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P06. First-line combination therapy with fifth generation cephalosporins plus daptomycin compared to other-antimicrobial-regimens for methicillin-resistant *Staphylococcus aureus* bacteraemia: a multicenter retrospective cohort study

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Background: This study aims to evaluate the effectiveness of 5th-generation-cephalosporins + daptomycin (5GC + DAP) comparedcto other antimicrobial regimens (OAR) for the treatment of methicillin-resistant *S. aureus* bacteremia (MR-SAB).

Methods: This retrospective observational study enrolled patients with MR-SAB from 01/01/2020 to 31/07/2023 at four large Italian Hospitals (Policlinc of Bari, Policlinic of Bologna, IRCCS Humanitas Rozzano, Centro-Cardiologico Monzino, Milan).cFirst-line-therapy (administered within 72 hours from BSI onset) with 5GC + DAP were compared with OAR. The primary endpoint was 90-day all-cause-mortality. Uni- and multivariable Cox regression was used for primary endpoint analysis; in addition, results were confirmed with propensity score adjustment (with IPTW-method). Treatment efficacy was also assessed using the desirability of outcome ranking (DOOR) approach, assigning 1 additional point beyond recovery for one of the following negative outcomes: a) persistent MRSA infection, b) persistent bacteremia (≥5 days), c) drug resistance, d) any adverse event, and e) 90-day relapse. A score of 7 was assigned for death at any time point.

Results: Overall, 465 patients were enrolled: median age was 76 (61–83), 59% male, with a Charlson comorbidity index (CCI) of 7 (4–8). Of them, 50 (11%) and 116 (25%) had endocarditis or metastatic infection. Importantly, 90-day mortality occurred in 181 (39%) patients, while 260 (56%) experienced at least one negative outcome included in DOOR analysis. Notably, 5GC + DAP was prescribed in younger patients (72 versus 76, $P = 0.008$] with lower Charlson Comorbidity Index (CCI) (7 versus 5, $P = 0.003$), but higher SOFA score at presentation (3 versus 2, $P = 0.003$). In multivariate analysis, increased age, CCI, SOFA-score, septic shock, acute kidney or respiratory failure were linked to worse outcomes, while combination therapy, and DAP use were protective. Particularly, 5GC + DAP reduced mortality-risk by 38% (aHR = 0.62 [0.39–0.96], $P = 0.036$), confirmed after adjustment with IPTW analysis. DOOR analysis showed recovery without complications in 46% of 5GC + DAP patients versus 28% with OAR. No differences were seen in recovery with 1–3 complications (scores 2–4). A score of 7 (death) occurred in 28% of 5GC + DAP patients versus 41% with OAR.

Conclusions: DAP + 5GC significantly reduces mortality and improves recovery in MR-SAB. These findings highlight its potential as a game-changing therapy, paving the way for future reaserach.