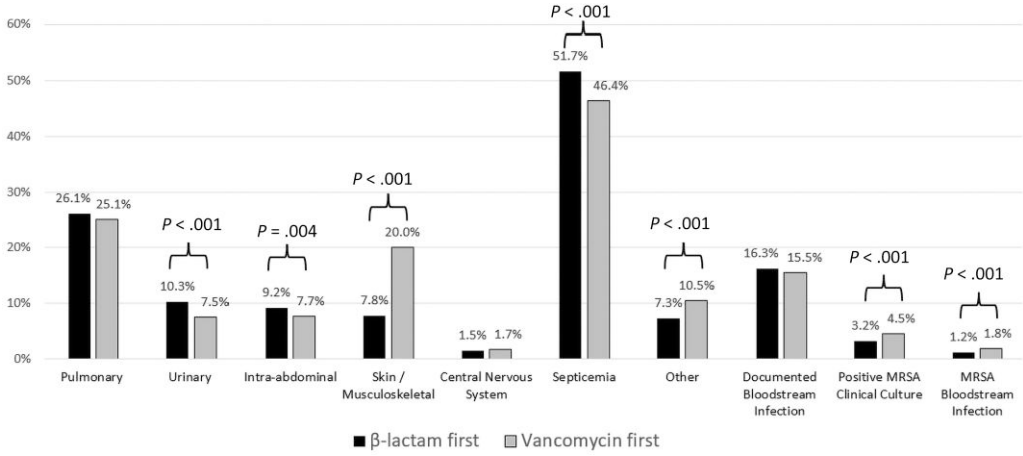

Figure 1. Distribution of infectious diagnoses and microbiologic results in β-lactam-first versus vancomycin-first groups. Pulmonary, urinary, intra-abdominal, skin/musculoskeletal, central nervous system, septicemia, and other infections were classified by present-on-admission ICD-10 codes. Bloodstream infections and MRSA clinical cultures were based on blood or clinical cultures drawn within 24 hours of emergency department arrival. Statistically significant differences with *P* values <.05 are denoted with text; unmarked comparisons were not statistically significant. Abbreviations: ICD-10, International Classification of Diseases, Tenth Revision; MRSA, methicillin-resistant *Staphylococcus aureus*.

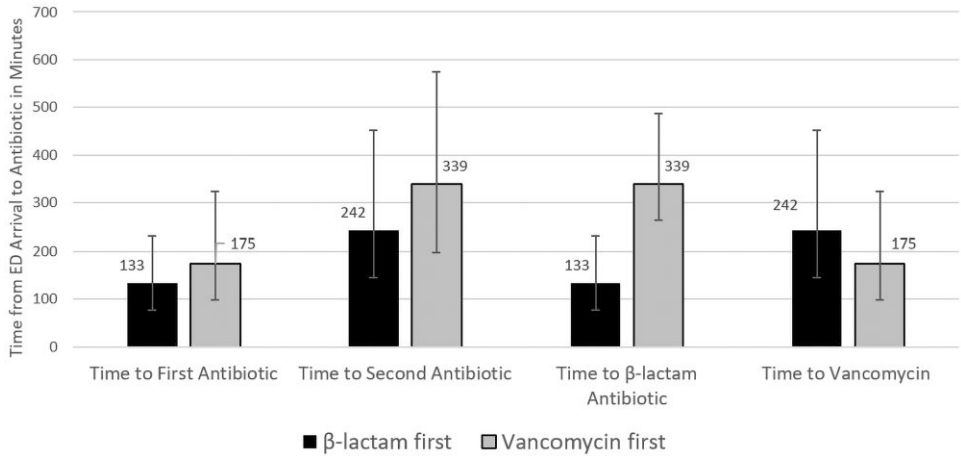

Figure 2. Median time (in minutes) from emergency department arrival to first and second antibiotics for the β-lactam-first and vancomycin-first groups. Error bars represent the 25th and 75th interquartile ranges.

β-lactams (n = 23 099; 91.0% of the cohort; aOR: .91; 95% CI: .81–1.02). However, in the subgroup of patients with sepsis without shock within 12 hours (n = 9474; 37.3% of the cohort), there was a significant association between the β-lactam-first strategy and lower mortality (aOR: .80; 95% CI: .64–.99); this association was not observed in the septic shock subgroup (n = 15 917; 62.7% of the cohort; aOR: .92; 95% CI: .81–1.05). Results were similar when using the stricter shock definition (persistent hypotension and lactate ≥2.0 mmol/L) and when using tighter time windows for antibiotics and organ dysfunction (12 hours/6 hours and 6 hours/3 hours) (Figure 4).

Examination of baseline characteristics of the sepsis versus septic shock subgroups (using the primary shock definition) revealed some notable differences, including longer median time to first and second antibiotics, lower comorbidity burden, lower illness severity (most vitals, labs, oxygen and vasopressor requirement), and more skin/musculoskeletal infections in the sepsis group (Supplementary Table 1). Notably, rates of MRSA clinical cultures and MRSA bacteremia were similar.

In the PSM sensitivity analysis, we were able to match 3938 patients in the β-lactam group to an equivalent number in the vancomycin group (post-match characteristics shown in Supplementary Table 2). The point estimates of the propensity

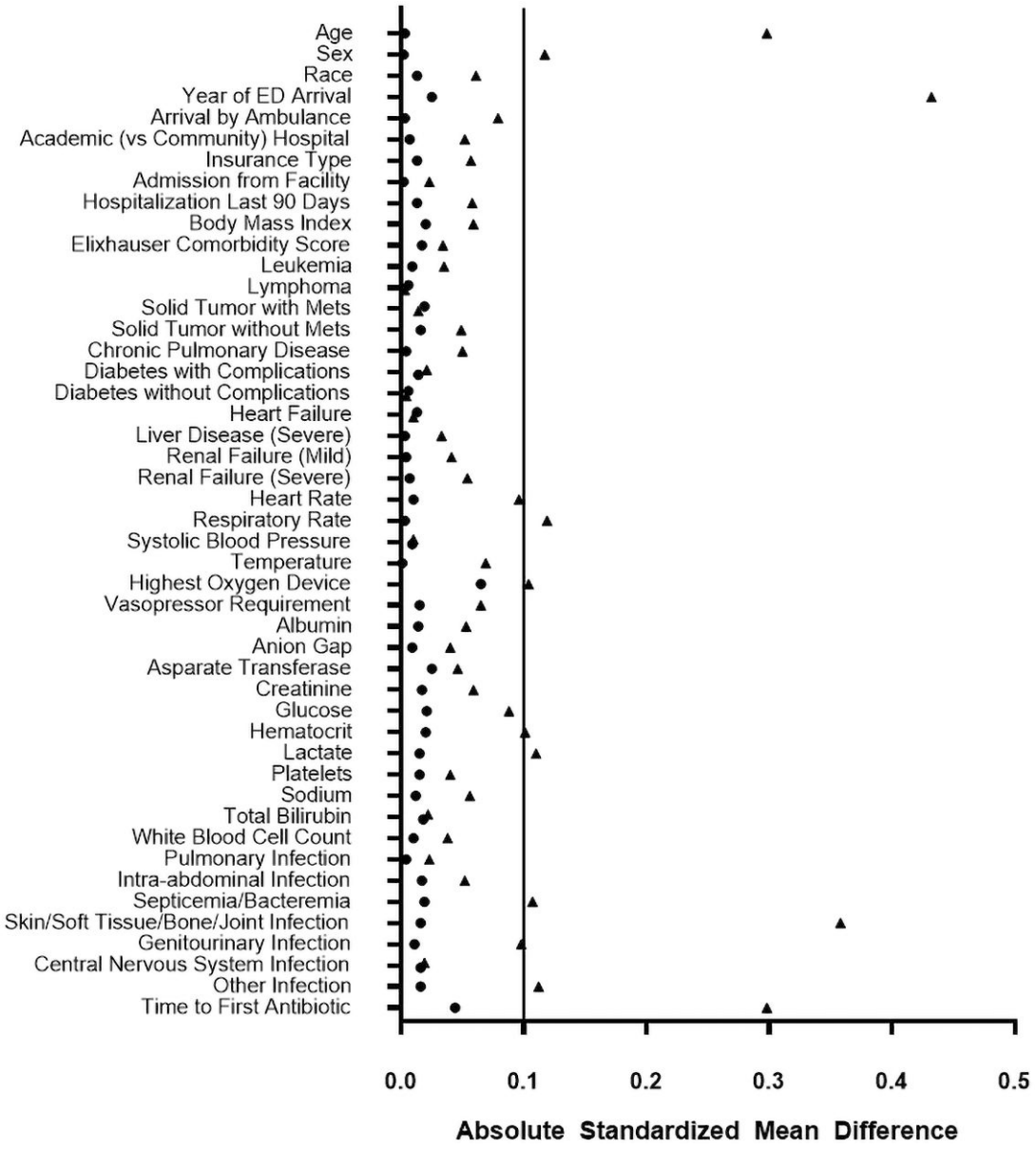

Figure 3. Standardized mean differences in the β-lactam-first versus vancomycin-first groups before and after IPW. Triangles indicate SMDs prior to IPW; circles indicate SMDs after IPW. Abbreviations: ED, emergency department; IPW, inverse probability weighting; Mets, metastases; SMD, standardized mean difference.

matching analyses were in the same direction as the IPW estimates but attenuated and nonsignificant (aOR: .94; 95% CI: .82–1.07) (Supplementary Table 3).

DISCUSSION

In this multihospital cohort of more than 25 000 patients admitted with suspected sepsis who received combination β-lactam and vancomycin therapy within 24 hours of ED arrival, 84% received β-lactams first and 16% received vancomycin first. Patients administered vancomycin first tended to be less severely ill and were more likely to have skin/soft tissue/musculoskeletal infections compared with those administered β-lactams first. The vancomycin-first group also received their first and second antibiotic doses later: there was almost a 3-hour median delay from vancomycin to β-lactam infusion compared with a less-than-2-hour median delay from β-lactam to vancomycin infusion; overall, half the patients in the vancomycin-first group received β-lactams more than 3.5 hours later relative to ED arrival compared with the β-lactam-first group. Using IPW to adjust for a comprehensive set of covariates, we found that β-lactam administration prior to vancomycin was associated with an 11% reduction in the odds of in-hospital mortality.

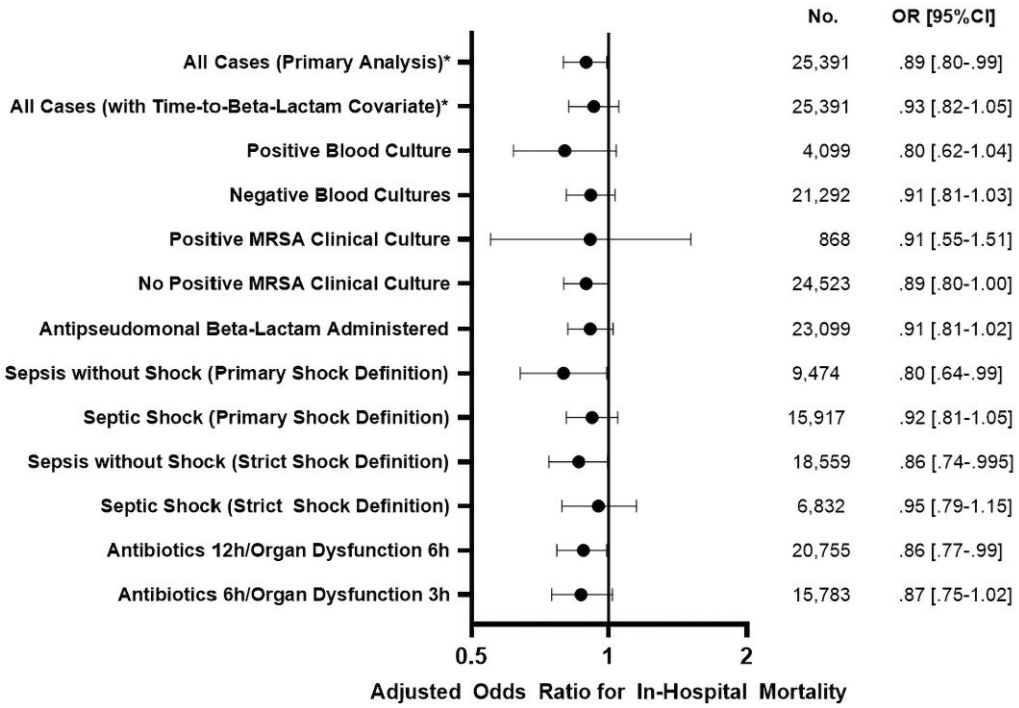

Figure 4. Primary and subgroup IPW analyses assessing the association between a β-lactam-first versus vancomycin-first strategy in patients with suspected sepsis. *The primary IPW analysis included time-to-first antibiotic as a covariate. A secondary analysis was also conducted where the time-to-first antibiotic covariate was replaced with time-to-β-lactam. The remaining subgroup analyses all utilized time-to-first antibiotic as a covariate. The primary shock definition included hypotension or lactate ≥4.0 mmol/L (within 12 hours). The stricter shock definition required 2 hypotension readings ≥15 minutes apart and lactate >2.0 mmol/L. The primary analysis required blood cultures and antibiotic administration (both vancomycin and β-lactam) within 24 hours of emergency department arrival and organ dysfunction within 12 hours. "Antibiotics 12h/Organ Dysfunction 6h" and "Antibiotics 6h/Organ Dysfunction 3h" refer to sensitivity analyses using stricter time windows. Abbreviations: IPW, inverse probability weighting; MRSA, methicillin-resistant *Staphylococcus aureus*; OR, odds ratio.

Point estimates were directionally similar but nonsignificant when using PSM and in multiple subgroup and sensitivity analyses.

The potential protective effect of a β-lactam-first strategy on sepsis mortality may reflect the benefits of treating with a broader spectrum agent sooner and possibly the greater bactericidal activity of β-lactams compared with vancomycin [21, 22]. Supporting this notion, the protective effect was attenuated and became nonsignificant when the time-to-first antibiotic covariate was replaced with time-to-first β-lactam antibiotic. This result conforms to the expected effect if earlier time-to-first β-lactam is on the causal pathway between β-lactam first and reduced mortality. Although some studies suggest that gram-positive organisms have become a more common cause of sepsis in recent decades, gram-negative infections are still highly prevalent [23]. Furthermore, MRSA infections constitute a small fraction of sepsis cases (only 3.4% in our cohort) and most β-lactams are active against common gram-positive organisms, including *Streptococcus* species and methicillin-susceptible S aureus [9, 24].

Our findings add more muted support for a β-lactam-first strategy compared with the recent study by Amoah et al [10] that reported a dramatic 52% reduction in the odds of death at 7 days with a β-lactam-first strategy among 3376 patients with documented bloodstream infections. There are several important differences in our study that may account for this. First, we focused on the broader population of patients with suspected sepsis rather than just confirmed bloodstream infections. However, in a subgroup analysis of patients with bloodstream infections (16% of the cohort), we found a similar mortality point estimate (aOR: .80 vs .89 in primary analysis) but with wide CIs. Second, the Amoah et al study only assessed mortality over very short follow-up periods (7 days and 48 hours); longer-term mortality (30–90 days or in-hospital death), a more common sepsis endpoint, was not examined [25]. Third, while their study also used IPW to address confounding, it did not adjust for several important covariates that we included in our study—in particular, infection source and granular vital signs. Detailed confounding adjustment is critical as we found that patients administered vancomycin before β-lactams were less severely ill and more likely to have more skin/musculoskeletal infections (and MRSA infections, although rare) versus urinary infections and septicemia diagnoses in the β-lactam group. This suggests that the sequence of

antibiotic administration is unlikely to be random in many cases. Fourth, the Amoah et al study included both community-onset and hospital-onset bloodstream infections, which carry very different prognoses [26, 27]; we focused exclusively on patients presenting to the ED with suspected community-onset sepsis.

Overall, our estimate of a possible 11% reduction in the odds of mortality associated with an approximately 3.5-hour difference in time to β-lactam administration is congruent with other large studies of time-to-antibiotics in sepsis, which have generally reported increases in the odds of death by 4%–7% for each hour delay in antibiotics [2, 28]. This effect estimate suggests that prioritizing antibiotic sequence may only lead to modest gains in sepsis survival, particularly since most patients in our cohort already received β-lactams first and this proportion increased over time. However, the proportion of patients with sepsis that could benefit may be greater in other healthcare systems where fewer may currently be receiving β-lactams first, and arguably even small gains in sepsis mortality at the individual level could translate into substantial public health benefit given the very high societal burden of sepsis.

We performed several subgroup analyses as well as a sensitivity analysis with an alternate causal inference method (PSM) to validate our main results. These yielded consistent point estimates in the same direction as the primary analysis, but given the decreased statistical power, most did not reach statistical significance. Importantly, the absence of a signal for harm in the subgroup analysis of patients with positive MRSA clinical cultures also provides further support for the safety of guidance that prioritizes β-lactam administration.

Interestingly, however, we found a significant protective association for the β-lactam-first strategy in patients with sepsis without shock but not in septic shock. This is counterintuitive given that prior studies have demonstrated that the time to first and second antibiotics is of greatest importance in septic shock [2, 12, 28–32]. We did not observe a higher prevalence of MRSA infections in the septic shock group that could explain this finding. One possible reason is that both the initial and subsequent antibiotics were administered sooner in the septic shock group, leading to less difference in time-to-β-lactams between the vancomycin-first versus β-lactam-first groups compared with those with sepsis alone. Alternatively, since the severity of illness was generally lower in the vancomycin-first group, risk adjustment with IPW shifted the mortality point estimate down for the β-lactam-first group; however, when limiting to a sicker subset (septic shock), the difference in severity of illness between the vancomycin- versus β-lactam-first groups was attenuated, leading to a less pronounced change in the adjusted mortality point estimate.

Our study has several limitations. First, our cohort included 5 hospitals in a single healthcare system. This may limit generalizability, particularly to regions with different MRSA prevalence. Second, not every patient with suspected sepsis has a bacterial infection; some have viral or fungal infections or noninfectious mimics [33, 34]. However, point estimates were similar in the subgroup of patients with documented bloodstream infections. Third, we did not account for other sepsis treatments, such as volume and timing of fluid resuscitation, that might affect the relationship between antibiotic sequence and mortality. However, prior large rigorous analyses have not demonstrated a clear association between time-to-fluid bolus completion and outcomes [2]. Fourth, it is unclear to what extent delays in β-lactam administration following vancomycin were due to logistical reasons (eg, limited intravenous access) versus evolution in providers' treatment plan. Fifth, we recognize the risk of residual confounding despite using a wide array of detailed administrative and clinical data. As such, we believe that the benefit of a β-lactam-first strategy would ideally be quantified with a randomized controlled trial, although, in practice, this could be difficult to organize given concerns around equipoise and risk of delaying gram-negative coverage. Alternatively, a larger study across diverse hospitals using a target trial-emulation approach and accounting for time-varying confounding could provide greater certainty regarding the potential benefits of a β-lactam-first strategy.

In conclusion, in this large multi-hospital cohort of patients with suspected sepsis prescribed combination vancomycin and β-lactams, β-lactam administration before vancomycin was associated with a modest reduction in the odds of in-hospital mortality in the primary analysis but an attenuated and nonsignificant effect in secondary analyses. These findings support prioritizing β-lactam therapy in most patients with sepsis but ideally merit confirmation in randomized trials given the risk of residual confounding in observational analyses.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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