Study of ventilator-associated tracheobronchitis in respiratory ICU patients and the impact of aerosolized antibiotics on their outcome

Hanaa Ali

Background Lower respiratory tract infections in intubated patients include ventilator-associated tracheobronchitis (VAT) and ventilator-associated pneumonia. Aerosol delivery to intubated patients has improved with advances in techniques and with the development of newer aerosol generators.

Aim The aim of the current study was to assess VAT and study the effect of aerosolized antibiotics (AAs) as an adjuvant to systemic antibiotic (SA) on outcome in VAT patients over 18 months, starting from December 2013, who were admitted to the respiratory ICU of Ain Shams University Hospital.

Patients and methods Seventy-four patients out of 104 mechanically ventilated patients admitted to the respiratory ICU were subjected to serial mini-BAL sputum sampling from the first day of mechanical ventilation (MV). Thirty-two patients who developed VAT were divided into two groups: group I (13 VAT patients who received AAs in the form of ceftazidime 500 mg/12 h+amikacin 400 mg/12 h added to the SA) and group II (10 VAT patients who received only SA). The current study included only those patients whose relatives agreed to share in the study. All patients were subjected to daily assessment for signs of respiratory tract infection and to twice weekly chest radiography, leukocytic count evaluation, and microbiological assessment using mini-BAL.

Results VAT incidence was found to be 22.1%. Eighty percent of patients who received AAs showed clinical improvement in the form of significant decrease in temperature, amount of sputum, and leukocytic count, and significant increase in PaO_2/FiO_2 ratio, in comparison with 30% in the SA group.

Conclusion The incidence of VAT was found to be 22.1%, and was mainly caused by Gram-negative bacteria. AAs adjuvant to SA were effective in rapid resolution of signs of respiratory infection, in causing decreased bacterial load, reduced bacterial resistance, reduced progression of VAT to ventilator-associated pneumonia, reduced days of SA use, decreased MV days and ICU stay days, and probably reduced cost of ICU admission, but did not affect mortality.

Egypt J Bronchol 2016 10:301–309

Egyptian Journal of Bronchology 2016 10:301–309

Keywords: aerosolized antibiotics, mini-BAL, ventilator-associated tracheobronchitis

Doctor of Chest, Chest ICU, Ain Shams University Hospital, Cairo, Egypt

Correspondence to Hanaa Ali, MD, 13 Gamal Al Din Wasel, Abbas Akkad, Cairo, Egypt, Tel: 01118757239;
e-mail: hanaamohammedali@gmail.com

Received 10 March 2016 **Accepted** 28 May 2016

Introduction

Lower respiratory tract infections (LRTIs) are the most common hospital-acquired infections in ICUs. They not only have an impact on each affected patient but also result in considerable financial burden on the healthcare system [1]. MV, while life-saving, also carries significant risks and complications. Infection/colonization propagates an inflammatory response within the airways that could damage the airway wall and lead to airway obstruction. LRTIs in intubated patients include ventilator-associated tracheobronchitis (VAT) and ventilator-associated pneumonia (VAP). The efficiency of aerosol delivery in patients receiving MV has improved with advancements in techniques for aerosol delivery and with the development of newer aerosol generators [2]. Sputum and lung tissue antibiotic levels achieved after inhalation are many-fold higher than those obtained after intravenous administration [3].

Aim of the work

The aim of the current study was to assess VAT and study the effect of aerosolized antibiotics (AAs) as adjuvant therapy to SA in VAT patients in the respiratory ICU (RICU) in Ain Shams University Hospital.

Patients and methods

The current study included 104 patients who were admitted to the RICU and were mechanically ventilated during the period from December 2013 to June 2015. This prospective observational study was conducted to investigate the development of VAT in mechanically ventilated patients. Patients diagnosed with VAT were subjected to a randomized controlled clinical trial in which they were divided into two groups: group I (patients with even numbers received AA along with SA) and group II (patients with odd numbers received only SA).

 DOI: 10.4103/1687-8426.193628

Exclusion criteria

Pregnant ladies, patients with ongoing nosocomial infection requiring antimicrobial treatment, patients on immunosuppressive therapies other than corticosteroids (except prednisolone at a dosage of 40 mg daily for a duration of >4 weeks), patients with neutropenia (<1000 WBC/mm^3), and patients with a history of allergy to the used antibiotics were excluded from the study.

The study was conducted in two stages. In stage I, the full history of each patient was obtained from relatives. The patients underwent a clinical examination; the ventilator mode and duration of ventilator use were recorded; they were subjected to arterial blood gas analysis and complete blood count evaluation, and to renal function assessment. The patients were also followed up to investigate the development of LRTI by means of the following tests:

(1) Clinical assessment through daily evaluation of modified clinical pulmonary infection scores and twice weekly assessment with chest radiographs in anteroposterior view using a portable machine, and leukocyte count.
(2) Microbiological assessment by serial quantitative culture of mini-BAL sputum samples [4] on day 1, after 48 h of MV, and twice weekly if culture was negative, and on day 5 of AA.

Bacterial culture growth was quantitated according to the number of colonies observed per plate and was counted as done by Dallas *et al*. [5].

The patient was diagnosed with VAT if he or she had no clinical or radiological evidence of pneumonia and had two of the following signs and symptoms in the absence of other obvious sources: fever (temperature>38°C or <36°C), leukocytosis greater than 12 000/mm^3, sputum production (increased amount and change in color to yellow, greenish, or purulent), and positive culture obtained with a mini-BAL catheter. We used less than 10^3 as the cutoff value for colony count for a diagnosis of VAT [6].

During stage II group I received AA ceftazidime 500 mg [7] and amikacin 400 mg [8] plus SA, and group II received SA only.

(1) All patients were followed up for clinical response by clinical pulmonary infection score, for bacteriological response (after 5 days of AA), development of VAP, days of mechanical ventilation, amount of systemic antibiotics administered, length of stay in the ICU, and mortality.
(2) Nebulized antibiotics were continued for 7 days or until extubation.

Statistical analysis

Data were analyzed using the Statistical Program for Social Sciences (SPSS), version 18.0. Quantitative data were expressed as mean±SD. Qualitative data were expressed as frequency and percentage.

The following tests were done: independent-samples *t*-test of significance was used to compare two means; the paired sample *t*-test of significance was used to compare related samples, and one-way analysis of variance to compare more than two means. A post-hoc test was used for multiple comparisons between different variables, and the χ^2-test of significance was used to compare proportions between two qualitative parameters. *P*-values less than 0.05 were considered significant, *P*-values less than 0.001 were considered highly significant, and *P*-values greater than 0.05 were considered nonsignificant.

Results

In stage I of the study, 30 patients out of 104 were excluded because they had chest infection. Seventy-four patients out of 104 were subjected to serial mini-BAL sputum sampling, quantitative culture, and sensitivity testing twice a week. Thirty-three patients showed positive cultures. Twenty-three patients were diagnosed with VAT, with an incidence of 22.1%, and 10 patients were diagnosed with early VAP.

In stage II of the study, group I (13 VAT patients) received AA plus SA and group II (10 VAT patients) received only SA. Data from three VAT patients from group I were not analyzed because of cessation of AA.

Discussion

VAP is an ICU-associated infection with the highest morbidity and mortality and high healthcare costs. VAT is considered an intermediate condition between of bacterial colonization and VAP. VAT and VAP have similar clinical presentations and microbiological diagnostic criteria, except the diagnosis of VAP requires the demonstration of a new and persistent infiltrate on chest radiograph [9,10].

VAT and VAP are caused by a wide spectrum of bacterial pathogens that enter the lower respiratory tract at the time of intubation or through leakage around the endotracheal tube cuff [11]. There are multiple ways to obtain sputum samples from

intubated patients, such as tracheal aspirate, blind-protected brushes, and blind mini-lavage (blind mini-BAL). Mini-BAL is less expensive, more widely available, and has a sensitivity and specificity of 80% [12]. Sputum and lung tissue antibiotic levels achieved after inhalation are many-fold higher than those obtained after intravenous administration [3].

In the present study the mean±SD age of patients who developed VAT was 55.2±19.11 years. An overall 43.47% of them were male and 56.52% were female (Table 1). The incidence of VAT in the present study was found to be 22.1%. These results match those of Dallas *et al.* [5], who screened patients intubated for greater than 48 h for the development of VAT and reported a mean age of 56.1±15.6 years for those who developed VAT; 50% of them were male and 50% were female.

The present study does not match that of Nseir *et al.* [13], who studied 30 patients in surgical and medical ICUs and reported the incidence of VAT as 15.3 and 11.2%, respectively. Our results were also not in agreement with those of Dallas *et al.* [5], who reported a VAT incidence in surgical and medical ICUs of 1.4 and 4%, respectively. This disagreement could be due to tracheal aspiration being used as a method for sputum sampling in those studies. Moreover, sampling was done weekly or if tracheobronchitis was suspected; further, the culture was considered positive at greater than 10^5 CFU/ml, which increased the possibility of missing pathogens in low quantity at the time of VAT. All of these factors may result in an underestimation of VAT. In the present study, the method of collection was mini-BAL twice weekly, which is a protected lower respiratory tract sampling method, and culture was considered positive at colony count less than 10^3 CFU/ml.

In the present study, the most frequent primary diagnoses at admission were chronic obstructive pulmonary disease (COPD) and interstitial lung disease (30.43% for each) (Table 2). The most common comorbidities were renal impairment and hypertension (26% each) (Table 3).

Our primary diagnosis agreed with that of Nseir *et al.* [14], who conducted a study in three different ICUs in Spain, Greece, and France on the transition from VAT to VAP. In their study the common primary diagnosis was acute exacerbation of COPD. Our result differs from that of Palmer *et al.* [15], who studied the effect of AA on outcome in 43 critically ill patients who developed VAT in the general ICU, where the cases diagnosed on admission were abdominal infection, cardiac problems, COPD, malnutrition, ARDS, shock, community-acquired pneumonia, healthcare-acquired pneumonia, neurologic diseases with comorbidities that included liver cirrhosis, cardiac failure, chronic renal failure, diabetes, heart failure, and immunosuppression. The variance in the cases may have been due to the difference in the type of ICU.

Table 1 Sex and age of ventilator-associated tracheobronchitis patients

	VAT group (23 patients) [*n* (%)]
Sex	
Male	10 (43.47)
Female	13 (56.52)
Age (years)	
Range	18–86
Mean±SD	55.2±19.11

VAT, ventilator-associated tracheobronchitis.

Table 2 Primary diagnoses of ventilator-associated tracheobronchitis patients

Primary diagnosis	VAT patients (*n*=23) [*n* (%)]
COPD	7 (30.43)
Bronchial asthma	1 (4.34)
Interstitial lung disease	7 (30.43)
Bronchogenic carcinoma	2 (8.69)
Mesothelioma+pleural effusion	1 (4.34)
Obese hypoventilation+obstructive sleep apnea	2 (8.69)
Postmechanical ventilation tracheal stenosis	1 (4.34)
Postcesarean section ARDS	1 (4.34)
ARDS secondary to drug toxicity	1 (4.34)

The most common primary diagnoses were COPD and ILD. COPD, chronic obstructive pulmonary disease; ILD, interstitial lung disease; VAT, ventilator-associated tracheobronchitis.

Table 3 Comorbidities of ventilator-associated tracheobronchitis patients

Comorbidities	VAT patients (*n*=23) [*n* (%)]
Cardiac diseases	3 (13.0)
Cerebrovascular accident	3 (13.0)
Diabetes mellitus	5 (21.7)
Hypertension	6 (26.0)
Chronic liver diseases	3 (13)
Renal impairment	6 (26.0)

The most common comorbidities were hypertension and renal impairment. VAT, ventilator-associated tracheobronchitis.

In the current study, for the diagnosis of VAT we used both clinical criteria (temperature>38°C or <36°C, leukocytosis>12 000/mm^3, and sputum study: increased amount and change in color to yellow, greenish, or purulent) and microbiological criteria (positive culture obtained with a mini-BAL catheter with a colony count $<10^3$ as the cutoff value for positive culture) (Table 4).

In the present work the clinical criteria for diagnosis of VAT match those of Craven *et al.* [16], who followed

Table 4 Diagnostic criteria of ventilator-associated tracheobronchitis patients

Clinical	VAT patients (*n*=23) [*n* (%)]
Secretion	
Color	
Colored	23 (100)
Not colored	0 (0)
Amount	
Scanty	4 (17.3)
Profuse amount	19 (82.6)
Temperature (°C)	
<38	8 (34.7)
>38	15 (65.2)
Range	37–39.5
Mean±SD	38±0.69
Leukocytic count (WBC)	
<12 000	8 (34.7)
>12 000	15 (65.2)
Range	5.7–21.9
Mean±SD ($\times 10^3$/ml)	13.4±3.89
PaO_2/FiO_2 ratio	
Range	114–230
Mean±SD	175.94±53.66
CXR suggesting VAP	0 (0)

VAP, ventilator-associated pneumonia; VAT, ventilator-associated tracheobronchitis; WBC, white blood cell.

up 188 mixed ICU patients intubated for more than 48 h for the development of VAT on the basis of at least two clinical criteria (fever, leukocytosis, or purulent sputum). The present study also agrees with that of Montgomery *et al.* [17], who evaluated the effect of AA on nine VAT patients regarding the clinical criteria for the diagnosis of VAT and also with the study of Rodriguez *et al.* [18], who conducted a survey in 16 different countries with 288 ICUs. They reported an incidence of 79.2% for VAT on the basis of both clinical and microbiological criteria. BAL and mini-BAL were more frequently utilized by Latin-America.

The clinical criteria used in the present study for the diagnosis of VAT do not match those of Palmer *et al.* [15], who relied on the presence of purulent secretion of at least 2 ml over a period of 4 h with organisms detected with Gram stain, or with the study of Nseir *et al.* [19],who suggested that using this clinical criterion makes the distinction of VAT from VAP a difficult task because fever and increased sputum amount are common in ICU patients and a portable chest radiograph is inaccurate in diagnosing new pulmonary infiltrate in ICU patients. Our study does not agree with that of Dallas *et al.* [5] either, who used increase sputum production of at least 2 ml over a period of 4 h and weekly culture of tracheal aspirate for the diagnosis of VAT, whereas in the current study the presence of profuse colored secretion (amount>30 m/day), fever greater than 38°C, and leukocytic count greater than 12 000/mm^3 were used for the diagnosis of VAT with mini-BAL sample culture twice weekly. Gram stain was not used in the current study because it is inaccurate in the diagnosis of LRTI.

In the present study the bacterial culture from patients who developed VAT showed that Gram-negative organisms are the most frequently isolated organism, with 47.8% of them being *Klebsiella*; infection was polymicrobial in 34.6% of cases (Tables 5 and 6). The current study agrees with that of Nseir *et al.* [19,20], who reported that Gram-negative organisms were the most frequent isolates from VAT patients (75%); *Pseudomonas aeruginosa* showed the highest proportion in their studies (27–34%), whereas in the current study *Klebsiella pneumoniae* was the most frequent.

In the study by Matrin-Loeches *et al.* [21], VAT was frequently caused by Gram-negative bacteria (37%), whereas *P. aeruginosa* showed a proportion of 25% and infection was polymicrobial in 22% of VAT patients. The present study also agrees with that by Craven *et al.* [16], in whose study Gram-negative bacteria were the most frequent organisms isolated (66%), but *P. aeruginosa* was the common organism (19%) and infection with polymicrobial pathogens was seen in 19% of cases.

The differences in the types and percentages of organisms isolated between the current study and the above-mentioned studies may be due to the wide spectrum of etiologic agents that can cause VAT and VAP, which vary by hospital, type of ICU, and patients. Consequently, local surveillance of microbiological data is important.

On day 1 of the study there were no significant differences between group I and group II as regards temperature (P=0.239), leukocytic count (P=0.484), or mean PaO_2/FiO_2 ratio (P>0.05) (Table 6).

During stage II of the present study 23 patients diagnosed with VAT were assigned at a ratio of 1 : 1 for treatment with aerosolized amikacin 400 mg/12 h and ceftazidime 500 mg/12 h as adjuvant therapy to SA. Patients were divided into two groups: group I (13 VAT patients received amikacin plus ceftazidime with SA) and group II (10 VAT patients received SA only) (Table 7).

All groups were followed up for signs of respiratory infections (colored secretions with increased amount, fever, and leukocytosis), PaO_2/FiO_2, and for the development of new shadows in chest X-ray (CXR) suggestive of pneumonia. Protected mini-BAL samples

Table 5 The bacteria isolated from the ventilator-associated tracheobronchitis patients and their colony count

Colony count	VAT patients (*n*=23) [*n* (%)]
Staphylococcus aureus (MSSA)	26%
$<10^3$	2 (8.6)
$>10^4$	1 (4.3)
10^3	2 (8.6)
10^5	1 (4.3)
MRSA	8.6%
$\geq10^5$	1 (4.3)
10^3	1 (4.3)
10^4	0 (0)
Klebsiella	47.8%
$<10^3$	1 (4.3)
$\geq10^4$	1 (4.3)
$>10^5$	0 (0)
$>10^6$	0 (0)
10^3	6 (26)
10^4	2 (8.6)
10^5	1 (4.3)
Acinetobacter	21.5%
$>10^4$	1 (4.3)
$>10^5$	1 (4.3)
10^3	2 (8.6)
10^4	1 (4.3)
Pseudomonas	13%
$<10^3$	1 (4.3)
$>10^6$	2 (8.6)
E. coli	
$\geq10^4$	1 (4.3)
$>10^6$	0 (0)

The most frequent cause of VAT was *Klebsiella*. VAT, ventilator-associated tracheobronchitis.

of the lower respiratory tract were collected for quantitative culture on day 5 of AA.

As regards the clinical outcome (at day 5), group I showed significant decrease in secretion amount, temperature, leukocytic count, and mean PaO_2/FiO_2 ratio on day 5 compared with day 1 (P=0.001,0.005, 0.018, and 0.021, respectively), whereas group II showed no significant difference between day 1 and day 5 (Figs 1–4); clinical improvement was 80% in group I and 30% in group II (Table 8).

The present study matches that of Palmer *et al.* [15], who studied the effect of AAs on respiratory tract infections in MV patients and showed that signs of respiratory infections decreased from 73.6% on day 1 to 35.7% for patients who received 14 days of treatment, compared with 75 and 78.6% in the placebo group; leukocytic count (LC) decreased in the group that received AA compared with the placebo group.

The current study also agrees with that of Lu *et al.* [7], who did a randomized trial of AA in patients with VAP due to

Table 6 Diagnostic criteria of the study groups on day 1

Secretion	Group I (10 patients) [*n* (%)]	Group II (10 patients) [*n* (%)]	*P*-value (group I vs. group II)
Color			
Colored	10 (100)	10 (100)	
Not colored	0 (0)	0 (0)	
Amount			
Scanty	0 (0)	4 (40)	
Profuse amount	10 (100)	6 (60)	
Temperature			
Range	37–39.5	37–38.5	0.239
Mean±SD	38.25±0.86	37.87±0.47	NS
Normal (<38°C)	2 (20)	4 (40)	
High (>38°C)	8 (80)	6 (60)	
Leukocytic count (WBC)			
Normal (<12 000)	4 (40)	3 (30)	
High (>12 000)	6 (60)	7 (70)	
Range	9–16.8	5.7–21.9	0.484
Mean±SD	12.9±2.48	14.18±5.04	NS
PaO_2/FiO_2 ratio			
Range	114–297.5	137–255	>0.05
Mean±SD	161.52±59.8	166.75±39.9	NS
CXR	0	0	

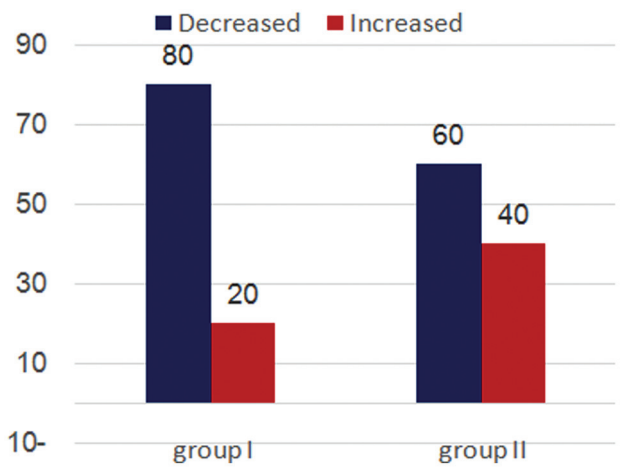
There were no statistically significant differences between group I and group II as regards mean temperature, leukocytic count, and mean PaO_2/FiO_2 ratio. WBC, white blood cell.

Table 7 Aerosolized antibiotics and their complications

Aerosolized antibiotics	Patients (*n*=10) [*n* (%)]
Ceftazidime	4 (40)
Amikacin	1 (10)
Amikacin+ceftazidime	5 (50)
Complications caused by AA	
Bronchospasm	1 (10)
Renal impairment	0 (0)

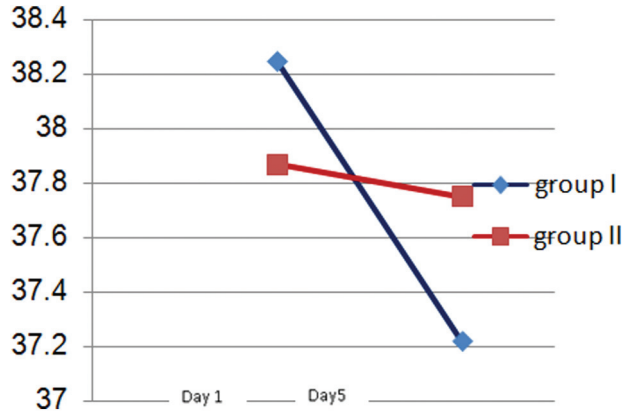
AA, aerosolized antibiotics.

Figure 1



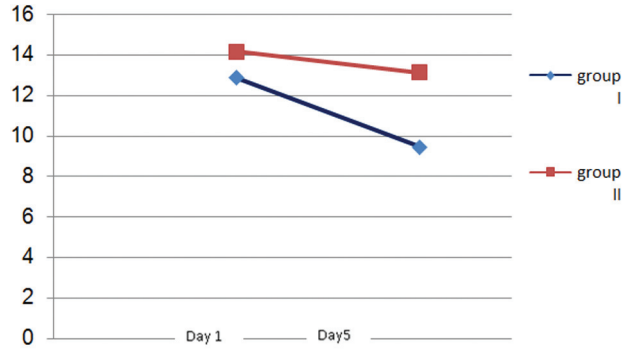
The difference between groups as regards change in the amount of secretion on day 5 of aerosolized antibiotics (AAs).

Figure 2



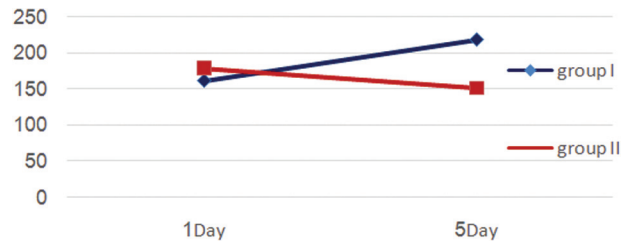
Comparison between groups on day 1 and day 5 of aerosolized antibiotics (AAs) regarding mean temperature.

Figure 3



Comparison between groups on day 1 and day 5 of aerosolized antibiotics (AAs) regarding LC.

Figure 4



Comparison between groups on day 1 and day 5 of aerosolized antibiotics (AAs) regarding PaO_2/FiO_2 ratio.

P. aeruginosa and reported that improvement in VAP was clinically observed in 70% of the group that received inhaled ceftazidime and amikacin plus SA compared with 55% of the control group that received SA. The present study also agrees with that of Niederman *et al.* [22], which showed that improvement in VAP clinically occurred in 94% of the group that received inhaled amikacin plus SA compared with 88% of the control group that received SA. In addition, in the study by Ali [23] on 18 patients diagnosed with VAP in El-Abbasia Chest Hospital who received aerosolized amikacin and ceftazidime as adjuvant to used systemic antibiotics clinical improvement was observed in the group that received AA in comparison with the group that did not receive AA.

Table 8 Comparison of outcomes in the two groups

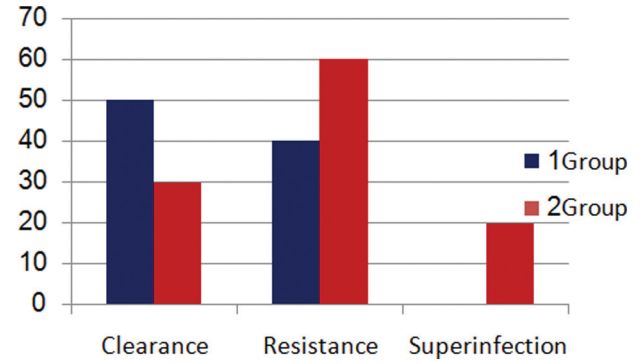
	Group I (10 patients) [*n* (%)]	Group II (10 patients) [*n* (%)]
Clinical improvement	8 (80)	3 (30)
Bacteriological clearance	5 (50)	3 (30)
Weaning	4 (40)	4 (40)
Death	6 (60)	6 (60)
Causes of death	2 cardiac arrest, 1 ARDS	2 septic shock
	1 metabolic acidosis	2 ARDS
	1 renal failure	1 cardiac arrest
	1 cerebral infarction	1 cerebral infarction

As regards microbiological outcomes, there was a nonsignificant increase in clearance in group I compared with group II (P=0.913) and a nonsignificant decrease in resistance and superinfection in group I in comparison with group II (P=0.894 and 1.491, respectively) (Fig. 5).

The current study matches that of Ghannam *et al.* [24], who studied the effect of inhaled aminoglycosides as an adjuvant to SA on VAP. Their study showed greater microbiological success for VAP in the group that received the adjuvant compared with the group that received intravenous antibiotics alone. Our study also agrees with that of Lu *et al.* [7], who demonstrated a cure for VAP microbiologically in 70% of the group that received inhaled ceftazidime and amikacin plus SA, compared with 55% of the group that received SA. Emergence of resistant strains was seen only in the group that received SA.

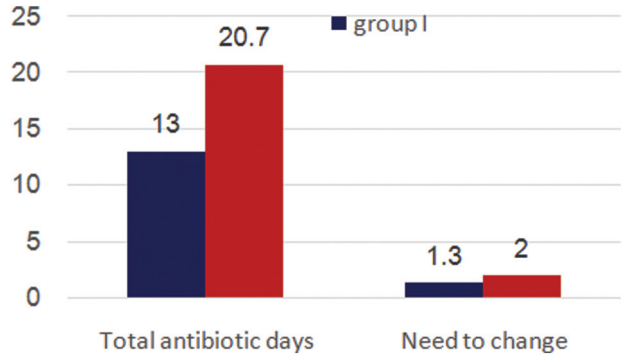
The present study also matches that of Lu *et al.* [25], who conducted a prospective observational trial of AA and found superinfection in 6% of patients in the aerosolized group that received inhaled amikacin adjuvant to SA and in 13% in the group that received SA only. In addition, Niederman *et al.* [22] conducted a trial on 69 patients with VAP who received aerosolized amikacin and found success in microbiological cure in 94% of the AA group compared with 88% of the group that received SA. The current study also agrees with that of Ali [23], which showed that clearance was nonsignificantly more frequent in the AA group compared with the SA group and bacterial resistance was nonsignificantly

Figure 5



Comparison between group regarding bacteriological outcome on day 5 of aerosolized antibiotics (AAs).

Figure 6



Comparison between groups regarding the number of days of systemic antibiotic use and rate of change.

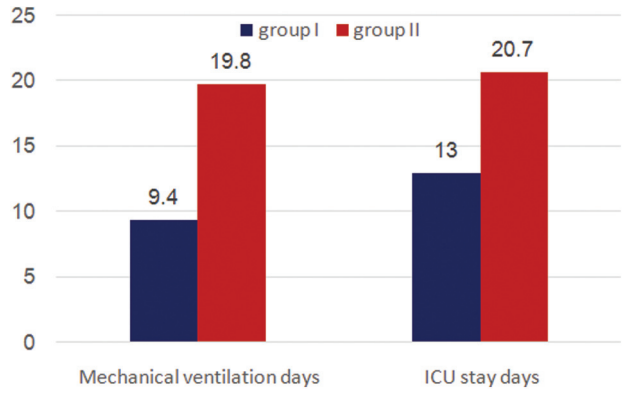
less frequent in the AA group compared with the group that received SA alone.

As regards the average number of days of SA required we found significant decrease in the number of SA days. Group I showed nonsignificant decrease in SA days in comparison with group II (P=0.178) (Fig. 6). As regards the frequency of need to change SA, group I showed nonsignificant decrease in the frequency of need to change SA in comparison with group II (P=0.355) (Figure 6). The present study matches that of Palmer *et al.* [15], which showed that AA reduced the use for additional systemic antibiotics for treatment of new or persistent infection.

As regards MV days, group I showed nonsignificant decrease in MV days in comparison with group II (P=0.140) (Fig. 7). The present study matches that of Palmer *et al.* [15], who showed that the number of ventilator-free days was higher in the AA group than in the placebo group, although not reaching statistical significance. It was also similar to the study by Palmer and Smaldone [26], who showed that total number of ventilator days was lower in the AA group but not significantly (AA group, 19.9±2.1; placebo, 13.5±2.1).

As regards total ICU stay days, group I showed nonsignificant decrease in the number of ICU stay days in comparison with group II (P=0.178) (Fig. 7). The current study matches that of Wood *et al.* [27], who showed that in 59 critically ill trauma patients with VAP length of stay was 11 days in the AA group receiving ceftazidime plus SA compared with 12 days in the control group. The present study also agrees with that of Ali [23], who showed that MV days and ICU stay days decreased in the AA group compared with the SA group.

Figure 7

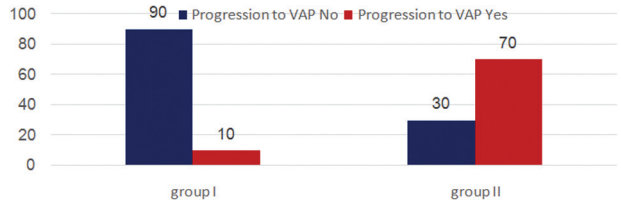


Comparison between MV days and ICU stay days.

In the present study as regards progression to VAP there was significant decrease in the rate of progression to VAP in group I in comparison with group II (P<0.001) (Fig. 8). The present study matches that of Palmer *et al.* [15], in whose study five AA patients with VAT did not progress to VAP.

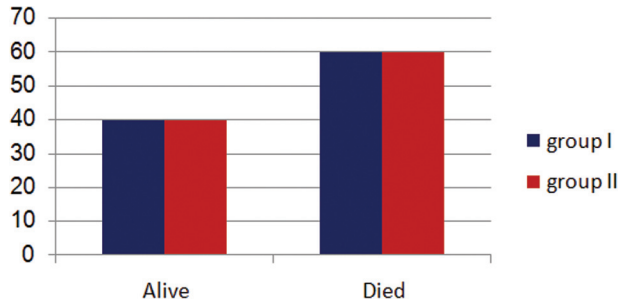
Regarding mortality there was no statistically significant difference between group I and group II (P=1.000) (Fig. 9). The current study agrees with those of Ioannidou *et al.* [28] and Palmer *et al.* [15], who showed no significant effect on mortality in the AA group and the control group; mortality was the same in both the AA group and the SA group. The current study also agrees with that of Lu *et al.* [25], who conducted a prospective observational study on the efficiency of nebulized colistin in treating 43 VAP patients infected with MDR Gram-negative organisms, compared with treatment with intravenous antibiotics, and found that mortality was not different between groups. The current work matches that of Palmer and Smaldone [26], who reported that mortality differences

Figure 8



Comparison between groups regarding progression to ventilator-associated pneumonia (VAP).

Figure 9



Comparison between groups as regards mortality.

were not significant between groups (AA 6/24 vs. placebo 2/18).

The present study does not agree with the results of Doshi *et al.* [29], who conducted a study comparing intravenous colistin in 24 patients versus colistin given in aerosolized and intravenous forms in 20 patients. He reported that the intravenous group demonstrated a trend toward higher mortality (70.4 vs. 40.7%). The disagreement could be due to the difference in the primary diagnosis on admission, presence of comorbidities, their response to treatment, and the sensitivity of the organisms to the used antibiotics.

Conclusion

The incidence of VAT in the RICU in Ain Shams University hospital was 22.1%, mainly caused by Gram-negative bacteria (mostly MDR). Mini-BAL was a technically simple and cheap procedure to obtain lower respiratory tract culture samples. AA was effective as an adjuvant to systemic antibiotics for the treatment of VAT. AA was effective in rapid resolution of signs of respiratory infection, decreased bacterial load, reduced bacterial resistance, reduced progression of VAT to VAP, reduced days of systemic antibiotic use, decreased mechanical ventilation days, ICU stay days, and probably reduced cost of ICU admission, but did not affect mortality.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1 Leistner R, Kankura L, Bloch A, Sohr D, Gastmeier P, Geffers C. Attributable cost of ventilator-associated lower respiratory tract infection acquired on intensive care units: a retrospectively matched cohort study. *Antimicrob Resist Infect Control* 2013; **2**:13.

2 Dhand R, Sohal H. Pulmonary drug delivery system for inhalation therapy in mechanically ventilated patients. *Expert Rev Med Devices* 2008; **5**:9–18.

3 Dhand R. Bronchodilator therapy. In: Tobin M, editor. *Principles and practice of mechanical ventilation*. 2nd ed. New York: McGraw Hill 2006. 1277–1310

4 Abd-Elfatah N, Madkour A, Sharkawy S, Fahmy G. The efficiency of a new, cheap and safe method in a acquiring a mini-BAL sample for VAP diagnosis: an initial Egyptian trial. *Chest* 2009; **136**:82–83.

5 Dallas J, Skrpky L, Abebe N, Boyle WA III, Kollef MH. Ventilator-associated tracheobronchitis in a mixed surgical and medical ICU population. *Chest* 2011; **139**:513–518.

6 Craven DE, Hudcova J, Lei Y. Diagnosis of ventilator-associated respiratory infections): microbiologic clues for tracheobronchitis (VAT) and pneumonia (VAP). *Clin Chest Med* 2011; **32**:547–557.

7 Lu Q, Yang J, Liu Z, Gutierrez C, Aymard G, Rouby JJ. Nebulized ceftazidime and amikacin in ventilator-associated pneumonia caused by *Pseudomonas aeruginosa*. *Am J Respir Crit Care Med* 2011; **184**:106–115.

8 Niederman MS, Chastre J, Corkery K, Marcantonio A, Fink JB, Luyt CE, Sanchez M. Inhaled amikacin reduces IV antibiotic use in intubated mechanically ventilated patients. *Am J Respir Crit* 2007; **11**:97.

9 Grgurich PE, Hudcova J, Lei Y, Sarwar A, Craven DE. Diagnosis of ventilator-associated pneumonia: controversies and working toward a gold standard. *Curr Opin Infect Dis* 2013; **26**:140–150.

10 Agrafiotis M, Siempos II, Falagas ME. Frequency, prevention, outcome and treatment of ventilator-associated tracheobronchitis: systematic review and meta-analysis. *Respir Med* 2010; **104**:325–336

11 American Thoracic Society and Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and health care associated pneumonia. *Am J Respir Crit Care Med* 2005; **171**:388–416.

12 Bregeon F, Papazian L, Visconti A. Diagnostic accuracy of protected catheter sampling in ventilator- associated bacterial pneumonia. *Eur Respir J* 2000; **5**:969–975.

13 Nseir S, Di Pompeo C, Pronnier P, Beague S, Onimus T, Saulnier F, Grandbastien B, Mathieu D, Delvallez-Roussel M, Durocher A. Nosocomial tracheobronchitis in mechanically ventilated patients: incidence, aetiology and outcome. *Eur Respir J* 2002; **20**:1483–1489.

14 Nseir S, Martin-Loeches I, Markris D, Jaillette E, Karvouniaris M, Valles J, *et al.* Impact of appropriate antimicrobial treatment on transition from ventilator-associated trachea-bronchitis to ventilator-associated pneumonia. *Crit Care Med* 2014; **18**:129.

15 Palmer LB, Smaldone GC, Chen JJ, Baram D, Duan T, Monteforte M, *et al.* Aerosolized antibiotics and ventilator-associated tracheobronchitis in the intensive care unit. *Crit Care Med* 2008; **36**:2008–2013.

16 Craven DE, Lei Y, Ruthazer R, Sarwar A, Hudcova J. Incidence and outcome of ventilator- associated tracheobronchitis and pneumonia. *Am J Med* 2013; **126**:542–549.

17 Montgomery AB, Vallance S, Abuan T, Tservistas M, Davies A. A randomized double-blind placebo-controlled dose-escalation phase 1 study of aerosolized amikacin and fosfomycin delivered via the PARI investigational eFlow® inline nebulizer system in mechanically ventilated patients. *J Aerosol Med Pulm Drug Deliv* 2014; **2**:441–448.

18 Rodriguez A, Povoa P, Nseir S, Salluh J, Curcio D, Martin-Loeches I. Incidence and diagnosis of ventilator-associated tracheobronchitis in the intensive care unit: an international online survey, *Crit Care* 2014; **18**: R32.

19 Nseir S, Favory R, Jozefowicz E, Decamps F, Dewavrin F, Brunin G, *et al.* Antimicrobial treatment for ventilator-associated tracheobronchitis: a randomized, controlled, multicenter study. *Crit Care* 2008; **9**:238–245.

20 Nseir S, Ader F, Marquette CH. Nosocomial tracheobronchitis. *Curr Opin Infect Dis* 2009; **22**:148–153.

21 Martin-Loeches I, Nseir S, Valles J, Artigas A. From ventilator-associated tracheobronchitis to ventilator associated pneumonia. *Reanimation* 2013; **22**:231–237.

22 Niederman MS, Chastre J, Corkery K, Fink JB, Luyt CE, Garcia MS. BAY41-6551 achieves bactericidal tracheal aspirate amikacin concentrations in mechanically ventilated patients with Gram-negative pneumonia. *Intensive Care Med* 2012; **38**:263–271.

23 Ali M. Effect of nebulized antibiotics in treatment of ventilator associated pneumonia in El Abbasia Chest Hospital ICU [thesis for Master Degree]. Egypt: Ain Shams University Hospital; 2014.

24 Ghannam DE, Rodriguez DH, Raad II, Safdar A. Inhaled aminoglycosides in cancer patients with ventilator-associated Gram-negative bacterial pneumonia: safety and feasibility in the era of escalating drug resistance. *Eur J Clin Microbiol Infect Dis* 2009; **28**:253–259.

25 Lu Q, Luo R, Bodin L, Yang J, Zahr N, Aubry A, *et al.* Efficacy of high-dose nebulized colistin in ventilator-associated pneumonia caused by multidrug-resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii*. *Anesthesiology* 2012; **117**:1335–1347.

26 Palmer LB, Smaldone GC. Reduction of bacterial resistance with inhaled antibiotics in the ICU. *Am J Respir Crit Care Med* 2014; **189**:1225.

27 Wood GC, Boucher BA, Croce MA, Hanes SD, Herring VL, Fabian TC. Aerosolized ceftazidime for prevention of ventilator-associated pneumonia and drug effects on the proinflammatory response in critically ill trauma patients. *Pharmacotherapy* 2002; **22**:972–978.

28 Ioannidou E, Siempos II, Falagas ME. Administration of antimicrobials via the respiratory tract for the treatment of patients with nosocomial pneumonia: a meta-analysis. *J Antimicrob Chemother* 2007; **60**:1216–1226.

29 Doshi NM, Cook CH, Mount KL, Stanislaw P, Erin N, Heather A, *et al.* Adjunctive aerosolized colistin for multidrug resistant Gram-negative pneumonia in the critically ill: a retrospective study. *BMC Anesthesiol* 2013; **13**:45.