KY Antimicrobial Stewardship Innovation Consortium

Educational Pearl

Gram-Negative Ventilator-Associated Pneumonia: The Last Breath of Nebulized Aminoglycosides?

Ventilator-associated pneumonia (VAP) is one of the most common hospital-acquired infections. Management of VAP caused by gram-negative bacteria, especially multidrug resistant isolates remains problematic.[1] Parenteral aminoglycosides achieved low concentration in bronchial secretions and epithelial lining fluid; thus, in practice adjunctive nebulized aminoglycosides in addition to systemic antibiotics were often considered by clinicians in hopes of optimizing alveolar concentrations while minimizing systemic exposure.[2]

Nebulized aminoglycosides: does it improve clinical outcomes?

	IASIS[3]	INHALE[4]
Study design	Prospective, randomized, double-blind, placebo-controlled, phase 2 study	Prospective, double-blind, randomized, placebo-controlled, phase 3 study
Patient population	Men and non-pregnant, non-lactating women 18-80 years old Intubated and mechanically ventilated with diagnosis of pneumonia	18 years or older Pneumonia diagnosed by chest radiography caused by or having at least 2 risk factors for multi-drug resistant (MDR) gram-negative pathogen Intubated and mechanically ventilated mCPIS score of at least 6
Location	ICUs in France, Hungary, Greece, Spain, Turkey and the United States	153 hospital ICUs in 25 countries across USA, Europe, South America, and Asia
Interventions	Placebo group: meropenem or imipenem x at least 7 days AFIS group: 300 mg amikacin base and 120 mg fosfomycin plus either meropenem or imipenem x at least 7 days	Group 1: SOC plus amikacin inhalation 400 mg every 12 hours x 10 days Group 2: SOC plus placebo inhalation x 10 days
Results	CPIS improvement at day 10 did not differ between groups (mean CPIS 5.0 ± 3.1 vs 4.8 ± 3.4, p=0.72). No difference noted between AFIS and placebo group in mortality through day 28 28% vs 17% (p=0.32) and clinical relapse 14% vs 20% (p=0.37). Days **free** of mechanical ventilation was significant favoring placebo group 9.8 ± 9.7 vs 12.5 ± 9.72 (p=0.02)	There was no difference in survival at days 28-32 (75% vs 77%, p=0.43). No differences noted in early clinical response (58% vs 57%), duration of mechanical ventilation (median 28 days for both groups), and duration of ICU stays (median 28 days for both groups).
Limitations	The use of CPIS as a marker for prognosis remains in question for debate	49% identified pathogens were not MDR
Author's conclusion	Adjunctive use of AFIS with SOC antibiotic therapy did not affect the clinical course of VAP	The findings do not support use of inhaled amikacin as adjunctive to IV antibiotics in gram-negative VAP.

AFIS = amikacin-fosfomycin inhaled system SOC = standard-of-care ICU = intensive care unit CPIS = clinical pulmonary infection score

IDSA Guidelines: 2016 HAP/VAP guideline recommended to use inhaled antibiotics if gram-negative bacteria are **only** susceptible to aminoglycosides or polymyxins. 2021-2022 MDR guidance documents do not recommend nebulized antibiotics as adjunctive therapy for pneumonia.

Key Takeaway: Routine use of nebulized inhaled aminoglycoside as adjunctive therapy is not recommended for ventilator-associated pneumonia

References

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