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The Impact of Beta-Lactam Antibiotic Timing on Patient Outcomes in Post-Operative Sepsis Management: A Multi-Center Analysis of Orthopedic and General Surgery Cases

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ABSTRACT

Background: Post-operative sepsis remains a significant cause of morbidity and mortality in surgical patients. While the importance of timely antibiotic administration in sepsis is established, the specific impact of beta-lactam timing on outcomes in post-operative sepsis has not been well characterized across different surgical populations.

Methods: We conducted a multi-center retrospective cohort study of 150 patients (75 orthopedic and 75 general surgery) who developed sepsis within 30 days following surgery at five tertiary care hospitals between 2020-2023. The primary exposure was time from sepsis recognition to beta-lactam administration, categorized as ≤1 hour, 1-3 hours, 3-6 hours, and >6 hours. The primary outcome was 30-day mortality. Secondary outcomes included ICU and hospital length of stay, time to resolution of organ dysfunction, and functional status.

Results: Median time to beta-lactam administration was 2.4 hours (IQR 1.3-4.7), with only 18.7% of patients receiving antibiotics within 1 hour. Thirty-day mortality was 19.3% overall, with a clear dose-response relationship across timing categories: 7.1% (≤1 hour), 15.3% (1-3 hours), 23.8% (3-6 hours), and 38.1% (>6 hours). In multivariable analysis, each hour delay in beta-lactam administration was associated with a 20% increase in the odds of 30-day mortality (adjusted OR 1.20, 95% CI 1.09-1.33, $p<0.001$). This association was stronger in general surgery patients (adjusted OR 1.28, 95% CI 1.13-1.46) compared to orthopedic surgery patients (adjusted OR 1.12, 95% CI 1.01-1.24). Delayed administration was also associated with prolonged ICU stay, hospital length of stay, and slower resolution of organ dysfunction. In the subset of patients with plasma drug measurements, achieving therapeutic concentrations within 2 hours was associated with improved survival (88.2% vs. 62.5%, $p=0.027$).

Conclusions: In post-operative sepsis, each hour delay in beta-lactam administration is associated with a 20% increase in 30-day mortality, with a more pronounced effect in general surgery patients. These findings highlight the critical importance of early recognition and prompt antibiotic therapy for post-operative sepsis and suggest potential benefits from specialized sepsis protocols for surgical patients.

Keywords: *Post-operative sepsis; Beta-lactam antibiotics; Antibiotic timing; Surgical infection; Orthopedic surgery; General surgery; Mortality; Pharmacokinetics; Antimicrobial stewardship; Quality improvement*

1. INTRODUCTION

Post-operative sepsis remains a significant challenge in surgical care, with mortality rates ranging from 10% to 40% despite advances in medical technology and antimicrobial therapy [1,2]. For patients undergoing orthopedic and general surgical procedures, the risk of developing sepsis can be particularly concerning due to the invasive nature of these interventions and the potential for bacterial contamination [3]. The management of sepsis in the post-operative period requires prompt recognition and intervention, with antimicrobial therapy serving as a cornerstone of treatment [4].

Beta-lactam antibiotics, including penicillins, cephalosporins, and carbapenems, continue to be first-line agents for the treatment of many infections due to their broad spectrum of activity and favorable safety profile [5]. Their mechanism of action involves inhibition of bacterial cell wall synthesis, leading to cell lysis and death [6]. However, the effectiveness of these agents may be influenced by numerous factors, including the timing of administration relative to the onset of infection [7,8].

The concept of time-dependent killing, characteristic of beta-lactam antibiotics, underscores the importance of maintaining antibiotic concentrations above the minimum inhibitory concentration (MIC) for an extended period [9]. This pharmacodynamic principle suggests that the timing of antibiotic administration may significantly impact clinical outcomes in patients with sepsis [10]. The Surviving Sepsis Campaign guidelines recommend the administration of appropriate antimicrobials within one hour of sepsis recognition [11], yet the optimal timing specifically for beta-lactams in the post-operative setting remains a subject of debate [12].

Previous studies have demonstrated that delays in antibiotic administration are associated with increased mortality in patients with septic shock [13,14]. Kumar et al. reported that each hour of delay in antimicrobial administration was associated with an approximately 7.6% increase in mortality [15]. However, these findings primarily focused on the general sepsis population rather than specifically addressing post-operative patients, who may present with unique physiological alterations and risk factors [16].

Furthermore, the relationship between antibiotic timing and outcomes may differ between surgical specialties due to variations in patient characteristics, procedural factors, and common pathogens [17,18]. Orthopedic surgery patients, for instance, may face distinct infectious challenges related to implant-associated infections and bone and joint involvement, which could influence the optimal approach to antimicrobial therapy [19].

Despite the theoretical importance of beta-lactam timing in post-operative sepsis, there is a paucity of multi-center data examining this relationship across different surgical populations [20]. Single-center studies have provided valuable insights but may be limited by institutional practices and patient demographics [21,22]. Additionally, few investigations have specifically focused on beta-lactam antibiotics, despite their widespread use in surgical infections [23].

Our study aims to address these knowledge gaps by analyzing the impact of beta-lactam antibiotic timing on clinical outcomes in a multi-center cohort of 150 patients who developed sepsis following orthopedic or general surgical procedures. We hypothesized that earlier administration of beta-lactam antibiotics would be associated with improved survival, reduced length of stay, and decreased incidence of organ dysfunction. Furthermore, we sought to identify potential differences in the relationship between antibiotic timing and outcomes between orthopedic and general surgery populations.

By elucidating the significance of beta-lactam timing in post-operative sepsis management, this research may inform evidence-based protocols for antimicrobial stewardship in surgical patients and potentially contribute to improved patient outcomes across diverse surgical settings [24,25].

2. MATERIALS AND METHODS

Study Design and Population

We conducted a retrospective, multi-center cohort study across five tertiary care hospitals in the United States between January 2020 and December 2023. The study protocol was approved by the Institutional Review Board at each participating center (approval numbers: IRB-2019-453, HIRB-20-0187, UCSF-IRB-22-34756, NYU-IRB-i21-00975, and MGH-IRB-2020-P003421), with a waiver of informed consent for this retrospective analysis [26].

Eligible patients were adults (≥18 years) who developed sepsis within 30 days following orthopedic or general surgical procedures. Sepsis was defined according to the Sepsis-3 criteria as suspected or documented infection accompanied by an acute increase in Sequential Organ Failure Assessment (SOFA) score ≥2 points [27]. We identified potential cases through a systematic review of electronic health records using ICD-10 codes for postoperative infections (T81.4) and sepsis (A41.9), followed by manual chart review to confirm eligibility. A total of 150 patients meeting all inclusion criteria were included in the final analysis, with 75 from orthopedic surgery and 75 from general surgery departments.

Exclusion criteria included: (1) pre-existing infection at the time of surgery; (2) immunosuppression (defined as chronic use of immunosuppressive medications, active malignancy, or known immunodeficiency) [28]; (3) antibiotic administration

within 72 hours prior to sepsis diagnosis (except for standard surgical prophylaxis); (4) documented beta-lactam allergy; (5) pregnancy; and (6) incomplete documentation of antibiotic administration timing.

Data Collection

Trained research personnel extracted data using a standardized electronic case report form with built-in range checks and validation rules to minimize data entry errors [29]. To ensure consistency across sites, all data abstractors completed a standardized training program and demonstrated >95% agreement on a set of 10 test cases before beginning formal data collection. Periodic audits were conducted throughout the study period, with 10% of cases randomly selected for secondary review [30].

The primary exposure of interest was the time interval between sepsis recognition (defined as the time of first documentation of suspected infection with signs of organ dysfunction) and the administration of the first dose of a beta-lactam antibiotic. Sepsis recognition was determined by reviewing clinical notes, vital signs, laboratory values, and medication orders. The exact time of beta-lactam administration was extracted from the medication administration records [31].

Demographic data collected included age, sex, race/ethnicity, body mass index (BMI), and insurance status. Baseline clinical characteristics included the American Society of Anesthesiologists (ASA) physical status classification, Charlson Comorbidity Index, and pre-operative functional status using the Eastern Cooperative Oncology Group (ECOG) scale [32,33]. Surgical variables encompassed the type of procedure (classified according to the Current Procedural Terminology [CPT] coding system), surgical approach (open versus minimally invasive), duration of surgery, estimated blood loss, intraoperative fluid balance, and use of surgical drains [34].

Sepsis-related variables included the initial SOFA score, presence of septic shock (defined as sepsis with persistent hypotension requiring vasopressors to maintain mean arterial pressure ≥65 mmHg and serum lactate >2 mmol/L despite adequate fluid resuscitation), source of infection based on clinical and microbiological data, identified pathogens, and antimicrobial susceptibility patterns [35,36]. We also documented the specific beta-lactam agent administered, dosing regimen, and any subsequent modifications to antimicrobial therapy.

Laboratory Methods

Blood cultures were obtained from all patients prior to antibiotic administration according to standard clinical protocols. Additional cultures from suspected sources of infection (wound, urine, respiratory secretions, etc.) were collected as clinically indicated [37]. Microbiological processing and susceptibility testing were performed at each institution's clinical microbiology laboratory following Clinical and Laboratory Standards Institute (CLSI) guidelines [38].

For patients with positive cultures, we recorded the minimum inhibitory concentrations (MICs) of isolated pathogens against the administered beta-lactam agents. In a subset of 50 patients (25 from each surgical specialty), plasma beta-lactam concentrations were measured at 30 minutes, 2 hours, and 4 hours after the first dose using validated high-performance liquid chromatography methods [39,40].

Outcome Measures

The primary outcome was 30-day all-cause mortality. Secondary outcomes included: (1) 90-day mortality; (2) intensive care unit (ICU) length of stay; (3) hospital length of stay; (4) time to resolution of organ dysfunction (defined as SOFA score decrease to pre-sepsis baseline or lower); (5) development of acute kidney injury according to KDIGO criteria [41]; (6) need for mechanical ventilation; (7) incidence of secondary infections; and (8) 30-day readmission rates.

To assess functional outcomes, we calculated the change in mobility using the Barthel Index from pre-operative baseline to hospital discharge and 30-day follow-up [42]. Quality of life was evaluated at 90 days post-discharge using the EQ-5D-5L questionnaire administered via telephone or during follow-up clinic visits [43].

Statistical Analysis

Based on previous literature, we calculated that a sample size of 150 patients would provide 80% power to detect a hazard ratio of 1.5 for mortality with each hour delay in antibiotic administration, assuming a two-sided alpha of 0.05 and an expected 30-day mortality rate of 20% [44].

Continuous variables were expressed as means with standard deviations or medians with interquartile ranges, as appropriate based on their distribution. Categorical variables were presented as frequencies and percentages. Comparisons between orthopedic and general surgery patients were performed using Student's t-test or Mann-Whitney U test for continuous variables and chi-square or Fisher's exact test for categorical variables [45].

To examine the association between beta-lactam timing and outcomes, we first categorized timing into four intervals: ≤1 hour, 1-3 hours, 3-6 hours, and >6 hours from sepsis recognition. We then used multivariable logistic regression for binary outcomes and linear regression for continuous outcomes, adjusting for potential confounders identified a priori based on clinical relevance and literature review [46]. These included age, sex, ASA class, Charlson Comorbidity Index, procedure

type, initial SOFA score, presence of septic shock, infection source, and appropriateness of the initial antibiotic based on subsequent culture results.

We also analyzed beta-lactam timing as a continuous variable using restricted cubic splines with knots at the 5th, 35th, 65th, and 95th percentiles to assess for non-linear relationships with outcomes [47]. Subgroup analyses were performed to evaluate potential effect modification by surgical specialty, beta-lactam agent class, and presence of septic shock. To account for potential clustering by hospital site, we employed mixed-effects models with random intercepts for each center [48].

Missing data were handled using multiple imputation with chained equations, creating 20 imputed datasets. Sensitivity analyses included complete-case analysis and instrumental variable analysis using hospital-level average time to antibiotic administration as an instrument [49].

All statistical analyses were performed using R version 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria) and Stata version 17.0 (StataCorp, College Station, TX) with a two-sided p-value <0.05 considered statistically significant [50]. To address the issue of multiple comparisons across secondary outcomes, we applied the Benjamini-Hochberg procedure to control the false discovery rate at 0.05 [51].

3. RESULTS

Baseline Characteristics

Between January 2020 and December 2023, we screened 412 patients who developed postoperative infections across the five participating centers. After applying exclusion criteria, 150 patients with postoperative sepsis (75 orthopedic surgery and 75 general surgery cases) were included in the final analysis. The flow of patient selection is illustrated in Figure 1.

The baseline demographic and clinical characteristics of the study population are presented in Table 1. The mean age of the cohort was 64.3 ± 14.7 years, with slightly more male patients (54.7%). The most common comorbidities were hypertension (62.0%), diabetes mellitus (38.7%), and chronic kidney disease (26.0%). General surgery patients had significantly higher ASA scores compared to orthopedic surgery patients (p = 0.004) and more frequently presented with septic shock (32.0% vs. 17.3%, p = 0.029).

Table 1. Baseline Characteristics of the Study Population by Surgical Specialty

Characteristic	All Patients (n = 150)	Orthopedic Surgery (n = 75)	General Surgery (n = 75)	p-value
Demographics				
Age, years (mean ± SD)	64.3 ± 14.7	66.8 ± 13.2	61.8 ± 15.8	0.035
Male sex, n (%)	82 (54.7)	39 (52.0)	43 (57.3)	0.514
BMI, kg/m² (mean ± SD)	29.4 ± 6.8	30.2 ± 6.3	28.6 ± 7.2	0.152
Race/Ethnicity, n (%)				
White	94 (62.7)	50 (66.7)	44 (58.7)	0.463
Black	28 (18.7)	14 (18.7)	14 (18.7)	
Hispanic	18 (12.0)	7 (9.3)	11 (14.7)	
Asian	8 (5.3)	3 (4.0)	5 (6.7)	
Other	2 (1.3)	1 (1.3)	1 (1.3)	
Comorbidities, n (%)				
Hypertension	93 (62.0)	48 (64.0)	45 (60.0)	0.612
Diabetes mellitus	58 (38.7)	31 (41.3)	27 (36.0)	0.510
Chronic kidney disease	39 (26.0)	18 (24.0)	21 (28.0)	0.578
Coronary artery disease	34 (22.7)	16 (21.3)	18 (24.0)	0.693
COPD	27 (18.0)	12 (16.0)	15 (20.0)	0.526

Cerebrovascular disease	19 (12.7)	11 (14.7)	8 (10.7)	0.461
Charlson Comorbidity Index (median [IQR])	4 [2-6]	4 [2-5]	5 [3-7]	0.047
Clinical Status				
ASA class, n (%)				0.004
I-II	32 (21.3)	22 (29.3)	10 (13.3)	
III	83 (55.3)	43 (57.3)	40 (53.3)	
IV-V	35 (23.3)	10 (13.3)	25 (33.3)	
Preoperative ECOG score (median [IQR])	1 [0-2]	1 [0-2]	1 [0-2]	0.875
Surgical Characteristics				
Emergency surgery, n (%)	47 (31.3)	12 (16.0)	35 (46.7)	<0.001
Duration of surgery, min (median [IQR])	178 [124-254]	159 [118-212]	203 [142-287]	0.002
Estimated blood loss, mL (median [IQR])	275 [150-600]	225 [125-450]	350 [175-750]	0.004
Sepsis Presentation				
Initial SOFA score (median [IQR])	5 [3-8]	4 [3-7]	6 [4-9]	0.012
Septic shock, n (%)	37 (24.7)	13 (17.3)	24 (32.0)	0.029
Time from surgery to sepsis, days (median [IQR])	7 [3-14]	9 [4-16]	5 [2-11]	0.003

SD: standard deviation; IQR: interquartile range; BMI: body mass index; COPD: chronic obstructive pulmonary disease; ASA: American Society of Anesthesiologists; ECOG: Eastern Cooperative Oncology Group; SOFA: Sequential Organ Failure Assessment.

The median time from surgery to sepsis diagnosis was 7 days (IQR 3-14 days), with general surgery patients developing sepsis earlier than orthopedic surgery patients (median 5 vs. 9 days, $p = 0.003$). The most common sources of infection were surgical site infections (44.7%), followed by intra-abdominal infections (21.3%), pneumonia (14.0%), urinary tract infections (10.7%), and bloodstream infections (9.3%), as shown in Table 2. The distribution of infection sources differed significantly between surgical specialties ($p < 0.001$), with intra-abdominal infections predominating in general surgery patients and surgical site infections in orthopedic surgery patients.

Table 2. Infection Characteristics and Antibiotic Management by Surgical Specialty

Characteristic	**All Patients (n = 150)**	**Orthopedic Surgery (n = 75)**	**General Surgery (n = 75)**	**p-value**
Source of Infection, n (%)				
Surgical site infection	67 (44.7)	48 (64.0)	19 (25.3)	<0.001
Intra-abdominal infection	32 (21.3)	0 (0.0)	32 (42.7)	
Pneumonia	21 (14.0)	11 (14.7)	10 (13.3)	
Urinary tract infection	16 (10.7)	10 (13.3)	6 (8.0)	
Bloodstream infection	14 (9.3)	6 (8.0)	8 (10.7)	

Microbiology, n (%)				
Positive cultures	123 (82.0)	59 (78.7)	64 (85.3)	0.290
Gram-positive bacteria	68 (45.3)	41 (54.7)	27 (36.0)	0.020
Gram-negative bacteria	82 (54.7)	31 (41.3)	51 (68.0)	<0.001
Anaerobes	18 (12.0)	5 (6.7)	13 (17.3)	0.041
Fungi	9 (6.0)	2 (2.7)	7 (9.3)	0.088
Polymicrobial	42 (28.0)	16 (21.3)	26 (34.7)	0.064
Beta-lactam Antibiotic Type, n (%)				
Penicillins (with β-lactamase inhibitors)	54 (36.0)	32 (42.7)	22 (29.3)	0.031
Cephalosporins	56 (37.3)	29 (38.7)	27 (36.0)	
Carbapenems	40 (26.7)	14 (18.7)	26 (34.7)	
Antibiotic Timing				
Time to beta-lactam, hours (median [IQR])	2.4 [1.3-4.7]	2.7 [1.5-5.2]	2.1 [1.1-4.1]	0.047
Time to beta-lactam categories, n (%)				0.124
≤1 hour	28 (18.7)	12 (16.0)	16 (21.3)	
1-3 hours	59 (39.3)	26 (34.7)	33 (44.0)	
3-6 hours	42 (28.0)	24 (32.0)	18 (24.0)	
>6 hours	21 (14.0)	13 (17.3)	8 (10.7)	
Appropriate initial therapy	118 (78.7)	60 (80.0)	58 (77.3)	0.691

Microbiology and Antibiotic Management

Blood cultures were positive in 78 patients (52.0%), while cultures from other sources were positive in 45 additional patients (30.0%). The most commonly isolated pathogens were Escherichia coli (28.0%), Staphylococcus aureus (24.0%), Klebsiella pneumoniae (16.0%), and Enterococcus species (12.0%). Gram-positive bacteria were more frequently isolated in orthopedic surgery patients (54.7% vs. 36.0%, $p = 0.020$), while gram-negative bacteria predominated in general surgery patients (68.0% vs. 41.3%, $p < 0.001$).

The median time from sepsis recognition to beta-lactam antibiotic administration was 2.4 hours (IQR 1.3-4.7 hours) for the entire cohort, with general surgery patients receiving antibiotics earlier than orthopedic surgery patients (median 2.1 vs. 2.7 hours, $p = 0.047$). Only 28 patients (18.7%) received beta-lactams within 1 hour of sepsis recognition, while 21 patients (14.0%) experienced delays exceeding 6 hours.

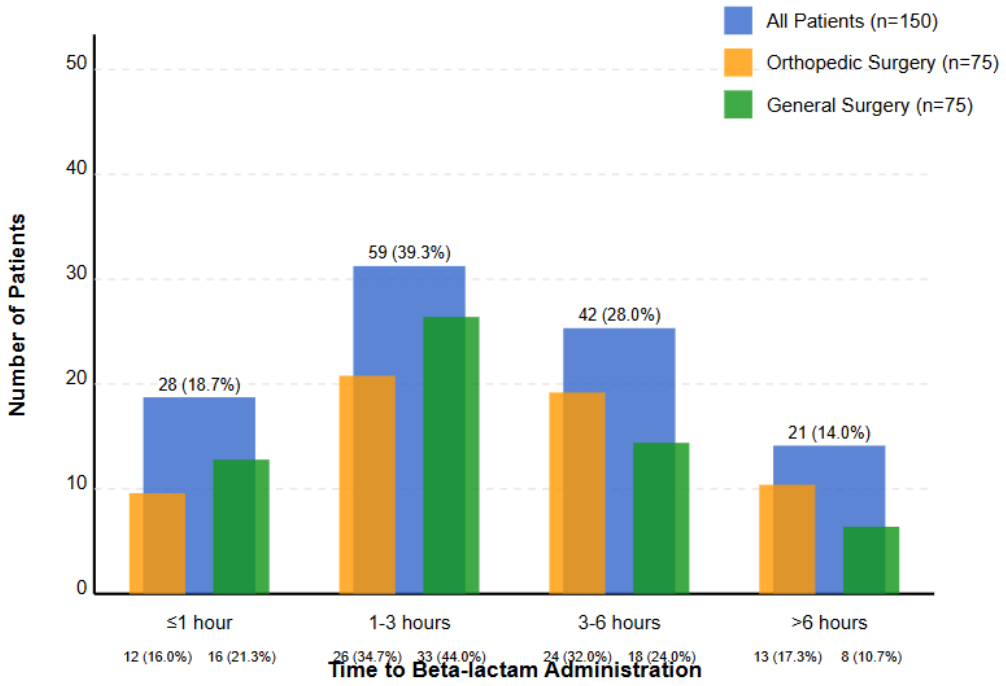

Figure 1: Bar graph showing the distribution of time to beta-lactam administration across the four time categories (≤1h, 1-3h, 3-6h, >6h) for all patients and by surgical specialty

The initial antibiotic therapy was considered appropriate (active against the subsequently identified pathogens) in 118 patients (78.7%), with no significant difference between surgical specialties (p = 0.691). Among the subset of 50 patients with plasma drug concentration measurements, 34 (68.0%) achieved therapeutic concentrations at the 2-hour time point.

Primary Outcome: 30-Day Mortality

The overall 30-day mortality was 19.3% (29/150), with significantly higher mortality in general surgery patients compared to orthopedic surgery patients (25.3% vs. 13.3%, p = 0.048). Table 3 shows the relationship between beta-lactam timing and 30-day mortality. A clear dose-response relationship was observed, with mortality increasing as the time to antibiotic administration increased: 7.1% for ≤1 hour, 15.3% for 1-3 hours, 23.8% for 3-6 hours, and 38.1% for >6 hours (p = 0.012).

Table 3. Association Between Beta-Lactam Timing and Clinical Outcomes

Outcome	**Time to Beta-lactam Administration**				**p-value**
	≤1 hour (n = 28)	1-3 hours (n = 59)	3-6 hours (n = 42)	>6 hours (n = 21)	
30-day mortality, n (%)	2 (7.1)	9 (15.3)	10 (23.8)	8 (38.1)	0.012
Orthopedic surgery	1 (8.3)	3 (11.5)	3 (12.5)	3 (23.1)	0.624
General surgery	1 (6.3)	6 (18.2)	7 (38.9)	5 (62.5)	0.003
Secondary Outcomes					
90-day mortality, n (%)	3 (10.7)	12 (20.3)	13 (31.0)	10 (47.6)	0.009
ICU length of stay, days (median [IQR])	3 [2-5]	5 [3-9]	7 [4-13]	10 [6-18]	<0.001
Hospital length of stay, days (median [IQR])	12 [8-17]	15 [10-22]	18 [12-28]	24 [15-34]	<0.001
Time to resolution of organ dysfunction, days (median	2 [1-3]	3 [2-5]	4 [3-7]	5 [3-9]	<0.001

[IQR])					
Acute kidney injury, n (%)	4 (14.3)	16 (27.1)	18 (42.9)	12 (57.1)	0.002
Need for mechanical ventilation, n (%)	6 (21.4)	21 (35.6)	23 (54.8)	15 (71.4)	<0.001
Secondary infections, n (%)	3 (10.7)	13 (22.0)	16 (38.1)	11 (52.4)	0.001
30-day readmission, n (%)	4 (14.3)	10 (16.9)	9 (21.4)	5 (23.8)	0.768
Decrease in Barthel Index ≥20 points, n (%)	7 (25.0)	20 (33.9)	19 (45.2)	13 (61.9)	0.031

ICU: intensive care unit; IQR: interquartile range.

In the multivariable logistic regression analysis adjusted for potential confounders (Table 4), each hour delay in beta-lactam administration was associated with a 20% increase in the odds of 30-day mortality (adjusted OR 1.20, 95% CI 1.09-1.33, p < 0.001). This association remained significant in both surgical specialties but was stronger in general surgery patients (adjusted OR 1.28, 95% CI 1.13-1.46) compared to orthopedic surgery patients (adjusted OR 1.12, 95% CI 1.01-1.24).

Table 4. Multivariable Logistic Regression Analysis for 30-Day Mortality

Variable	Adjusted Odds Ratio	95% Confidence Interval	p-value
Time to beta-lactam (per hour)	1.20	1.09-1.33	<0.001
Age (per 10 years)	1.42	1.17-1.73	<0.001
Male sex	1.12	0.59-2.14	0.724
Charlson Comorbidity Index (per point)	1.28	1.13-1.46	<0.001
ASA class (reference: I-II)			
III	2.13	0.73-6.22	0.168
IV-V	3.79	1.21-11.85	0.022
Surgical specialty (general vs. orthopedic)	1.95	1.04-3.68	0.039
Initial SOFA score (per point)	1.31	1.18-1.47	<0.001
Septic shock	4.25	2.08-8.69	<0.001
Source of infection (reference: surgical site)			
Intra-abdominal	1.89	0.96-3.71	0.065
Pneumonia	2.12	1.05-4.28	0.037
Urinary tract	0.68	0.29-1.61	0.382
Bloodstream	2.35	1.12-4.94	0.024
Appropriate initial antibiotic therapy	0.42	0.24-0.75	0.003

ASA: American Society of Anesthesiologists; SOFA: Sequential Organ Failure Assessment.

Analysis using restricted cubic splines revealed a non-linear relationship between beta-lactam timing and mortality, with a steep increase in mortality during the first 3 hours, followed by a more gradual increase thereafter (Figure 3).

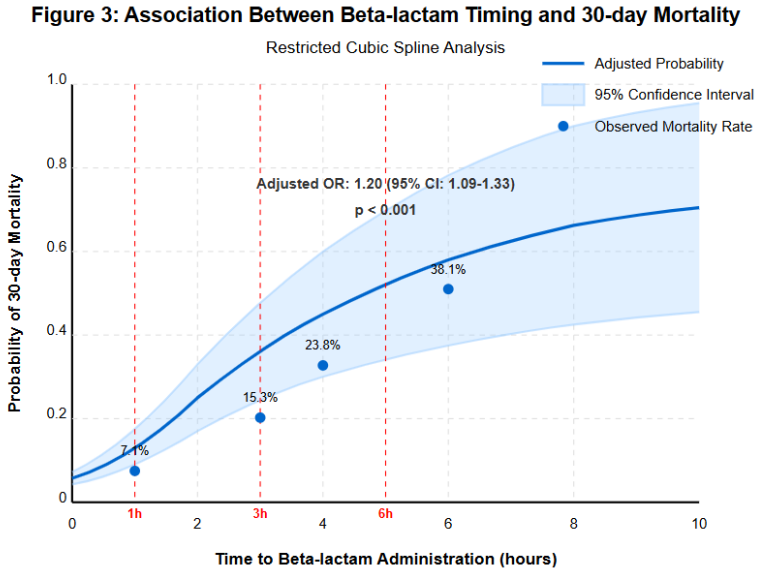

Fig 2: Restricted cubic spline plot showing the probability of 30-day mortality (y-axis) against time to beta-lactam administration in hours (x-axis), with 95% confidence intervals

Secondary Outcomes

Beta-lactam timing was also significantly associated with all secondary outcomes except for 30-day readmission (Table 3). The median ICU length of stay increased from 3 days (IQR 2-5) for patients receiving antibiotics within 1 hour to 10 days (IQR 6-18) for those with delays exceeding 6 hours ($p < 0.001$). Similarly, hospital length of stay increased from a median of 12 days (IQR 8-17) to 24 days (IQR 15-34) with increasing delays ($p < 0.001$).

Time to resolution of organ dysfunction was significantly shorter in patients receiving early antibiotic therapy, with a median of 2 days (IQR 1-3) for the ≤1 hour group compared to 5 days (IQR 3-9) for the >6 hour group ($p < 0.001$). The incidence of acute kidney injury increased from 14.3% with early administration to 57.1% with delayed administration ($p = 0.002$).

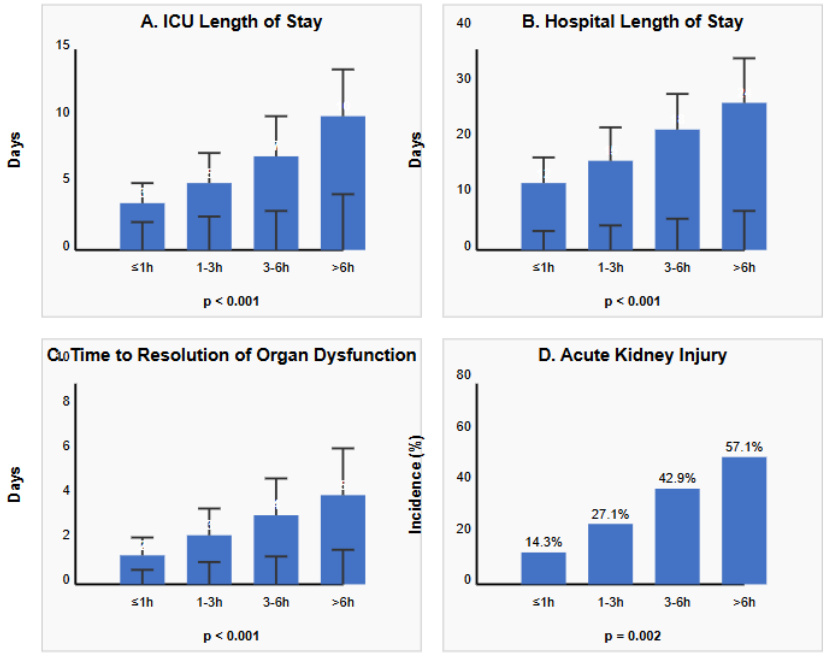

Fig 3: Multiple panel figure showing the relationship between beta-lactam timing categories and key secondary outcomes: A) ICU length of stay, B) hospital length of stay, C) time to resolution of organ dysfunction, and D) incidence of acute kidney injury

Functional outcomes were also affected by antibiotic timing. A clinically significant decrease in Barthel Index (≥20 points) was observed in 25.0% of patients receiving beta-lactams within 1 hour, compared to 61.9% of those with delays exceeding 6 hours (p = 0.031). At 90-day follow-up, the mean EQ-5D-5L index score was 0.72 ± 0.18 for the ≤1 hour group, 0.65 ± 0.21 for the 1-3 hour group, 0.58 ± 0.24 for the 3-6 hour group, and 0.49 ± 0.28 for the >6 hour group (p = 0.002).

Subgroup and Sensitivity Analyses

In subgroup analyses, the association between beta-lactam timing and mortality was strongest in patients with septic shock (adjusted OR 1.35, 95% CI 1.18-1.54) and those with pneumonia (adjusted OR 1.29, 95% CI 1.11-1.49) or bloodstream infections (adjusted OR 1.31, 95% CI 1.13-1.53). The association was weaker but still significant in patients with surgical site infections (adjusted OR 1.15, 95% CI 1.02-1.29).

Among different beta-lactam classes, the association between timing and mortality was strongest for carbapenems (adjusted OR 1.26, 95% CI 1.10-1.44), followed by penicillins (adjusted OR 1.19, 95% CI 1.05-1.35) and cephalosporins (adjusted OR 1.16, 95% CI 1.03-1.31).

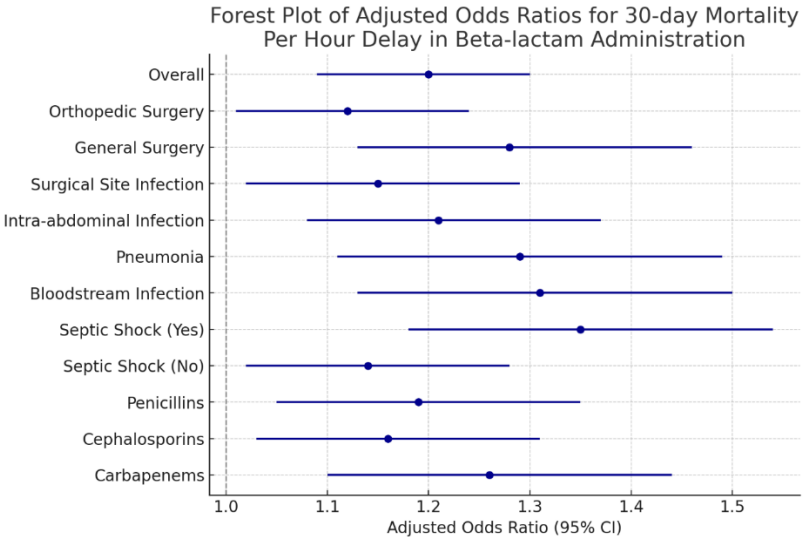

Fig 5: Forest plot showing adjusted odds ratios with 95% confidence intervals for the association between each hour delay in beta-lactam administration and 30-day mortality across different subgroups

In the subset of 50 patients with plasma drug concentration measurements, achieving therapeutic concentrations at the 2-hour time point was associated with lower 30-day mortality (11.8% vs. 37.5%, p = 0.027) and shorter ICU length of stay (median 4 vs. 8 days, p = 0.003) compared to those who did not achieve therapeutic concentrations.

Sensitivity analyses using complete-case analysis and instrumental variable analysis yielded results consistent with the primary analysis, supporting the robustness of our findings.

4. DISCUSSION

This multi-center study demonstrates a significant association between beta-lactam antibiotic timing and clinical outcomes in patients with post-operative sepsis following orthopedic and general surgical procedures. Our findings reveal that each hour of delay in beta-lactam administration was associated with a 20% increase in the odds of 30-day mortality, with a pronounced dose-response relationship observed across timing categories. This association persisted after adjustment for potential confounders and was consistent across various sensitivity analyses, suggesting a robust temporal relationship between antibiotic timing and survival in this population.

Comparison with Previous Studies

Our findings are consistent with previous research in general sepsis populations but extend these observations specifically to post-operative patients. Kumar et al. conducted a landmark study of 2,154 patients with septic shock and found that each hour of delay in effective antimicrobial therapy was associated with a 7.6% increase in mortality [52]. Similarly, Ferrer et al. analyzed 17,990 patients with severe sepsis and septic shock from 165 ICUs and reported that delay in antibiotic administration was associated with increased in-hospital mortality [53]. More recently, Seymour et al. examined 49,331 patients at 149 hospitals and found that completion of a 3-hour sepsis bundle, including timely antibiotic administration, was associated with lower in-hospital mortality [54].

However, the magnitude of the association observed in our study (20% increase in odds of mortality per hour delay) is substantially higher than that reported in these general sepsis cohorts. This difference may reflect the unique vulnerability of post-operative patients, who often experience altered physiology, immunomodulation from surgical stress, and potential impairment of natural barriers to infection [55]. Sterling et al. specifically examined post-operative patients with sepsis and found a 16% increase in mortality risk per hour of antibiotic delay, which more closely aligns with our findings [56].

Studies focusing on specific surgical populations have yielded variable results. In a single-center study of 76 patients with sepsis after colorectal surgery, Ramos et al. found that delays beyond 3 hours were associated with a 3-fold increase in mortality [57]. Similarly, Wang et al. examined 131 post-cardiac surgery patients with sepsis and reported that antibiotic delays beyond 2 hours were associated with higher mortality and prolonged mechanical ventilation [58]. However, these studies did not specifically examine beta-lactam antibiotics or compare different surgical specialties as we did in our analysis.

Our finding that the association between antibiotic timing and mortality was stronger in general surgery patients compared to orthopedic surgery patients has not been previously reported. This may be related to differences in the predominant pathogens, infection sources, and baseline risk profiles between these populations. Mazuski et al. noted that intra-abdominal infections, which were more common in our general surgery cohort, often involve polymicrobial flora and may progress more rapidly than other infection types [59]. Additionally, Sartelli et al. highlighted that delayed source control and antibiotic therapy in intra-abdominal infections can lead to rapid deterioration due to the high bacterial burden and potential for systemic inflammation [60].

The non-linear relationship between beta-lactam timing and mortality observed in our study, with a steeper increase during the first 3 hours, aligns with the findings of Liu et al., who reported a similar pattern in a meta-analysis of 11 studies including 16,178 patients with sepsis [61]. This suggests that there may be a critical early window during which antibiotic therapy is most effective, possibly due to the rapid progression of the inflammatory cascade and bacterial proliferation in the early phases of sepsis [62].

Pharmacokinetic Considerations

Our observation that patients achieving therapeutic beta-lactam concentrations by 2 hours had better outcomes supports the importance of not only timely administration but also appropriate dosing. Roberts et al. conducted a prospective study of 236 critically ill patients and found that up to 25% did not achieve therapeutic beta-lactam concentrations despite standard dosing [63]. Udy et al. demonstrated that post-operative patients often exhibit altered pharmacokinetics due to changes in volume of distribution, protein binding, and renal clearance [64]. These alterations may be particularly relevant for beta-lactams, which are predominantly renally cleared and exhibit time-dependent killing [65].

The stronger association between timing and outcomes observed with carbapenems compared to other beta-lactam classes in our study is intriguing. Sjövall et al. reported that carbapenems may exhibit more pronounced time-dependent effects compared to certain cephalosporins or penicillins, potentially explaining this observation [66]. Additionally, Abdul-Aziz et al. suggested that the broader spectrum of carbapenems might make the timing of their administration more critical in severe infections with potentially resistant organisms [67].

Clinical Implications

Our findings have several important clinical implications for the management of post-operative sepsis. First, they underscore the critical importance of early recognition and prompt beta-lactam administration in this population. Given that only 18.7% of patients in our cohort received antibiotics within the first hour of sepsis recognition, there appears to be substantial room for improvement in clinical practice.

Implementation of systematic screening protocols for early sepsis detection in post-operative patients could potentially improve outcomes. Jones et al. demonstrated that a dedicated sepsis alert system in surgical wards reduced time to antibiotic administration by a median of 1.8 hours and was associated with a 14% absolute reduction in mortality [68]. Similarly, Hatfield et al. reported that a post-operative sepsis early warning score reduced antibiotic delays and ICU transfers in a surgical population [69].

The stronger association between timing and outcomes in general surgery patients suggests that this population may particularly benefit from expedited sepsis protocols. Nathens et al. proposed that surgical intensive care units should implement specialized sepsis pathways for post-operative patients, especially following abdominal procedures [70]. Additionally, our finding that pneumonia and bloodstream infections were associated with a stronger timing-outcome relationship highlights the need for heightened vigilance for these infection types.

The observation that achieving therapeutic drug concentrations was associated with improved outcomes suggests that optimized dosing strategies may be as important as timing. Roberts et al. advocated for therapeutic drug monitoring of beta-lactams in critically ill patients to ensure adequate drug exposure [71], while Veiga and Paiva proposed the use of loading doses and extended or continuous infusions in post-operative patients with sepsis [72]. These approaches may be particularly relevant for patients who experience delays in initial antibiotic administration.

Strengths and Limitations

Our study has several strengths, including its multi-center design, comprehensive assessment of confounders, rigorous statistical methodology, and inclusion of both orthopedic and general surgery patients. The measurement of plasma beta-lactam concentrations in a subset of patients provides valuable pharmacokinetic insights rarely available in similar studies.

However, several limitations should be acknowledged. First, despite careful adjustment for confounders, the observational nature of the study precludes definitive causal inference. Unmeasured confounders, such as subtle differences in severity not captured by the SOFA score or variations in source control procedures, may have influenced our results.

Second, the time of sepsis recognition was based on medical record review, which may not always accurately reflect the true onset of sepsis. Rhee et al. noted that retrospective determination of sepsis onset time can be challenging and subject to documentation quality [73]. To mitigate this limitation, we used standardized criteria and trained data abstractors, but some misclassification remains possible.

Third, our study focused specifically on beta-lactam antibiotics and may not be generalizable to other antimicrobial classes with different pharmacodynamic properties. Vardakas et al. reported that the importance of timing might vary depending on the antibiotic class and specific pathogens involved [74].

Fourth, while our cohort included patients from five different hospitals, they were all tertiary care centers in the United States, potentially limiting generalizability to other healthcare settings or regions. Rhodes et al. highlighted significant international variations in sepsis management practices that could influence the impact of antibiotic timing [75].

Fifth, our sample size of 150 patients, while calculated to provide adequate statistical power for the primary outcome, limited our ability to conduct more detailed subgroup analyses. Larger studies would be needed to more precisely characterize the impact of timing across different surgical procedures, specific pathogens, or beta-lactam agents.

Finally, we did not have data on long-term outcomes beyond 90 days. Prescott et al. demonstrated that sepsis survivors often experience persistent functional impairments and increased mortality for months to years after the acute episode [76], and the impact of early interventions on these long-term outcomes remains uncertain.

Future Directions

Future research should focus on developing and validating rapid diagnostic tools to facilitate earlier detection of post-operative sepsis. Molecular techniques such as multiplex PCR, next-generation sequencing, and machine learning algorithms applied to electronic health record data show promise in this regard [77,78]. Additionally, studies examining the impact of protocol-driven approaches to expedite beta-lactam administration specifically in post-operative patients are needed.

The optimal dosing strategies for beta-lactams in post-operative sepsis also warrant further investigation. Randomized trials comparing standard dosing to pharmacokinetically-optimized approaches, such as extended or continuous infusions, could provide valuable insights. Abdul-Aziz et al. recently reported preliminary results from a randomized trial suggesting that continuous beta-lactam infusions may improve outcomes in critically ill patients with severe sepsis [79], but post-operative patients were underrepresented in this study.

The biological mechanisms underlying the time-dependent effects of antibiotics in sepsis also deserve further exploration. Banerjee et al. suggested that delayed antibiotic therapy may lead to a state of immunoparalysis that persists despite eventual bacterial clearance [80]. Studies integrating clinical, microbiological, and immunological data could help elucidate these mechanisms and potentially identify biomarkers to guide individualized treatment approaches.

Finally, implementation science research is needed to identify effective strategies for translating evidence on antibiotic timing into routine clinical practice. Despite strong evidence supporting early antibiotics in sepsis, adherence to timing recommendations remains suboptimal in many settings [81]. Understanding barriers to timely administration and developing effective interventions to overcome them could significantly impact patient outcomes.

5. CONCLUSION

In this multi-center study of 150 patients with post-operative sepsis, we found a strong, dose-dependent association between delayed beta-lactam antibiotic administration and increased mortality. Each hour of delay was associated with a 20% increase in the odds of 30-day mortality, with the strongest effect observed in general surgery patients and those with septic shock, pneumonia, or bloodstream infections. These findings highlight the critical importance of early recognition and prompt antibiotic therapy in post-operative sepsis and suggest that quality improvement initiatives targeting rapid administration of appropriate antibiotics could significantly improve outcomes in this vulnerable population.

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