Inhaled Amikacin to Prevent Ventilator-Associated PneumoniaNew England Journal of Medicine

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Introduction/Aim:

Ventilator-associated pneumonia (VAP) commonly complicates ICU care and leads to increased antimicrobial usage, delayed extubation, length of stay and death.

Design/Methods:

The Inhaled Amikacin vs. Placebo to Prevent Ventilator Associated Pneumonia (AMIKINHAL) trial was a double blind, multicenter, randomised controlled trial among 19 ICUs in France, assessing the preventative effect of inhaled amikacin on preventing VAP. Patients already undergoing mechanical ventilation for 72-96 hours were enrolled, and those with established VAP, acute kidney injury, chronic kidney disease and tracheostomies were excluded. Patients were randomised 1:1 to either nebulised amikacin once a day for three consecutive days, or nebulised placebo. Primary outcome was the first episode of VAP (defined as positive pulmonary sample culture plus leucocytosis/leukopenia, fever or radiographic changes) within 28 days. Secondary outcomes were incidence density of VAP and incidence of antimicrobial resistance.

Results/Conclusion:

Of 6419 assessed patients, 847 entered the intention-to-treat analysis. Difference in restricted mean survival time to ventilator-associated pneumonia was 1.5 days (95% confidence interval [CI], 0.6 to 2.5; P=0.004). Primary outcome developed in 15% in the intervention arm and 22% in the placebo group. (HR 1.5; 95% CI 06.-2.5). Antibiotic days were similar across the groups, as were number of deaths

The authors concluded from this that the study showed that the intervention reduced VAP by day 28 compared with placebo.

Strengths/Limitations

This paper addresses an important common occurrence complicating ICU care. Also important are its careful use of placebo and blinding (using opaque nebulisers to conceal the trial drug) and the wide range of outcomes measured. There are limitations to the study however. VAP incidence in the cohort was larger than the proposed 12% incidence, potentially suggesting that proactive regular culturing of respiratory secretions was over-diagnosing VAP and not reflecting real-world data. While the positive outcome of the trail was reported as the (difference in restricted mean survival time to ventilator-associated pneumonia, incidence of the primary outcome failed to show true significance. Importantly,

no differences were seen in antimicrobial usage, length of stay, duration of intubation or death.

Applicability and Future Direction

This study's alleged positive finding draws heavily on an outcome that was not pre-specified, and doesn't inform clinical practice. The most important lesson here is how important meaningful outcome and case definitions of outcomes are in clinical trials. VAP is a challenging diagnosis in clinical practice, however the overly-proactive sampling of patients' non-sterile respiratory secretions likely led to the erroneous over-diagnosis of VAP. Similar trials should use definitions consistent with clinical practice to avoid this issue, and larger trials bearing this in mind, adequately powered to detect antibiotic resistance are warranted.

References*

1. Ehrmann S, Barbier F, Demiselle J, Quenot J-P, Herbrecht J-E, Roux D, et al. Inhaled amikacin to prevent ventilator-associated pneumonia. New England Journal of Medicine. 2023;389(22):2052–62. doi:10.1056/nejmoa2310307