ORIGINAL ARTICLE

Inhaled Amikacin to Prevent Ventilator-Associated Pneumonia

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ABSTRACT

BACKGROUND

Whether preventive inhaled antibiotics may reduce the incidence of ventilator-associated pneumonia is unclear.

METHODS

In this investigator-initiated, multicenter, double-blind, randomized, controlled, superiority trial, we assigned critically ill adults who had been undergoing invasive mechanical ventilation for at least 72 hours to receive inhaled amikacin at a dose of 20 mg per kilogram of ideal body weight once daily or to receive placebo for 3 days. The primary outcome was a first episode of ventilator-associated pneumonia during 28 days of follow-up. Safety was assessed.

RESULTS

A total of 850 patients underwent randomization, and 847 were included in the analyses (417 assigned to the amikacin group and 430 to the placebo group). All three daily nebulizations were received by 337 patients (81%) in the amikacin group and 355 patients (83%) in the placebo group. At 28 days, ventilator-associated pneumonia had developed in 62 patients (15%) in the amikacin group and in 95 patients (22%) in the placebo group (difference in restricted mean survival time to ventilator-associated pneumonia, 1.5 days; 95% confidence interval [CI] 0.6 to 2.5; P=0.004). An infection-related ventilator-associated complication occurred in 74 patients (18%) in the amikacin group and in 111 patients (26%) in the placebo group (hazard ratio, 0.66; 95% CI, 0.50 to 0.89). Trial-related serious adverse effects were seen in 7 patients (1.7%) in the amikacin group and in 4 patients (0.9%) in the placebo group.

CONCLUSIONS

Among patients who had undergone mechanical ventilation for at least 3 days, a subsequent 3-day course of inhaled amikacin reduced the burden of ventilator-associated pneumonia during 28 days of follow-up. (Funded by the French Ministry of Health; AMIKINHAL ClinicalTrials.gov number, NCT03149640; EUDRA Clinical Trials number, 2016-001054-17.)

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Ventilator-associated pneumonia is the most frequent presentation of hospital-acquired infection of the lower respiratory tract, the leading nosocomial infection worldwide. It affects patients who undergo invasive mechanical ventilation in intensive care units (ICUs) worldwide, regardless of country income level.[1-4] The estimated incidence varies (depending on definition, screening methods, and patient populations) from 2 to 30 episodes per 1000 days of mechanical ventilation, and the disease develops in 5 to 40% of intubated, critically ill patients.[5-8]

Microaspirations around the tracheal-tube cuff and the formation of biofilm lead to progressive bacterial spread in the tracheobronchial tree, ultimately leading to pneumonia.[9,10] Ventilator-associated pneumonia is a disease with an attributable mortality of up to 13% and contributes to increased systemic antibiotic consumption, duration of mechanical ventilation and ICU lengths of stay, and costs.[11-14] Because the disease progression to overt pneumonia takes several days, with the peak incidence occurring after 7 days of ventilation, a therapeutic window of opportunity exists to hinder the infectious process early on.[15] Despite decades of research and implementation of preventive measures against ventilator-associated pneumonia (e.g., reduced sedation and weaning protocols, patient positioning, management of the tracheal-tube cuff, and oral care), the burden of ventilator-associated pneumonia remains unacceptably high.[16]

Inhaled antibiotic therapy enables delivery of very high antibiotic concentrations to the tracheobronchial tree, lung parenchyma, and tracheal-tube biofilm.[17] A meta-analysis of six trials with small sample sizes suggested efficacy of inhaled antibiotics to prevent ventilator-associated pneumonia.[18] We hypothesized that a 3-day course of inhaled amikacin initiated after the third day of invasive mechanical ventilation might reduce the incidence of ventilator-associated pneumonia.

Methods

Trial Design and Oversight

The Inhaled Amikacin vs. Placebo to Prevent Ventilator Associated Pneumonia (AMIKINHAL) trial was an investigator-initiated, multicenter, double-blind, randomized, controlled superiority trial conducted in 19 ICUs in France. The trial was conducted by the Regional University Hospital Center of Tours and funded by a grant from the French Ministry of Health. The trial protocol (available with the full text of this article at NEJM.org) was approved by a national ethics committee (Comité de Protection des Personnes Ouest I) and has been published previously.[19]

An independent data and safety monitoring board periodically reviewed the trial outcomes and safety. The authors vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol. All the authors approved the final version of the manuscript and made the decision to submit the manuscript for publication.

Patients

Adult patients were eligible for enrollment if they had undergone invasive mechanical ventilation for at least 72 hours. Patients were not eligible for enrollment after 96 hours of invasive mechanical ventilation or if they had suspected or confirmed ventilator-associated pneumonia, severe acute kidney injury without renal-replacement therapy, chronic kidney disease (glomerular filtration rate, <30 ml per minute), or a tracheostomy tube; if extubation was scheduled within the next 24 hours; or if they were receiving systemic aminoglycoside therapy. Detailed inclusion and exclusion criteria are provided in the Supplementary Appendix (available at NEJM.org). All the patients provided written informed consent in accordance with French law.

Randomization

Patients were randomly assigned in a 1:1 ratio to receive inhaled amikacin or inhaled placebo, with stratification according to the trial center and administration of systemic antibiotics on the day of randomization. Allocation concealment and block size (blocks of four patients generated by a statistician not otherwise involved in the trial) were ensured by a centralized secured online server and were not disclosed to patients or persons involved in patient care or the trial conduct or analysis.

Intervention

Nebulization was performed once a day for 3 consecutive days in both groups with the use of a vibrating mesh nebulizer (Aerogen Solo, Aerogen) that was filled with amikacin at a dose of 20 mg per kilogram of ideal body weight (amikacin group) or an equivalent volume of 0.9% sodium

A Quick Take is available at NEJM.org

chloride (placebo group). The second and third scheduled nebulizations were not performed in case of extubation, occurrence of acute kidney injury meeting exclusion criteria, or indication for systemic aminoglycoside therapy as determined by the attending physician. Preparation of the trial drug and placebo was performed by staff not involved in the care of the patients or otherwise involved in the trial.

To ensure that the trial was conducted in a blinded manner throughout, the nebulizers were taped with opaque stickers, and measurements of serum concentrations of amikacin were prohibited. Simplifying nebulization implementation was a major objective to enhance the feasibility of the technique. The nebulizer was placed upstream in the inspiratory limb of the ventilator; different ventilator circuits were used with or without active humidification according to the preference of the attending physician (see the Supplementary Appendix).

Ventilator settings, sedation, and muscle relaxation were at the discretion of the attending physician; however, general guidance on aerosol delivery was provided to investigators. In both groups, all centers adhered to international guidelines regarding prevention of ventilator-associated pneumonia.[16]

OUTCOMES

The primary outcome was a first episode of ventilator-associated pneumonia from randomization to day 28. The primary outcome was adjudicated by a blinded centralized committee on the basis of definitions from international guidelines (requiring a positive quantitative bacterial culture in a pulmonary sample and at least two of the following findings: hyperleukocytosis, leukopenia, fever, or purulent secretions with a new infiltrate on a chest radiograph).[20-22] The diagnostic workup for ventilator-associated pneumonia was standardized among the centers according to international guidelines (see the Supplementary Appendix).

Key secondary outcomes were incidence density (per 1000 patient-days of invasive mechanical ventilation) of adjudicated ventilator-associated pneumonia; the incidence of ventilator-associated pneumonia due to gram-negative bacteria with in vitro susceptibility to amikacin; ventilator-associated events comprising ventilator-associated conditions (i.e., worsening oxygenation over 2 days after a stable or improvement period), infection-related ventilator-associated complications (i.e., worsening oxygenation associated with signs of infection and initiation of antibiotic therapy), and possible ventilator-associated pneumonia (an infection-related ventilator-associated complication accompanied by a documented bacterial component)[23]; the number of days with administration of at least one systemic antibiotic; the number of antibiotic-days (the sum of the number of systemic antibiotic treatments received each day); the number of days of mechanical ventilation from randomization to day 28; the number of days in the ICU and the hospital from randomization to day 90; mortality at day 28 and day 90; and evaluation of nebulization safety and side effects, including ICU-acquired infection with antibiotic-resistant bacteria. A prespecified subgroup analysis involving patients with tracheobronchial bacterial colonization and tracheobronchitis at randomization was planned (see the Supplementary Appendix for the complete list of secondary outcomes and prespecified subgroup analyses and for comprehensive definitions).

STATISTICAL ANALYSIS

Taking into account the competing risk of death and extubation and an expected incidence of ventilator-associated pneumonia of 6% in the amikacin group and 12% in the placebo group, we calculated that a sample size of 850 patients would provide the trial with 80% power to show efficacy with a two-sided alpha level of 0.05.[24-26] Analyses were performed according to the intention-to-treat principle (see the statistical analysis plan, available with the protocol). The threshold for statistical significance was set at 5%, and two-sided 95% confidence intervals were calculated for all estimates. Time from randomization to the first ventilator-associated pneumonia episode was represented by cumulative incidence curves. On evaluation of the data, the proportional-hazards assumption was not met; therefore, a between-group analysis of the restricted mean survival time to ventilator-associated pneumonia was adopted, with death and extubation as competing events.[27]

For time-to-event analyses, a hazard ratio was computed from the total group populations with the use of a Fine and Gray regression model. Extubation, death, ICU discharge, and hospital

discharge were considered to be competing events according to the outcome, and trial exit (i.e., withdrawal of consent) was used as a censor, if applicable.

Statistical analyses for secondary outcomes were not adjusted for multiplicity; therefore, secondary-outcome findings should be interpreted as exploratory. Quantitative outcomes were compared between the two groups with the use of median differences. Between-group comparisons of count outcomes were conducted with the use of a quasi-Poisson regression model, with the duration of mechanical ventilation or the duration of stay in the ICU as the offset. Binary outcomes were analyzed with the use of proportion differences.

For prespecified subgroups, differences in restricted mean survival time to ventilator-associated pneumonia in each subgroup were reported. Additional information on statistical analyses is provided in the Supplementary Appendix.

RESULTS

PATIENTS

From July 3, 2017, to March 9, 2021, a total of 6419 patients were assessed for eligibility, and 850 patients were enrolled — 420 in the amikacin group and 430 in the placebo group. After quality control, the database was locked on November 18, 2022. Three patients withdrew informed consent; thus, 417 patients in the amikacin group and 430 patients in the placebo group were included in the intention-to-treat analyses (Fig. 1). Characteristics of the patients at randomization were well balanced between the groups (Table 1) and were considered to be representative of the target population (Table S4 in the Supplementary Appendix). At the time of randomization, 78% of the patients were receiving systemic antibiotics.

INTERVENTION

Most patients received all three scheduled nebulizations — 337 patients (81%) in the amikacin group and 355 patients (83%) in the placebo group (Fig. 1). In the amikacin group, a mean (±SD) daily dose of 1625±250 mg of amikacin was nebulized over 47±12 minutes, and in the placebo group, 13±2 ml of 0.9% sodium chloride was nebulized over 49±14 minutes (details regarding nebulization conditions are provided in Tables S5, S6, and S7).

OUTCOMES

At 28 days of follow-up, a first episode of ventilator-associated pneumonia (the primary outcome) had developed in 62 patients (15%) in the amikacin group and in 95 patients (22%) in the placebo group (difference in restricted mean survival time to ventilator-associated pneumonia, 1.5 days; 95% confidence interval [CI], 0.6 to 2.5; P=0.004) (Table 2). The first episode of ventilator-associated pneumonia after randomization occurred at a median of 10 days (interquartile range, 7 to 16) after randomization in the amikacin group and at a median of 9 days (interquartile range, 7 to 12) in the placebo group (Fig. 2).

In an analysis that accounted for the duration of risk exposure, the incidence of a first episode of ventilator-associated pneumonia per 1000 days of invasive mechanical ventilation was 16 in the amikacin group and 23 in the placebo group (rate ratio, 0.68; 95% CI, 0.49 to 0.94). A first episode of ventilator-associated pneumonia due to infection with a gram-negative bacteria susceptible to amikacin occurred in 31 patients (7%) in the amikacin group and in 61 patients (14%) in the placebo group (difference in restricted mean survival time to ventilator-associated pneumonia, 1.9 days; 95% CI, 1.1 to 2.8). All ventilator-associated pneumonia episodes were microbiologically documented; microbiological documentation of the primary outcome is provided in Tables S9 and S12. Patient outcomes according to ventilator-associated pneumonia occurrence are shown in Table S10.

A ventilator-associated condition occurred in 137 patients (33%) in the amikacin group and in 170 patients (40%) in the placebo group (hazard ratio, 0.79; 95% CI, 0.64 to 0.99) (Fig. 3). An infection-related ventilator-associated complication occurred in 74 patients (18%) in the amikacin group and in 111 patients (26%) in the placebo group (hazard ratio, 0.66; 95% CI, 0.50 to 0.89). The definition of a possible case of ventilator-associated pneumonia among patients who had a ventilator-associated event was met by 19 patients (5%) in the amikacin group and 42 patients (10%) in the placebo group (hazard ratio, 0.46; 95% CI, 0.27 to 0.78). The number of days with at least one administration of a systemic

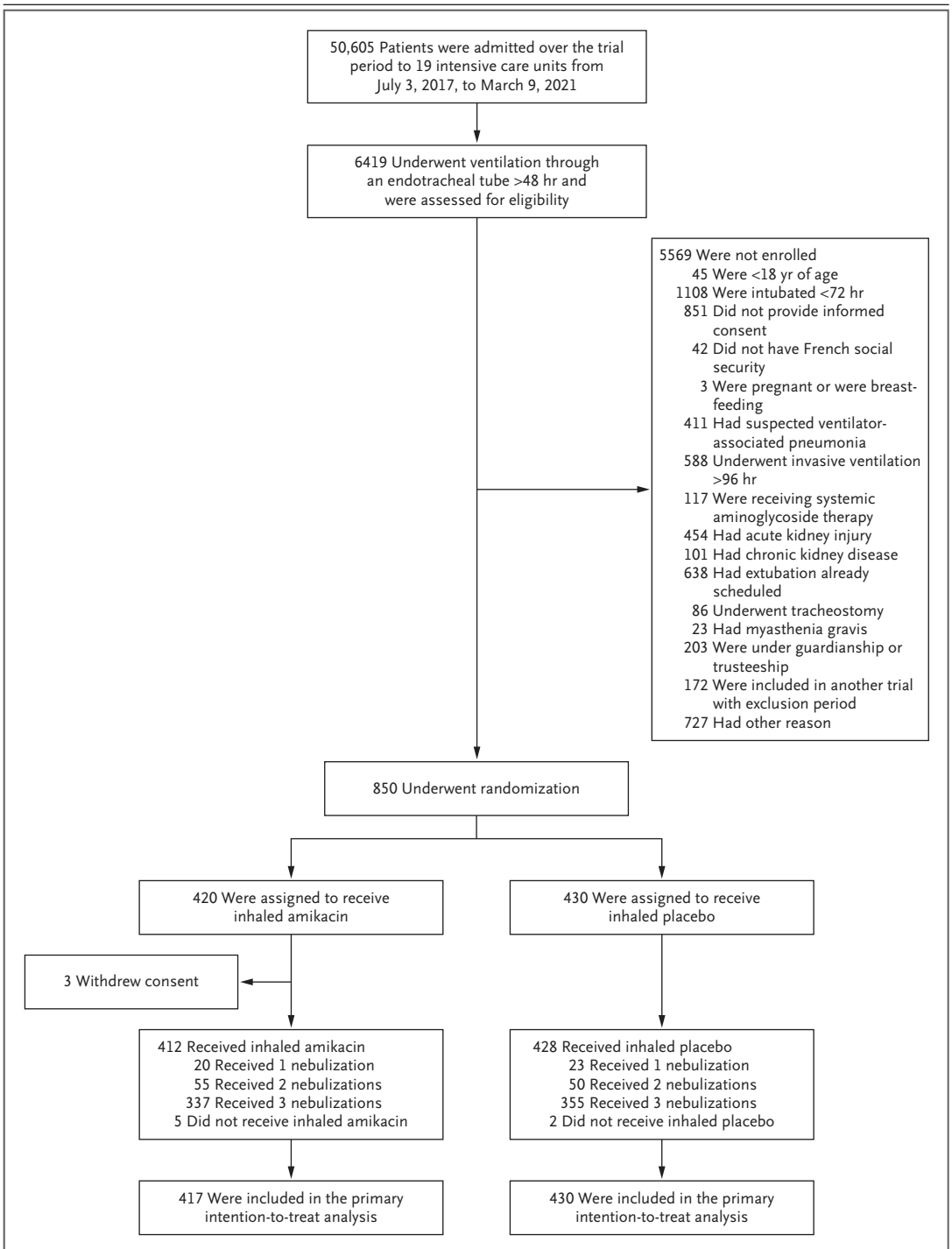

Figure 1. Enrollment, Randomization, Intervention, and Follow-up.

antibiotic per 1000 ICU days was 570 per 1000 in the amikacin group and 589 per 1000 in the placebo group (rate ratio, 0.97; 95% CI, 0.92 to 1.01). The number of antibiotic-days (the sum of the number of systemic antibiotic treatments received each day) per 1000 days of ICU stay was 887 per 1000 in the amikacin group and 968 per 1000 in the placebo group (rate ratio, 0.92; 95%

CI, 0.81 to 1.03). The number of days spent undergoing invasive and noninvasive mechanical ventilation from randomization to day 28 among patients discharged alive was 9 (interquartile range, 6 to 16) and 2 (interquartile range, 1 to 4), respectively, in the amikacin group and 9 (interquartile range, 6 to 15) and 2 (interquartile range, 1 to 4), respectively, in the placebo group.

A total of 99 patients (24%) in the amikacin group and 112 patients (26%) in the placebo group died in the ICU (hazard ratio, 0.89; 95% CI, 0.68 to 1.17). A description of all secondary-outcome results is provided in the Supplementary Appendix.

SENSITIVITY AND SUBGROUP ANALYSES

Among 185 patients with tracheobronchial colonization at randomization, a first episode of ventilator-associated pneumonia occurred in 16 patients (20%) in the amikacin group and in 29 patients (27%) in the placebo group (difference in restricted mean survival time to ventilator-associated pneumonia, 1.3 days; 95% CI, −0.5 to 2.6). Among 104 patients with tracheobronchitis at randomization, a first episode of ventilator-associated pneumonia occurred in 15 patients (32%) in the amikacin group and in 19 patients (33%) in the placebo group (difference in restricted mean survival time to ventilator-associated pneumonia, 1.7 days; 95% CI, −1.0 to 4.7). Analyses restricted to other prespecified subgroups and sensitivity analyses were concordant with those of the primary analysis (see the Supplementary Appendix).

SAFETY OUTCOMES

A serious adverse effect that was considered by central review to be related to the trial occurred in 7 patients (1.7%) in the amikacin group (4 with increased resistance of the expiratory limb filter, 1 with obstruction of the tracheal tube, and 2 with bronchospasms) and in 4 patients (0.9%) in the placebo group (1 with increased resistance of the expiratory limb filter, 1 with obstruction of the tracheal tube, 1 with bronchospasm, and 1 with a decrease in pulse oximetry measurements). Among the patients who did not have an acute kidney injury at the time of randomization, an acute kidney injury developed by day 28 in 11 patients (4%) in the amikacin group and in 24 patients (8%) in the placebo group (hazard ratio, 0.47; 95% CI, 0.23 to 0.96).

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Amikacin Group (N=417)	Placebo Group (N=430)
Age — yr	62±15	61±15
Sex		
Female	135 (32)	157 (36)
Male	282 (68)	273 (63)
Body-mass index†	29±7	29±8
Serum creatinine — mg/dl	1.2±1.1	1.1±1.0
Type of admission — no. (%)		
Scheduled surgery	9 (2)	5 (1)
Unscheduled surgery or trauma	50 (12)	51 (12)
Medical	358 (86)	374 (87)
Charlson Comorbidity Index score‡	4±3	4±2
Simplified Acute Physiology Score II§	52±19	52±18
Sequential Organ Failure Assessment score¶	8±4	8±4
Primary admission diagnosis — no. (%)		
Infection	139 (33)	131 (30)
Respiratory failure	100 (24)	107 (25)
Cardiac arrest	35 (8)	45 (10)
Stroke	30 (7)	29 (7)
Trauma	21 (5)	27 (6)
Poisoning	16 (4)	9 (2)
Status epilepticus	12 (3)	7 (2)
Coma	8 (2)	13 (3)
Gastrointestinal bleeding	7 (2)	8 (2)
Cardiogenic pulmonary edema	6 (1)	5 (1)
Other	43 (10)	49 (11)
Invasive mechanical ventilation before randomization — days	3.5±0.3	3.5±0.3
Systemic antibiotic therapy at randomization — no. (%)	326 (78)	331 (77)

* Plus–minus values are means ±SD. To convert the values for creatinine to micromoles per liter, multiply by 88.4.

† The body-mass index is the weight in kilograms divided by the square of the height in meters.

‡ The Charlson Comorbidity Index score was calculated on the basis of age and 19 coexisting conditions present before admission. Scores range from 0 to 42, with higher scores indicating a greater burden of coexisting conditions and a higher risk of death.

§ The Simplified Acute Physiology Score II was calculated on the basis of 17 variables, information about previous health status, and information obtained over the first 24 hours after intensive care unit (ICU) admission. Scores range from 0 to 163, with higher scores indicating more severe disease. Data were missing for 7 patients in the amikacin group and 6 patients in the placebo group.

¶ The Sequential Organ Failure Assessment score was obtained on the day of ICU admission. Scores range from 0 to 24, with higher scores indicating more severe organ failure. Data were missing for 20 patients in the amikacin group and 23 patients in the placebo group. The serum creatinine level was missing for 1 patient in the amikacin group; no data were missing for other variables.

Table 2. Outcomes.*

Outcome	Amikacin Group (N=417)	Placebo Group (N=430)	Hazard Ratio, Rate Ratio, or Difference (95% CI)	P Value
Primary outcome				
A first VAP episode from randomization to day 28 — no. (%)	62 (15)	95 (22)	1.5 (0.6 to 2.5)†	0.004
Key secondary outcomes				
A first VAP episode due to gram-negative bacteria susceptible to amikacin — no. (%)	31 (7)	61 (14)	1.9 (1.1 to 2.8)†	
Ventilator-associated events — no. (%)				
Ventilator-associated condition	137 (33)	170 (40)	0.79 (0.64 to 0.99)‡	
Infection-related ventilator-associated complication	74 (18)	111 (26)	0.66 (0.50 to 0.89)‡	
Possible VAP according to ventilator-associated events definition framework	19 (5)	42 (10)	0.46 (0.27 to 0.78)‡	
Days with administration of at least one antibiotic — no. per 1000 patient-days of ICU stay	570	589	0.97 (0.89 to 1.01)§	
Antibiotic-days — no. per 1000 patient-days of ICU stay¶	887	968	0.92 (0.81 to 1.03)§	
Median no. of days from randomization to first successful spontaneous breathing trial (IQR)	7 (5 to 12)	8 (6 to 12)	0.96 (0.81 to 1.14)‡	
Median no. of days on mechanical ventilation from randomization to day 28 (IQR)				
Invasive	9 (6 to 16)	9 (6 to 15)	0 (–2 to 1)‖	
Noninvasive	2 (1 to 4)	2 (1 to 4)	0 (–1 to 0)‖	
Median length of stay in days (IQR)				
ICU	12 (9 to 20)	13 (9 to 19)	–1 (–3 to 1)‖	
Hospital	27 (17 to 45)	27 (18 to 43)	0 (–3 to 4)‖	
Deaths — no. (%)				
ICU	99 (24)	112 (26)	0.89 (0.68 to 1.17)‡	
Hospital	123 (29)	136 (32)	0.91 (0.71 to 1.16)‡	
Safety outcomes				
Any serious adverse event — no. (%)	15 (4)	15 (3)		>0.99
Respiratory tract–disorders event — no. (%)	9 (2)	7 (2)		0.62
Serious adverse effect — no. (%)**	7 (2)	4 (1)		0.38
Respiratory tract effect — no. (%)	7 (2)	3 (1)		0.22
Acute kidney injury occurrence from randomization to day 28 — no./total no. (%)	11/294 (4)	24/309 (8)		0.03
Isolation on routine bacteriological samples of bacteria with acquired resistance to amikacin — no. (%)††	41 (10)	41 (10)		0.91
Acquired rectal carriage of resistant bacteria from randomization to ICU discharge — no. (%)				
Extended-spectrum beta-lactamase enterobacterales	16 (4)	9 (2)		0.16
High-level cephalosporinase-producing enterobacterales	11 (3)	8 (2)		0.49
Vancomycin-resistant enterococcus species	1 (<1)	0		>0.99

* ICU denotes intensive care unit, IQR interquartile range, and RMST restricted mean survival time without ventilator-associated pneumonia (VAP). Other than for the primary outcome, widths of the confidence intervals have not been adjusted for multiplicity and thus should not be used to reject or not reject treatment effects.
† The value shown is the difference in days in the RMST.
‡ The value shown is a hazard ratio.
§ The value shown is a rate ratio.
¶ Antibiotic-days represent the sum of the number of systemic antibiotic treatments received each day.
‖ The value shown is a difference.
** A serious adverse effect was a serious adverse event related to a trial procedure.
†† The comprehensive antibiotic resistance pattern of bacteria isolated on routine samples is provided in the Supplementary Appendix.

DISCUSSION

In this large multicenter trial, a 3-day course of amikacin reduced the burden of ventilator-associated pneumonia by day 28 as compared with placebo. Results were consistent with regard to ventilator-associated events (Fig. 3). Less than 2% of the patients had a serious adverse effect.

Trials evaluating the use of inhaled preventive antibiotics in patients undergoing mechanical ventilation have tested colistin, ceftazidime, and gentamicin nebulization for 7 to 15 days[28-31] and even up to extubation,[32,33] with the goal of a potential inhaled-antibiotic–induced reduction in tracheobronchial bacterial burden and a decreased risk of subsequent development of ventilator-associated pneumonia. The present trial shows that a 3-day course of amikacin at a dose of 20 mg per kilogram of ideal body weight is effective in reducing the risk of ventilator-associated pneumonia with an effect size of the same extent as the pooled estimate of those previous, smaller, and mostly single-center trials.[18] A large, multicenter, international trial of adjunctive inhaled amikacin that implemented a different strategy (i.e., treating patients with established ventilator-associated pneumonia with inhaled amikacin for 10 days) did not improve survival.[34]

In our trial, the choice of a 3-day preventive therapy course represented a compromise between efficacy and feasibility on the basis of previous experience with inhaled amikacin and other forms of preventive antibiotic therapy in the ICU.[35-37] The enrollment of patients after at least 3 days of invasive mechanical ventilation may have enabled amikacin to act sufficiently early to control the tracheobronchial spread of bacteria before pneumonia occurred, with a majority of patients being extubated a few days after the end of the intervention and thus no longer at risk for ventilator-associated pneumonia. This approach also provided a simple manner of selecting a patient population initially at high risk for ventilator-associated pneumonia while avoiding exposure to preventive antibiotics among patients with short ventilation durations. The incidence of ventilator-associated pneumonia was higher than the conservative 12% estimate that was used in the control group for calculation of a sample size based on studies that enrolled patients at the time they began receiving mechanical ventilation. Intervening earlier than the third day would increase patient exposure to preventive inhaled antibiotics, potentially increasing antibiotic-resistance selective pressure. Conversely, because only 22% of the patients had tracheal bacterial colonization at the time of randomization, later intervention, such as after day 4 or 5, may deserve evaluation.

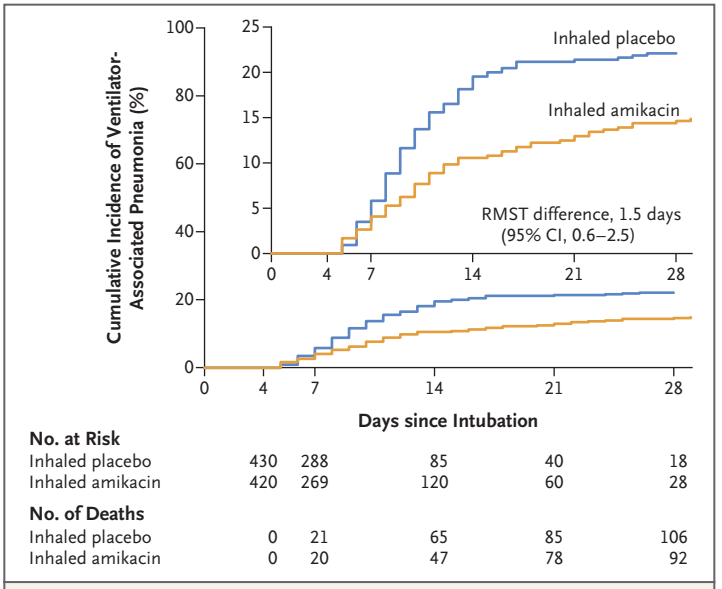

Figure 2. Ventilator-Associated Pneumonia.

Shown are the results of the primary outcome of a first episode of ventilator-associated pneumonia with inhaled amikacin or placebo from randomization to day 28. The inset shows the same data on an expanded y axis. RMST denotes restricted mean survival time to ventilator-associated pneumonia.

Our trial has several limitations. First, although ventilator-associated pneumonia is an important complication with a notable effect on the course of illness, our trial was not powered to investigate other patient-centered outcomes such as death or length of stay in the ICU and hospital. Similarly, at the population level, a potential benefit of preventive inhaled antibiotics may be to reduce the use of systemic antibiotics in order to limit antibiotic-resistance selection pressure, a potential drawback of preventive antibiotic therapy in the long term; however, our trial was not powered for this objective, either. Of note, among all the patients in the trial in whom ventilator-associated pneumonia developed, the lengths of mechanical ventilation and ICU stay and the administration of systemic

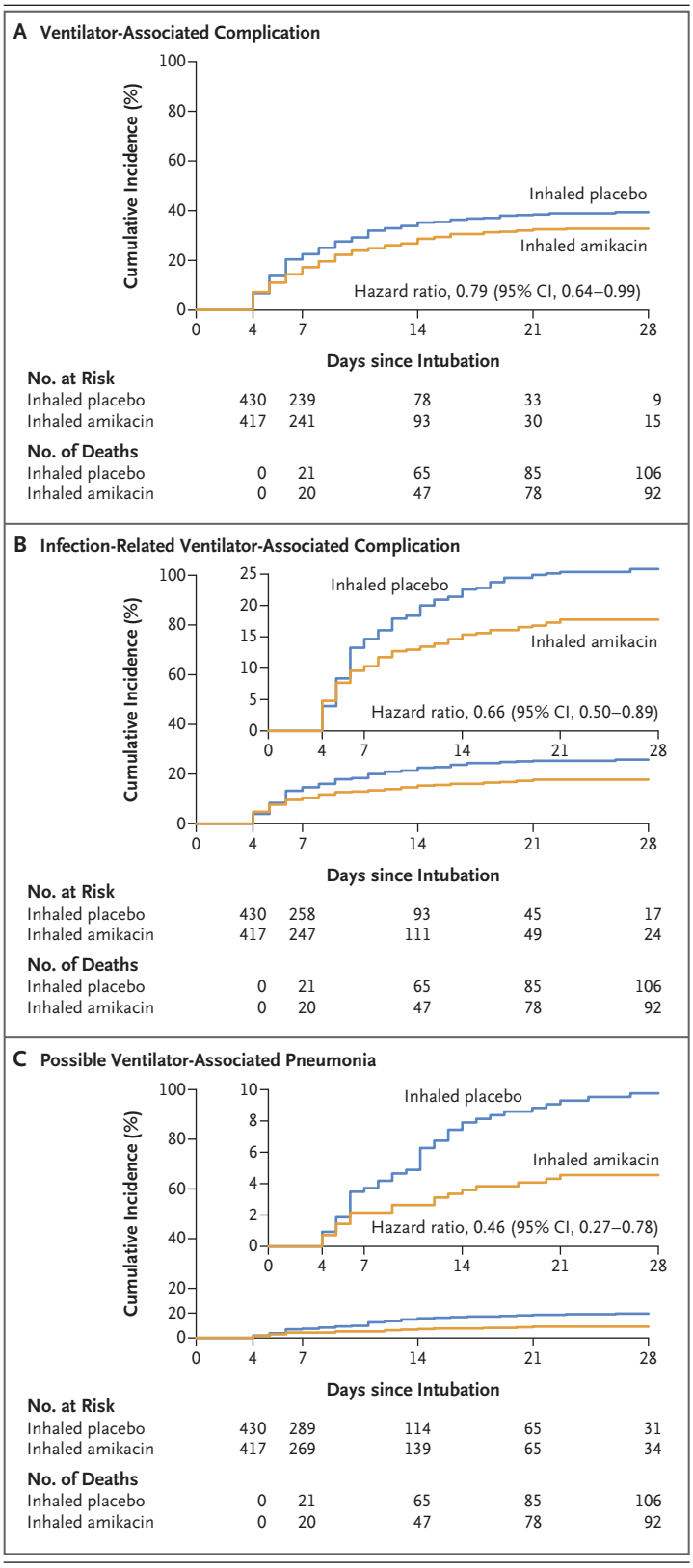

Figure 3. Ventilator-Associated Events.

Shown are the cumulative incidence of ventilator-associated conditions (Panel A) and infection-related ventilator-associated complications (Panel B) and possible ventilator-associated pneumonia based on the definitions framework for ventilator-associated events (Panel C) from randomization to day 28. The widths of the confidence intervals have not been adjusted for multiplicity and should not be used to reject or not reject treatment effects. Insets (in Panels B and C) show the same data on an expanded y axis.

antibiotics were twice as high as those observed in patients in whom ventilator-associated pneumonia did not develop (Table S10). Definitive evaluation of these outcomes would require larger trials. Second, although the double-blind, placebo-controlled design of the trial represents a strength, the pragmatic choice to use inhaled 0.9% sodium chloride as the placebo may be questioned. It is very unlikely that inhaling 0.9% sodium chloride increased the incidence of ventilator-associated pneumonia in the placebo group. Alternatives such as not including a nebulized placebo treatment would have jeopardized blinding, an essential trial feature given the risk of bias related to the diagnostic workup for ventilator-associated pneumonia conducted by the attending physicians. Nebulizing amikacin drug excipients would have led to the same theoretical risk of an intrinsic effect owing to the inhaled route of administration.

Among patients who had received invasive mechanical ventilation for at least 3 days, a subsequent 3-day course of preventive inhaled amikacin reduced the burden of ventilator-associated pneumonia during 28 days of follow-up.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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APPENDIX

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