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Original Article

Evaluation of β-lactam monotherapy and conventional anti-staphylococcal combination therapy for polymicrobial MSSA infections

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Abstract

Introduction: *Staphylococcus aureus* (SA) remains a major pathogen in both community-acquired and healthcare-associated infections, necessitating effective treatment strategies. Management of infections involving methicillin-susceptible *S. aureus* (MSSA) has traditionally included the use of targeted anti-staphylococcal antibiotics in combination with broad-spectrum agents. Recent evidence suggests that beta-lactam antibiotics may provide equivalent or superior outcomes in MSSA infections, challenging conventional treatment paradigms.

Methodology: This retrospective cohort study evaluated adult patients with polymicrobial infections involving MSSA across multiple healthcare facilities from January 2019 to December 2023. Patients receiving beta-lactam monotherapy were compared with those receiving beta-lactam therapy plus a traditional anti-staphylococcal agent. Primary outcomes included treatment failure, defined as recurrence or escalation of infection within 90 days. Secondary outcomes were 90-day hospital readmission rates and all-cause mortality.

Results: Of 1,000 patient records reviewed, 108 met the inclusion criteria. Beta-lactam monotherapy was associated with a significantly lower treatment failure rate compared with combination therapy (1.6% vs. 17.0%, $p = 0.035$). Hospital readmission rates (24.6% vs. 51.1%, $p = 0.093$) and all-cause mortality (11.5% vs. 19.1%, $p = 0.784$) were lower in the beta-lactam group, though the differences were not statistically significant.

Conclusions: Beta-lactam monotherapy demonstrated comparable or superior efficacy to traditional anti-staphylococcal combination regimens for polymicrobial infections with MSSA. These findings support the potential for simplifying treatment regimens, reducing unnecessary antibiotic exposure, and enhancing antibiotic stewardship. Further prospective studies are needed to confirm these results and inform clinical practice guidelines.

Key words: *Staphylococcus*; MSSA; stewardship; antibiotics; beta-lactam; monotherapy.

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Introduction

Staphylococcus aureus remains a major cause of both community-acquired and healthcare-associated infections, contributing substantially to global morbidity and mortality [1,2]. Traditionally, management of polymicrobial infections involving methicillin-susceptible *S. aureus* (MSSA) included the addition of specific anti-staphylococcal agents, such as cefazolin, nafcillin, vancomycin, daptomycin, or linezolid; to broader spectrum regimens [3,4]. This approach has been grounded in the belief that targeted MSSA therapy is essential to reduce treatment failure and prevent complications [5]. However, emerging evidence indicates that certain beta-lactam antibiotics that are not traditionally classified as anti-staphylococcal may achieve comparable or even superior clinical outcomes in MSSA infections, suggesting a potential shift in established treatment paradigms [6,7].

The use of broad-spectrum beta-lactam antibiotics, such as ceftriaxone, cefepime, ertapenem, meropenem, ampicillin-sulbactam, and piperacillin-tazobactam, has become increasingly prevalent, supported by evidence demonstrating comparable efficacy to traditional anti-staphylococcal agents in treating MSSA, alongside favorable safety profiles and reduced resistance rates [8,9]. This evolving practice prompts critical evaluation of clinical outcomes, particularly treatment failure and hospital readmission rates, which serve as key indicators of therapeutic effectiveness [10]. As the role of combination regimens targeting *S. aureus* in polymicrobial infections is reconsidered, comprehensive assessment of patient outcomes under these newer treatment strategies is essential.

Rationale

The impetus for this study lies in the shifting priorities of antibiotic stewardship and the growing demand for evidence-based strategies to optimize the management of polymicrobial infections involving MSSA [11]. Escalating concerns over antimicrobial resistance and the adverse effects linked to prolonged broad-spectrum antibiotic use [12] underscore the importance of evaluating beta-lactam alternatives as a

potential advancement in infectious disease therapy [13]. In addition, the economic considerations of antibiotic selection, encompassing cost-effectiveness and healthcare resource utilization, further highlight the need for robust outcome data [14]. This study seeks to inform both clinical decision-making and the development of future antibiotic guidelines by comparing rates of treatment failure and hospital readmission in patients receiving beta-lactam therapy versus traditional anti-staphylococcal combination regimens.

Methodology

Study design

This study utilized a retrospective cohort design to evaluate clinical outcomes among patients diagnosed with polymicrobial infections involving MSSA across multiple healthcare facilities. The cohort included adult patients (≥ 18 years) who received either a beta-lactam antibiotic as monotherapy or a beta-lactam in combination with an additional anti-staphylococcal agent. All eligible cases treated between January 2019 and December 2023 at a tertiary care hospital were included in the analysis.

Inclusion and exclusion criteria

Eligible patients were adults with culture-confirmed polymicrobial infections involving MSSA who initiated antibiotic therapy within 48 hours of diagnosis. The patients were stratified according to the primary antibiotic class received:

Beta-lactam group: ceftriaxone, cefepime, ertapenem, meropenem, ampicillin-sulbactam, or piperacillin-tazobactam.

Antistaphylococcal group: nafcillin, oxacillin, vancomycin, daptomycin, linezolid, or clindamycin.

The exclusion criteria were: (1) polymicrobial infections involving resistant organisms, (2) receipt of combination therapy incorporating both antibiotic classes, and (3) documented allergy to beta-lactam antibiotics.

Treatment groups

The patients were classified into two cohorts based on the antibiotic regimen administered:

Beta-lactam monotherapy group: Patients who received a beta-lactam antibiotic not traditionally categorized as an antistaphylococcal agent. Eligible agents included ceftriaxone, cefepime, ertapenem, meropenem, ampicillin-sulbactam, and piperacillin-tazobactam.

Beta-lactam plus antistaphylococcal therapy group: Patients who received a beta-lactam antibiotic in combination with a traditional antistaphylococcal agent, vancomycin, daptomycin, or linezolid. In some cases, these patients also received additional broad-spectrum antibiotics as part of polymicrobial infection management; however, the inclusion criterion for this group was the administration of at least one of the aforementioned antistaphylococcal agents as part of the treatment for polymicrobial infection with MSSA.

Outcomes of interest

The primary outcomes of interest were: (1) treatment failure: defined as the recurrence of infection, requiring change in the antibiotic regimen within 90 days of initial treatment, or (2) progression of the infection necessitating surgical intervention. The secondary outcomes were all cause mortality and 90-day hospital readmissions, where readmission for any cause within 90 days of discharge was counted.

Data collection

Data was extracted from electronic health records, including demographic information, clinical presentation, laboratory findings, treatment regimens, and outcomes.

Statistical analysis

Descriptive statistics were used to summarize patient demographics and clinical characteristics. The categorical variables were compared using Chi-square tests, and the continuous variables were analyzed using independent t-tests. Multivariate logistic regression models were constructed to adjust for potential confounders, including age, comorbidities (e.g., diabetes, immunosuppression), infection severity, and infection source. The results are presented as odds ratios (ORs) with 95% confidence intervals (CIs). Propensity score matching was performed to further minimize confounding. Statistical significance was defined as a two-tailed p value < 0.05 for all analyses.

Ethical considerations

This study adhered to ethical standards, with institutional review board (IRB) approval obtained before data collection. Patient confidentiality was maintained by anonymizing data prior to analysis, in compliance with the Health Insurance Portability and Accountability Act (HIPAA).

Results

A total of 1,000 patient records were screened for eligibility. Of these, 892 were excluded due to

Table 1. Patients' characteristics—baseline age, race, gender, and comorbid conditions—were comparable between the beta-lactam alone and the anti-staphylococcal treatment groups.

Variable	Beta-lactam alone	Anti-staphylococcal combination regimens
Number of patients	61	47
Median age (years)	61	62
Gender (Male)	37 (60.7%)	28 (59.7%)
Race (White)	32 (68%)	40 (66%)
Renal failure	22 (36.1%)	16 (34.0%)
Diabetes	24 (39.3%)	27 (57.5%)
Hypertension	31 (50.8%)	29 (61.7%)
Congestive heart failure	12 (19.7%)	10 (21.3%)
End stage renal disease (ESRD)	20 (32.8%)	18 (38.3%)
Malignancy	7 (11.5%)	12 (25.5%)
Cirrhosis	2 (3.3%)	1 (2.1%)
Chronic obstructive pulmonary disease (COPD)	4 (6.6%)	4 (8.5%)
Illicit drug use	19 (31.2%)	9 (19.2%)
Immunocompromising state	12 (19.7%)	11 (23.4%)
Peripheral vascular disease	15 (24.6%)	10 (21.3%)

incomplete data or failure to meet the inclusion criteria. The final cohort comprised 108 patients, with 61 receiving beta-lactam monotherapy and 47 receiving an antistaphylococcal antibiotic in addition to beta-lactam therapy. The baseline demographics, including age, gender, race, and comorbid conditions, were comparable between groups (Table 1).

The infectious diagnoses included abscesses, hardware-associated infections, empyema, osteomyelitis, urinary tract infections, surgical wound infections, and bacteremia with endocarditis. The distribution of infection types was similar between treatment arms, with osteomyelitis being the most common diagnosis in both groups (Table 2).

The primary outcome—treatment failure, defined as recurrence or progression of infection, need for change in antibiotic regimen within 30 days, or requirement for surgical intervention—occurred in 1 patient (1.6%) in the beta-lactam monotherapy group compared with 8 patients (17.0%) in the antistaphylococcal group ($p = 0.035$; OR 1.80, 95% CI 1.20–3.40).

In the case of secondary outcomes, hospital readmission for any cause within 90 days occurred in 15 patients (24.6%) in the beta-lactam group and 24 patients (51.1%) in the anti-staphylococcal group ($p = 0.093$); a difference that did not reach statistical significance (Table 3). All-cause mortality was observed in 7 patients (11.5%) receiving beta-lactam monotherapy and 9 patients (19.1%) receiving anti-staphylococcal therapy ($p = 0.784$).

Discussion

Polymicrobial infections—defined as infections involving two or more microorganisms—are typically associated with greater severity and management complexity than single-organism infections [14]. This heightened severity is often attributed to factors such as increased pathogen virulence and immune evasion mechanisms [15]. Treatment is further complicated by the need for broad-spectrum or combination antibiotic regimens, which can increase the risk of antimicrobial resistance.

In recent years, antibiotic stewardship initiatives have emphasized minimizing broad-spectrum antibiotic use and tailoring therapy to reduce resistance. Beta-lactam antibiotics offer a less toxic alternative to traditional anti-staphylococcal agents, such as vancomycin, daptomycin, or linezolid, with generally fewer adverse effects. However, real-world evidence regarding their efficacy in polymicrobial infections with MSSA, particularly in terms of bacterial clearance and clinical outcomes such as treatment failure and hospital readmission, remains limited.

Table 2. Types of infections. The cause of infection was comparable between the two arms.

Infection type	No	Yes
Abscess	4 (6.6%)	2 (4.3%)
Hardware associated infection	9 (14.8%)	5 (10.6%)
Empyema	7 (11.5%)	2 (4.3%)
Osteomyelitis	35 (57.4%)	33 (70.2%)
Urinary	1 (1.6%)	0 (0.0%)
Complicated surgical wound infection	4 (6.6%)	4 (8.5%)
Bacteremia with endocarditis	1 (1.6%)	1 (2.1%)

Table 3. Primary and secondary outcomes.

Outcome	Beta-lactam alone	Anti-staphylococcal combination regimen	*p* value	Odds ratio (95% CI)
Change in treatment due to a lack of improvement	1 (1.6%)	8 (17.0%)	0.035	5.62 (1.16-27.19)
The patient had to be readmitted	15 (24.6%)	24 (51.06%)	0.094	1.91 (0.8-4.27)
All-cause mortality	7 (11.5 %)	9 (19.1%)	0.784	0.82 (0.31-2.17)

In this study, the clinical outcomes in patients with polymicrobial infections involving MSSA who were treated with beta-lactam monotherapy versus those who received combination regimens including traditional anti-staphylococcal agents were compared. Beta-lactam therapy alone was associated with a significantly lower treatment failure rate, as evidenced by fewer regimen changes within 90 days, compared with anti-staphylococcal regimens. No statistically significant differences were observed in hospital readmission rates or all-cause mortality.

The findings suggest that beta-lactam monotherapy may represent an effective alternative to combination regimens for treating polymicrobial MSSA infections, challenging the long, standing practice of dual agent therapy. These results are consistent with previous studies reporting comparable efficacy between beta lactams and traditional agents, with the added advantages of improved safety profiles and lower resistance rates [8,9]. The lower treatment failure rate observed in the beta-lactam group may reflect both the broad-spectrum coverage and favorable tolerability of these agents, contributing to a more stable therapeutic response.

The potential clinical and stewardship implications of these findings are considerable. Adoption of beta-lactam monotherapy in appropriate cases could streamline treatment protocols, reduce unnecessary exposure to additional antibiotics, minimize adverse events, and decrease healthcare costs [16]. While further prospective and multicenter studies are warranted to validate these results, the data support consideration of beta-lactam antibiotics as a viable, and potentially preferable alternative to traditional anti-staphylococcal combination regimens in the management of polymicrobial infections involving MSSA.

Strengths/limitations

This study encompassed a broad range of polymicrobial infection types, enhancing the external validity and generalizability of the findings. Nonetheless, several limitations should be acknowledged. The relatively small sample size, attributable to stringent inclusion criteria, incomplete data, and limited follow-up, may have reduced the statistical power to detect significant differences in secondary outcomes, such as 90-day readmission rates. Furthermore, the retrospective design inherently limits control over potential confounding factors, including variations in infection severity, comorbidity burden, and concurrent interventions, which may have influenced clinical outcomes.

Future research should aim to address these limitations through larger, prospective investigations that more precisely evaluate the long-term efficacy and safety of beta-lactam monotherapy in polymicrobial MSSA infections. Subgroup analyses focusing on specific infection types, such as hardware-associated infections or osteomyelitis, may yield valuable insights into infection-specific therapeutic responses. Additionally, randomized controlled trials would provide the highest level of evidence by minimizing residual confounding, thereby strengthening the evidence base for incorporating beta-lactam monotherapy into treatment guidelines for MSSA infections.

Conclusions

This study demonstrated that beta-lactam monotherapy may represent a viable, and potentially superior, alternative to traditional anti-staphylococcal combination regimens for the treatment of polymicrobial infections involving MSSA. Beta-lactam therapy was associated with significantly lower treatment failure rates and a non, significant trend toward reduced hospital readmissions. These findings contribute to the growing evidence base supporting beta-lactam use in this context and highlight the need for larger, prospective studies to validate and expand upon these results.

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Authors' contributions

All authors, study conception and design, manuscript review; KT, GA, JS, AC, material preparation, data collection and analysis; KT, GA, manuscript-first draft. All authors read and approved the final manuscript.

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Conflict of interest

No conflict of interest is declared.

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