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LETTER

Effect of adjunctive tobramycin inhalation versus placebo on early clinical response in the treatment of ventilator-associated pneumonia: the VAPORISE randomized-controlled trial

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Dear Editor,

The relatively poor response rates seen with intravenous (IV) antibiotic (AB) therapy and the emergence of multidrug-resistant (MDR) microorganisms requires the development of new treatment strategies for ventilator-associated pneumonia (VAP) [1].

We investigated in a prospective double-blind randomized-controlled trial performed in a single center, whether empiric adjunctive therapy with inhalation tobramycin could ameliorate prognosis in VAP patients (ClinicalTrials.gov Identifier: NCT02440828). Patients with a clinically defined VAP were randomly assigned to a treatment group receiving twice-daily tobramycin inhalation 300 mg and standard IV AB therapy for 8 days or to a control group which received twice-daily placebo inhalation and standard IV AB treatment for 8 days. Inclusion and exclusion criteria are described in the protocol as supplementary file. Primary outcome was treatment failure at day 4, defined as one of the following four criteria present at day 4: (1) no improvement of the PaO_2/FiO_2 ratio, (2) persistence of fever (≥ 38 °C) or hypothermia (<35.5 °C) together with purulent respiratory secretions, (3) increase in the pulmonary infiltrates on chest radiograph of $\geq 50\%$, and (4) occurrence of septic shock or multiple organ dysfunction syndrome, defined as three or more organ system failures not present on day 1. Secondary outcomes were 30-day mortality and number of ventilation free days at day 28. The target sample size would be 84 patients, which provides an 80% power to detect a difference of 32% in cure rate between treatments. The study was approved by independent and local ethics committee (ethical approval number = NL48009.078.14).

The study was terminated prematurely due to insufficient inclusion. Twenty-six patients were included (treatment, $n=13$; control, $n=13$) (Table 1). Treatment failure was present in four patients (31%) of the treatment group and in eight control patients (62%) ($p=0.24$, relative risk = 0.5). There was no difference in 30-day mortality (treatment, $n=4$ (31%) vs control, $n=4$ (31%). The number of ventilation free days at day 28 was 18 days [0–21] in the treatment group and 17 days [5–22] in the control group.

A meta-analysis conducted by Xu et al. suggests that treatment with aerosolized tobramycin resulted in clinical recovery benefits, but this was mostly based on observational studies [2]. Two recent prospective trials did not show a benefit of inhaled AB therapy as adjunctive treatment for VAP [3, 4]. The findings of our explorative double-blind randomized-controlled trial failed to show a beneficial effect of adjunctive tobramycin inhalation therapy in the treatment of VAP. However, due to the small number of patients, the current study was underpowered. The relative risk for therapy failure at day 4 in the study group compared to the control group is 0.5 (95% CI 0.19–1.3), meaning that therapy failure occurred twice as often in the control group. The next step is to investigate whether inhalation antibiotics could be beneficial in certain subgroups, such as an infection with

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Table 1 Baseline values and clinical outcomes

	Treatment group, $n=13$	Control group, $n=13$	Risk difference (95% confidence interval)	Relative risk (95% confidence interval)	p value
Baseline variables					
Age, median [IQR]	58 [42–69]	59 [43–66]			
Male, *n* (%)	10 (77%)	7 (54%)			
Smoking					
Never	3 (23%)	1 (8%)			
Former	4 (31%)	2 (15%)			
Current	1 (8%)	2 (15%)			
Unknown	5 (39%)	8 (62%)			
Apache II score at inclusion (median)	21 [12–24]	14 [13–24]			
CPIS score (median)	7 [5–10]	6 [5–9]			
Duration of ventilation before VAP (median)	7.4 [2–22]	15.2 [2–63]			
Microbiological confirmation, *n* (%)	10 (77%)	7 (54%)			
Outcome values					
Therapy failure, *n* (%)	4 (31%)	8 (62%)	31% (− 6.6 to 58.3%)	0.5 (0.19–1.18)	0.24
Causes of treatment failure[a]					
Criteria, no. 1	0 (0%)	2 (15%)			
Criteria, no. 2	1 (8%)	3 (23%)			
Criteria, no. 3	0 (0%)	0 (0%)			
Criteria, no. 4	1 (8%)	0 (0%)			
30-day mortality	4 (31%)	4 (31%)	0% (− 32.4 to 32.4%)	1 (0.33–3.06)	1
Ventilation-free days (median)[b]	18 [0–21]	17 [5–22]			
Days in ICU[c]	16 [7–35]	13 [8–17]			
Adverse events, *n* (%)	6 (46%)	4 (31%)	− 15% (− 46 to 19.9%)	1.5 (0.57–4.13)	0.69
None	7 (54%)	9 (70%)			
Bronchospasm	1 (8%)	0 (0%)			
Renal disfunction	0 (0%)	1 (8%)			
Other	5 (38%)	3 (23%)			

[a] Criteria for treatment failure: 1. No improvement of the arterial O_2 tension to inspired O_2 fraction ratio. 2. Persistence of fever ($\geq$ 38°) of hypothermia (< 35.5°) together with purulent respiratory secretions. 3. Increase in the pulmonary infiltrates on chest radiograph of greater than or equal to 50%. 4. Occurrence of septic shock or multiple organ dysfunction syndrome defined as three or more organ system failures not present on day 1

[b] Ventilation-free days at day 28 after inclusion

[c] Days stayed at ICU after inclusion until discharge

MDR microorganisms, as has also been recommended in a recent review [5].

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Electronic supplementary material
The online version of this article (https://doi.org/10.1007/s00134-019-05914-5) contains supplementary material, which is available to authorized users.

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Compliance with ethical standards

Conflicts of interest
The authors declare that at the time of the study there were no conflict of interest.

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