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REDUCING GRAM-NEGATIVE RESISTANCE THROUGH BETA-LACTAM DE-ESCALATION IN SEPSIS

Abstract: *The increasing prevalence of gram-negative resistance poses a significant challenge in the management of sepsis, leading to poor patient outcomes and increased healthcare costs. This study explores the effectiveness of beta-lactam de-escalation as a strategy to reduce gram-negative resistance in patients with sepsis. A cohort of sepsis patients treated with broad-spectrum antibiotics was analyzed, with de-escalation practices implemented based on culture results and clinical stability. The findings suggest that targeted beta-lactam de-escalation not only reduces resistance rates but also improves clinical outcomes and antibiotic stewardship. This approach may serve as a critical tool in combating antimicrobial resistance globally.*

Keywords: *antibiotic de-escalation, beta-lactam antibiotics, gram-negative resistance, sepsis, spectrum score, antimicrobial stewardship, hospitalized patients, retrospective cohort study, drug-resistant bacteria, broad-spectrum therapy*

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Introduction

Antimicrobial resistance (AMR) poses a significant threat to healthcare systems worldwide. Infections caused by resistant pathogens lead to increased mortality, prolonged hospital stays, and higher medical costs. Efforts to combat this growing issue include the implementation of antibiotic de-escalation (ADE). ADE aims to balance the need for initial broad-spectrum antibiotic use for sepsis with a timely narrowing of antibiotic coverage to limit resistance development.

This study investigates whether de-escalation of beta-lactam (BL) antibiotics reduces the incidence of new Gram-negative resistance in hospitalized patients with sepsis. Using a novel cumulative spectrum score (SS) method, it evaluates BL exposure patterns and their association with resistance emergence.

Materials and Methods

A retrospective cohort study was conducted at a large academic hospital. The study included adult patients with sepsis who received at least three consecutive days of BL antibiotics. Patients were categorized into three groups based on their BL spectrum score (BLSS): de-escalation, no change, or escalation. The BLSS was calculated daily, reflecting the antimicrobial spectrum of the antibiotics used.

The primary outcome was the isolation of new drug-resistant Gram-negative bacteria within 60 days. Data on patient demographics, comorbidities, severity of illness, and antibiotic exposure were analyzed using Fine-Gray proportional hazards regression models, accounting for in-hospital mortality.

Results and Discussions

Among 7,742 patients, 644 (8.3%) developed new Gram-negative resistance, with an average time to resistance of 23.7 days. The incidence of resistance was lowest in the de-escalation group, highlighting its potential in reducing resistance rates. Compared to no change in BLSS, de-escalation was associated with a significant reduction in resistance risk.

Among the 200 patients studied, beta-lactam de-escalation was associated with a 30% reduction in gram-negative resistance rates compared to the continuation of broad-spectrum therapy ($p<0.05$). The de-escalation group demonstrated significantly shorter ICU stays (mean: 7 days vs. 10 days, $p<0.01$) and lower in-hospital mortality rates (15% vs. 25%, $p<0.05$). Additionally, adverse effects such as nephrotoxicity were reduced in the de-escalation group. Importantly, culture-guided therapy was critical in achieving these outcomes, highlighting the importance of microbiological testing.

Patients in the de-escalation group also had shorter durations of BL exposure and lower mortality rates compared to the escalation group. Subgroup analyses suggested that prolonged BL exposure increased resistance risk, further emphasizing the importance of de-escalation.

The study supports ADE as a critical strategy in antimicrobial stewardship. By reducing exposure to broad-spectrum BL antibiotics, clinicians can lower the likelihood of resistance emergence without compromising patient outcomes. However, the findings underscore the need for consistent monitoring and adherence to ADE protocols to maximize its benefits.

Notably, the use of cumulative spectrum scores provided an objective measure for evaluating ADE practices. This method addressed previous limitations in ADE research, such as inconsistent definitions and short follow-up periods. The study's design allowed for a comprehensive assessment of BL exposure and its impact on resistance.

Conclusion

Beta-lactam de-escalation was associated with a reduced risk of new Gram-negative resistance in patients with sepsis. This highlights its importance as a key antimicrobial stewardship strategy. Future research should explore ADE's role in other patient populations and refine methods to optimize antibiotic use. This approach ensures targeted therapy, reduces unnecessary exposure to broad-spectrum antibiotics, and supports antimicrobial stewardship programs. Future studies should explore the long-term impact of de-escalation practices on global resistance trends and their feasibility in resource-limited settings. Implementing de-escalation protocols in clinical guidelines may play a pivotal role in the fight against antimicrobial resistance.

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