Effect of Vancomycin or Daptomycin With or Without an Antistaphylococcal β-Lactam on Mortality, Bacteremia, Relapse, or Treatment Failure in Patients with MRSA Bacteremia

BACKGROUND:

- In 2017 there were approximately 120,000 cases of Staphylococcus aureus bacteremia that resulted in 20,000 deaths.
- Methicillin-resistant Staphylococcus aureus (MRSA) bacteremia has a mortality of over 20%. Using typical standard therapy combined with β-lactam antibiotics has shown reduced mortality but more studies are needed to determine clinical use of combination therapy and its place in practice.

OBJECTIVE:

- To determine whether combining an anti-staphylococcal β-lactam, of either flucloxacillin or dicloxacillin, with standard therapy, of either daptomycin or vancomycin, is more effective than standard therapy alone in patients with MRSA bacteremia.

METHODS:

- **Design**: Open-label, multicenter, parallel group, randomized clinical trial
- **Duration:** The β-lactam therapy was given for 7 days after randomization and the duration for the standard therapies (vancomycin or daptomycin) was determined by the clinician. However, the protocol of this study recommended to clinicians that it be from 14-42 days.
- **Inclusion criteria**: Had to meet all of the following: 1) have a positive blood culture for MRSA, 2) able to be randomized within 72 hours of the first positive culture, 3) 18 years or older, and 4) likely to remain hospitalized for at least 7 days after randomization.
- **Exclusion criteria**: 1) history of type 1 hypersensitivity reaction to β-lactams, 2) polymicrobial bacteremia (excluding those judged to be contaminants), 3) previous participation in the trial, 4) known pregnancy, 5) treating physician didn't allow the patient to be enrolled, 6) patient was receiving a β-lactam that couldn't be stopped or substituted for a non- β-lactam antibiotic, 7) patient is expected to die in the next 48 hours, and 8) treatment limitations precluding use of antibiotics.
- **# patients enrolled**: 345 patients were included in the primary analysis, 170 in the combination group and 175 in the standard group
- **Drug regimens/dosages used**: Patients in the standard therapy group were randomized to either vancomycin or daptomycin according to clinician preference where the duration was determined by the clinician but recommended by protocol to be 14-42 days. Patients in the combination group received the standard therapy plus an IV β-lactam of either flucloxacillin or cloxacillin for the first 7 days after randomization.
- **Primary outcome measure**: A 90-day composite of all cause mortality, persistent bacteremia at study day 5, microbiological relapse (a positive blood culture for MRSA at least 72 hours after a prior negative culture), and treatment failure (positive sterile site culture for MRSA at least 14 days after randomization).
- **Secondary outcome measure**: All-cause mortality at 14, 42, and 90 days, persistent bacteremia at day 2, persistent bacteremia on day 5, acute kidney injury (AKI), microbiological relapse, treatment failure, and duration of IV antibiotic use.

- With 440 patients, which accounted for a 10% drop out, the power was 80% with an α=0.05 to detect a 12.5% difference between groups.
- Data handling method used was exclusion of subjects.

RESULTS

- In the combination group 144 were included in the per-protocol analysis and 175 in the standard per-protocol group.
- **Primary outcome measure**: 59 of 170 patients (35%) in the combination group and 68 out of 175 (39%) in the standard group met the primary outcome, which was not statistically significantly different (95% CI= -14.3-6%, P=0.42)
- **Secondary outcome measures**: Bacteremia at day 5 was significantly less common in the combination group, 19/166 (11%) versus the standard group, 35/172 (20%) (95% CI=-16.6 to -1.2%). AKI was significantly more common in the combination group, 34/145 (23%) versus the standard group, 9/145 (6%) (95% CI= 9.3-25.2%).
- **Author's conclusions**: In patients with MRSA bacteremia, the addition of the β-lactam for 7 days did not statistically significantly reduce the primary outcome composite of 90-day mortality, microbiological persistence, relapse, or treatment failure.

STRENGTHS

- The study was randomized, parallel, and controlled.
- The study used exclusion of subjects data handling which shows data for only those patients that received the full course of therapy as intended. This would depict the actual difference in efficacy between the two treatment groups whereas including everyone would have shown patients that only received a few doses and therefore might not have been efficacious due to low concentrations in the body.

LIMITATIONS

- Power was not met in this study which causes concern for type 2 error in the primary and secondary outcomes that were not statistically significant.
- This study was open label which introduces the possibility for risk of bias. This is definitely a concern in this study since the physicians were able to choose their preferred regimen and they may have thought one to be better than another.
- Very few patients received daptomycin and cefazolin, so the majority of findings represented vancomycin use
- Primarily studied older patients (over 47) and mostly male
- May be hard to generalize the results to other countries and populations due to medicinal practice within the countries used and it may not be able to be generalized to other β-lactams like nafcillin.
- Adverse events were not well reported

CONCLUSIONS

- This study did not show a statistically significant difference in a composite outcome that included all-cause mortality, persistent bacteremia at study day 5, microbiological relapse, and treatment failure between standard therapy and combination with β-lactam therapy for 7 days. Additionally, the power was not met in this study due to AKI occurrence and safety concern.

- Future research:
    - Further studies are needed to determine the place combination β-lactam therapy with standard therapy has in clinical practice and its practicality. An adequately powered study with more equally distributed treatment groups in regard to the number of patients who receive vancomycin versus daptomycin is needed.

Tong SYC, Lye DC, Yahav D, et al. Effect of Vancomycin or Daptomycin With vs Without an Antistaphylococcal β-Lactam on Mortality, Bacteremia, Relapse, or Treatment Failure in Patients With MRSA Bacteremia: A Randomized Clinical Trial. *JAMA*. 2020;323(6):527-537.

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