Ventilator-associated tracheobronchitis in a surgical ICU population

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Introduction Ventilator-associated tracheobronchitis (VAT) rates in the ICU are variable and may depend on the population examined. The overlap between VAT and ventilator-associated pneumonia (VAP) remains poorly defined.

Aim This study aims to determine the incidence of VAT and its relation to VAP in the surgical ICU.

Patients and methods Patients who were intubated postoperatively for more than 48 h in surgical ICUs of the Ain Shams University Hospital were monitored daily for the development of VAT and VAP during a 2-year period. Patients were followed until ICU discharge or death. Patient demographics, causative pathogens and clinical outcomes were recorded.

Results Among the 50 patients studied, there were five (10%) patients with VAT and 12 (24%) patients with VAP. VAT progressed to VAP in two patients (40%) despite antibiotic therapy. The incidence of VAP was significantly greater than the incidence of VAT. The mean onset times of VAT and VAP were 4 ± 1 and 5.1 ± 0.8 days, respectively. VAT and VAP were caused by multidrug-resistant pathogens in two patients (40%) and six patients (50%), respectively. VAT occurrence was the most common among patients undergoing cardiothoracic surgery and neurosurgery. There was no significant difference in the duration of mechanical ventilation and ICU stay and days of antibiotic use between the VAT and the VAP groups. There was no significant difference in the ICU mortality between patients with VAP and VAT (33.3 vs. 40%; $P = 0.70$).

Conclusion VAT occurs less commonly than VAP. VAT does not appear to be a necessary precursor for all VAP cases. VAT patients had outcomes similar to those with VAP. *Egypt J Broncho* 2014 8:153–159

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Keywords: surgical intensive care unit, ventilator-associated pneumonia, ventilator-associated tracheobronchitis

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Introduction

Mechanical ventilation (MV), while life saving, also carries significant risks and complications [1]. Nosocomial lower respiratory tract infections are a common cause of morbidity and mortality in ICU patients receiving MV. Many studies have investigated the management and the prevention of ventilator-associated pneumonia (VAP), but few have focused on the role of ventilator-associated tracheobronchitis (VAT) [2].

Tracheobronchitis is characterized by lower respiratory tract inflammation and increased sputum production resulting in weaning difficulties and longer MV duration [3,4]. The main cause to develop infection in the airways is the imbalance between host defenses and excess mucus that can become stagnant and serve as a medium for bacterial growth by potentially pathogenic organisms [1]. The pathogenesis of lower respiratory tract infections often begins with tracheal colonization, which may progress to VAT, and in selected patients to VAP [2]. VAT is probably a continuum between bronchitis and pneumonia in MV patients [1].

Controversies concerning the definition of VAT and its true distinction from VAP exist [2,4]. However, the most specific definition includes fever (>38°C) with no other recognizable cause, purulent sputum production, positive culture of respiratory specimen at a significant threshold and no radiographic signs of new pneumonia [4].

The reported VAT rates in the literature are variable [4]. Recent data suggest that VAT appears to be an important risk factor for VAP. VAT is associated with a longer duration of MV and longer ICU length of stay [2,4]. Targeted antibiotic therapy for VAT may be a new paradigm for VAP prevention and better patient outcomes [2,4]. However, beneficial effects of antimicrobial treatment for VAT patients have been refuted by some studies [5–7].

Few prospective studies have been published that directly evaluate the adverse outcomes of VAT [5,6,8]. The purpose of this study was to determine the incidence of VAT and its relation to VAP in MV patients in the surgical ICU postoperatively.

Patients and methods

Study population

This prospective study was conducted in surgical ICUs of the Ain Shams University Hospital during the period from June 2011 to June 2013, including 50 adult patients (≥18 years) who were intubated postoperatively for more than 48 h. Patients were monitored daily for the development of either VAT and/or VAP. The following patients were excluded: patients with chronic respiratory failure, patients with little chance of survival as defined by APACHE (Acute Physiology and Chronic Health Evaluation) II (>65 points) [9], the presence of another ongoing nosocomial infection requiring antimicrobial treatment, the presence of a tracheostomy at the time of VAT or VAP suspicion, significant immune suppression defined as prolonged neutropenia (>1 week), HIV-positive patients or patients on chronic steroid therapy at a dosage equivalent to or greater than 40 mg of prednisolone daily for a duration at least 4 weeks.

Data collection

At the time of VAT or VAP diagnosis, the following data were recorded for each patient: age, sex, the presence of comorbid conditions, the leukocyte count, the quantity and the nature of pulmonary secretions, the APACHE II [9] score at ICU admission, partial arterial oxygen pressure (PaO_2)/fraction of inspired oxygen (FiO_2) and the causative organism (s) associated with VAT and/or VAP.

Study endpoint

Patients who were diagnosed with VAT and/or VAP were followed until ICU discharge or death, and the following parameters were recorded: the duration of MV, the length of ICU stay and days of antibiotic use for the treatment of VAT and/or VAP.

Some patients were judged to progress from VAT to VAP on the basis of the development of a new or progressive infiltrate in the 96 h after the initial diagnosis of VAT. To be included in this group, patients had to display continued evidence of ongoing infection as evidenced by temperature more than 38.3°C or less than 36.0°C or leukocyte 12 000/mm^3. If a new organism associated with VAP was isolated from the respiratory cultures of a patient previously diagnosed with VAT, then they were judged not to have progressed from VAT to VAP. These patients were instead considered to have a new episode of VAP, which was included in the analysis. Subsequent distinct episodes of VAT or VAP occurring more than 96 h after the initial episode of VAT or VAP were not included in this analysis [6].

The secretion volume and the nature were routinely recorded every 8 h by nurses caring for intubated patients. The secretion volume was graded on the following scale: none, small (<30 ml/day), moderate (30–100 ml/day), or large (>100 ml/day) [6]. Respiratory secretions were sent for microbiological analysis on admission (baseline) and then at the time of suspected infections. No routine surveillance of respiratory secretion was performed.

Endotracheal tube aspirate sampling

ETA sampling was obtained by sterile means using a 22-inch catheter. A length of ~24 cm of the catheter was passed through the endotracheal tube, and secretions were collected in a 25-ml mucus collector (mucus extractor, Model no 4004; Ultra for Medical Project, Abnoub, Assiut, Egypt) (Fig. 1) without instilling saline.

Definitions

Definition of ventilator-associated tracheobronchitis

VAT was defined as the presence of all of the following in a patient endotracheally intubated and receiving MV for more than 48 h: body temperature more than 38.3°C or less than 36.0°C, new or increased purulent tracheal secretions, positive culture of ETAs at a concentration of at least 10^5 CFU/ml and no new or progressive infiltrate on portable chest radiography [6].

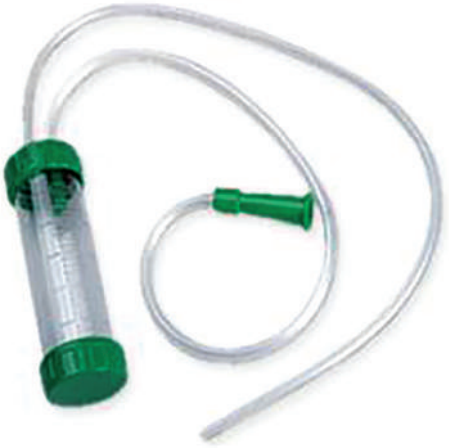
Definition of ventilator-associated pneumonia

VAP was defined by the presence of a new or progressive pulmonary infiltrate and two of the following: temperature more than 38.3°C or less than 36.0°C, leukocyte count more than 12 000/mm^3 or less than 4000/mm^3 or purulent tracheal secretions. The diagnosis of VAP was considered to be microbiologically confirmed if there was positive culture of ETAs at a concentration of at least 10^5 CFU/ml [10].

Definition of multidrug resistance

Pathogens were considered MDR if they were resistant to two or more antibiotics used to treat nosocomial

Fig. 1



The mucus extractor.

pneumonia at our hospital (ceftazidime, piperacillin/tazobactam or meropenem).

Definition of prior antibiotic therapy

Prior antibiotic therapy was defined as any regular antibiotic treatment 2 weeks before ICU admission except for an intraoperative antibiotic dose.

Colonization

Colonization was defined as a positive microbiologic culture without clinical signs of infection [10].

Microbiology methods

ETA cultures were processed using quantitative methods as described previously in detail [11]. A 0.01-ml calibrated loop was placed into the respective specimens and then onto the center of three media plates (blood agar, chocolate agar and MacConkey agar). The media plates were then streaked using the pin-wheel streak method and incubated in CO_2 at 35°C. Bacterial culture growth was quantitated according to the number of colonies observed per plate: less than 10 colonies per plate represented less than 10^3 CFU/ml; 10–100 colonies per plate represented 10^3–10^4 CFU/ml; 100–1000 colonies per plate represented 10^4–10^5 CFU/ml; and more than 1000 colonies per plate represented more than 10^5 CFU/ml. All identified microorganisms were reported with their antibiotic sensitivity [6].

The institutional review board approved the study, and the patients' relatives were consented before enrolment in the study.

Statistical analysis

The data collected were revised, coded, tabulated and introduced into a PC using the statistical package for social science (SPSS 15.0.1 for windows; SPSS Inc., Chicago, Illinois, USA). Data were presented and suitable analysis was performed according to the type of data obtained for each parameter.

Descriptive statistics for numerical parametric data were presented as mean ± SD and range, whereas frequency and percentage were used for non-numerical data.

Analytical statistics were carried out as follows: the Student *t*-test was used to assess the statistical significance of the difference between two study group means. The ANOVA test was used to assess the statistical significance of the difference between more than two study group means. The χ^2-test was used to examine the relationship between two qualitative variables. Fisher's exact test was used to examine the relationship between two qualitative variables when the expected count was less than 5 in more than 20% of the cells.

Levels of significance were as follows: *P* value less than 0.05 was significant and *P* value more than 0.05 was nonsignificant.

Results

Demographic data

During the study period, 50 patients admitted to surgical ICUs required MV for more than 48 h and fulfilled the study inclusion and exclusion criteria. Among these patients, 17 patients (34%) were identified as having either VAT or VAP. There were five (10%) patients with VAT and 12 (24%) patients with VAP. Baseline characteristics of the patients are shown in Table 1. There was no significant statistical difference between the VAT and the VAP groups regarding their age, sex, baseline APACHE II scores, the type of surgery and patients' co-morbidities as shown in Table 1. Diabetes, hypertension and chronic liver disease were the only comorbidities encountered among the studied patients. No prior antibiotic therapy was given to any of the patients.

Among the 50 patients studied, 10, 5, 5, 11, 9, and 10 patients underwent general abdominal surgery, plastic surgery, orthopedic surgery, neurological surgery, obstetric surgery, and cardiothoracic surgery, respectively. The incidence of VAT was two (40%), two (40%), and one (20%) among neurosurgery, cardiothoracic and obstetric surgery patients, respectively. However, the incidence of VAP was 5 (42%), 6 (50%) and 1 (8%) among neurosurgery, obstetric, and orthopedic surgery patients, respectively. None of the abdominal and the plastic surgery patients developed VAT or VAP.

Regarding respiratory secretions, four (80%) patients with VAT had a small volume, whereas 1one (20%) patient had a moderate volume

Table 1 Patient characteristics

Characteristics	VAT (*n* = 5) [*n* (%)]	VAP (*n* = 12) [*n* (%)]	*P*-value
Age	44 ± 18	39 ± 12	0.511
Sex (male)	2 (40)	4 (33)	0.452
APACHE II (mean ± SD)	15 ± 3	19 ± 2	0.291
Type of surgery			
Cardiothoracic	2 (40)	0	0.561
Orthopedic	0	1 (8.3)	0.611
Neurosurgery	2 (40)	6 (50)	0.551
Obstetric	1 (20)	5 (41.6)	0.541
Comorbidities			
Diabetes	1 (20)	2 (16.6)	1
Hypertension	2 (40)	3 (25)	0.597
Chronic liver disease	0	1 (8.3)	1

APACHE II, Acute Physiology and Chronic Health Evaluation II; VAP, ventilator associated pneumonia; VAT, ventilator-associated tracheobronchitis.

collected during the 24-h period. However, five (41.7%) patients with VAP had a moderate volume, whereas seven (58.3%) had a small volume collected during the 24-h period.

Incidence of ventilator-associated tracheobronchitis and ventilator-associated pneumonia

Among the 50 cases studied, there were five (10%) patients with VAT and 12 (24%) patients with VAP. VAT progressed to VAP in two patients (40%) despite the fact that all patients underwent culture-based antibiotic therapy for the VAT-causative organisms. The incidence of VAP was significantly greater than the incidence of VAT ($P < 0.05$) (Table 2).

The day of occurrence of ventilator-associated tracheobronchitis and ventilator-associated pneumonia among the study cases

The occurrence of VAT and VAP relative to intubation and the start of MV are shown in Table 3 and Fig. 2. The mean onset of VAT was 4 ± 1 days and the mean onset of VAP was 5.1 ± 0.8 days, with a minimum of 3 days for VAT and 4 days for VAP.

Microbiology

The causative organisms are shown in Table 4. VAT was caused by MDR in two patients (40%) and was polymicrobial in two patients (40%).VAP was caused by an MDR pathogen in six patients (50%) and was polymicrobial in two patients (16.7%). Overall, there was no significant difference among the individual causative bacterial pathogens for patients with VAT compared with patients with VAP.

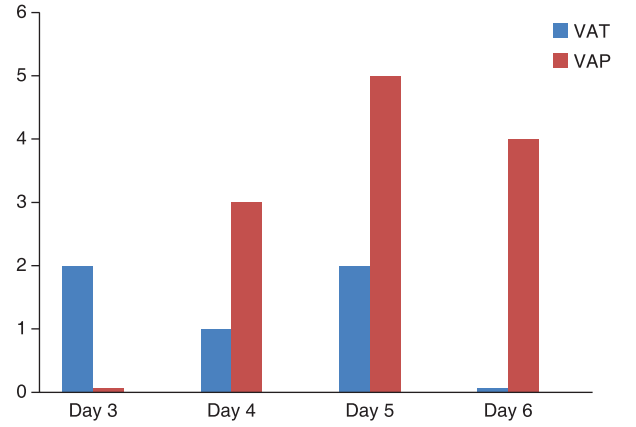
Patient outcomes

Among the 50 patients studied, there was no mortality among all 33 patients (100%) without VAP or VAT diagnosis. The mortality among patients who developed VAT was two patients (40%), of whom one of them progressed from VAT to VAP. In contrast, four patients (33.3%) died in the VAP group. There was no significant difference in the ICU mortality between patients with VAP and VAT (33.3 vs. 40%; $P = 0.70$).

VAT and/or VAP were significantly associated with a longer duration of MV, ICU stay, antibiotic use and survival to ICU discharge when compared with intubated ICU patients without VAT and/or VAP, and the P values were $P = 0.001$ (10.1 ± 3.5 vs. 2.9 ± 0.6), $P = 0.001$ (12.4 vs. ± 3.8 vs. 3.6 ± 0.7), $P = 0.001$ (14 ± 7 vs. 7 ± 7), and $P = 0.006$ (11 vs. 33), respectively.

Outcomes of patients with VAT and VAP diagnoses studied are shown in Table 5 regarding the number of antibiotics days, days of MV, ICU stay, and survival to ICU discharge.

Fig. 2



The day of occurrence of VAT and VAP. VAP, ventilator-associated pneumonia; VAT, ventilator-associated tracheobronchitis.

Table 2 Incidence of ventilator-associated tracheobronchitis and ventilator-associated pneumonia

Incidence	VAT (n = 5)	VAP (n = 12)	P-value
Incidence (%)	10	24	0.022

VAP, ventilator-associated pneumonia; VAT, ventilator-associated tracheobronchitis.

Table 3 Day of occurrence of ventilator-associated tracheobronchitis and ventilator-associated pneumonia

Days of VAT/VAP	Mean ± SD	Minimum	Maximum
Day of VAT	4.0 ± 1.0	3.0	5.0
Day of VAP	5.1 ± 0.8	4.0	6.0

VAP, ventilator-associated pneumonia; VAT, ventilator-associated tracheobronchitis.

Table 4 Causative organisms

Organism	VAT [n (%)]	VAP [n (%)]	P-value
Acinetobacter	2 (40)	4 (33.3)	1
MRSA	1 (20)	4 (33.3)	0.286
Klebsiella	1 (20)	3 (25)	0.736
Pseudomonas	2 (40)	1 (8.3)	0.571
Streptococci	0 (0)	1 (8.3)	1
E. coli	1 (20)	1 (8.3)	1
Polymicrobial[a]	2 (40)	2 (16.6)	0.232
MDR	2 (40)	6 (50	0.761

MDR, multidrug resistance; MRSA, methicillin-resistant *Staphylococcus aureus*; VAP, ventilator-associated pneumonia; VAT, ventilator-associated tracheobronchitis; [a]Some patients show more than one pathogen.

Table 5 Patients' outcome in ventilator-associated tracheobronchitis and ventilator-associated pneumonia diagnosis

Outcome	VAT	VAP	P-value
ICU days	11.7 ± 6.4	11.8 ± 2.4	0.269
Mechanical ventilator days	7.7 ± 2.1	10 ± 2.3	0.094
Antibiotic days	7 ± 7	14 ± 5	0.538
Survive to ICU discharge [n (%)]	3 (60)	8 (66.6)	0.703

VAP, ventilator-associated pneumonia; VAT, ventilator-associated tracheobronchitis.

There was no significant difference in the duration of MV, the ICU length of stay, days of antibiotic use and patients' survival to ICU discharge between the VAT and the VAP groups. When the two patients with VAT who subsequently developed VAP were removed from the analysis, there still were no significant differences between the VAT and the VAP groups for any of the outcomes measured.

Discussion

This was a prospective study conducted only on postoperative surgical ICU patients who were intubated for more than 48 h. This was in contrast to other studies that dealt with both medical and surgical ICU patients [6,12] or that were limited to a special surgical patient population such as head injury [13], postcardiac surgery [14], and tertiary peritonitis [15].

The incidence of VAT is difficult to compare because different definitions have been used by studies aiming to determine the VAT frequency. However, the incidence of VAT varies in recent literature from 1.4 to 16.5% according to the most accepted definition of VAT [4,16]. Surgical and medical ICU patients differ in VAT incidence and are likely to have different risk factors and outcomes of VAT [17]. Earlier and current data show that surgical patients are at a greater risk for VAT than medical patients [6,12,17].

Two major studies were published that evaluated prospectively the incidence of VAT on the basis of the criteria that are most accepted currently. The Nseir *et al*'s. [12] study that was performed in a French teaching hospital involving both medical and surgical ICU patients reported an incidence of VAT of 15.3 and 9.9% in surgical and medical patients, respectively, with an overall incidence of 10.6%. Another study was performed by Dallas *et al.* [6] in the USA, also involving both medical and surgical ICU patients, with an accounted incidence of VAT 1.3 and 1.5% in surgical and medical patients, respectively, with an overall incidence of 1.4%.

The higher incidence of VAT among surgical patients in the Nseir *et a*l's. study [12] (15.3%) compared with the current study (10%) could be explained by the higher prevalence of chronic obstructive pulmonary disease (COPD) in part, which is a known risk factor for VAT [4]. Nseir *et al.* [12] reported an incidence of COPD of 26% in their surgical patient population compared with the current study, which excluded all patients with chronic chest diseases including COPD patients. Patients with COPD might be diagnosed more frequently with VAT as they are more likely to produce larger quantities of purulent secretions and may be more likely to have bacterial colonization of their upper airways [6]. A study performed on 127 patients requiring MV in a pulmonary step-down unit reported the highest VAT incidence in the literature (16.5%). This highest incidence was attributed to the confinement of the patients studied only to those presenting with acute or chronic respiratory diseases requiring MV [18].

Another part that explains the higher incidence of VAT among surgical patients in the Nseir *et al.*'s study compared with the current study was the routine surveillance for infection in the Nseir *et al.*'s, study, which might have increased VAT incidence [12]. ETA cultures were performed in the current study on admission, and then repeated only if there was a clinical suspicion for the presence of VAT or VAP. However, Nseir *et al.* [12] reported that aspirates were routinely sent on admission and weekly thereafter in addition to testing at times of suspicion of infection [6].

Several potential factors may have contributed to the higher incidence of VAT reported in the current study (10%) compared with that in the surgical patients in the Dallas *et al.*'s [6] study (1.3%), including the presence of highly virulent bacterial species among patients in the current study and the absence of an effective infection control policy in the ICU. VAT was caused by an MDR pathogen in 40 and 32% of the patients, respectively, and by polymicrobial organisms in 40 and 25% of the patients, respectively, in the current study as against the Dallas *et al.*'s [6] study.

Among all types of surgeries, cardiothoracic surgery and neurosurgery showed more occurrence of VAT in the current study as reported previously by Hortal and colleagues [14,19]. This could be explained by the longer duration of intubation expected with these patients with postoperative hemodynamic instability or alteration of the conscious level. A large multicenter study conducted to determine the incidence of and risk factors for ventilator-associated respiratory infections after major heart surgery reported a VAT incidence of 10.6% for those mechanically ventilated for more than 72 h [14]. However, patients with neurosurgical admission present with VAT significantly more than any other types of admission and they were also associated with a prolonged stay in the ICU [19].

In the present study, only two of the patients (40%) initially diagnosed with VAT evolved to fulfill the VAP criteria. The incidence of VAT that progress to VAP varies in the literature. In an earlier study, it was 9% [12], whereas in more recent studies it was 34, 32.1, and 29% as reported by Nseir *et al.* [20], Dallas *et al.* [6], and Craven *et al.* [16], respectively.

The lower incidence of VAT (10%) compared with VAP (24%) in the current study was similar to that reported in previous studies [6,12,20]. This could be explained by the recent hypothesis that suggests that VAT is not necessarily a precursor of VAP, but that both VAT and VAP are two distinct entities that can arise from the non-infected state and can either coexist or exist separately [6]. However, the progression from colonization to VAT and, in some cases, to VAP or the occurrence of de novo VAP will always depend on the quantity and the virulence of the bacterial pathogen and alveolar and airway host defenses [2,6].

Overall, there was no significant difference among individual causative bacterial pathogens in patients with VAT compared with patients with VAP, which was comparable to Dallas *et al.*'s results [6]. However, pseudomonas aeruginosa was the most common bacteria (40%) in VAT patients in accordance with previous studies [4,12]. VAT is frequently caused by Gram-negative bacteria, in particular *Pseudomonas aeruginosa* [4].

The day of development of VAT or VAP was between the third and the sixth days of intubation. The mean onset of VAT was 4.0 ± 1 days and the mean onset of VAP was 5.1 ± 0.8 days. This result shows that the median time for the onset of VAT or VAP is almost similar, which should draw the attention to the overlap between them and to the peak onset of their occurrence, thus helping one to choose the perfect time for their prevention. Also, early extubation of patients postoperatively may be one of the most important factors in preventing VAT or VAP development.

In agreement with previous studies [3,4,12], VAT and/or VAP were significantly associated with a longer duration of MV, ICU stay and antibiotic use when compared with intubated ICU patients without VAT and/or VAP in the current study. However, this was not the case when VAT was compared with VAP (Table 5). Many previous studies pointed out the role of tracheobronchitis in the duration of MV and subsequent ICU stay and antibiotic use. Tracheobronchitis is characterized by lower respiratory tract inflammation and increased sputum production [21,22]. These factors may generate weaning difficulties, resulting in a longer duration of MV [4]. Extubation failure and difficult weaning have been reported to be associated with increased sputum volume in mechanically ventilated patients [23].

In the current study, all patients received systemic broad antibiotics as soon as VAT was suspected, and then according to culture and sensitivity tests. In a recent meta-analysis, the impact of systemic antimicrobials (with or without inhaled ones) in patients with VAT was associated with beneficial effects such as lowering the frequency of subsequent pneumonia and more ventilator-free days, but it was not associated with lower mortality [5].

The VAT mortality rate in the present study was 40%, which was midway between the rates reported by Nseir *et al.* [12] (55%) and Dallas *et al.* [6] (20%). In accordance with the current study, Dallas *et al.* [6] and Craven *et al.* [16] found no significant difference in the ICU mortality between patients with VAT and those with VAP.

Our study, like any other study, has its own limitations that should be noted.

First, a probable overlap between VAT and VAP patients might have occurred due to limitations of the portable chest radiograph to detect new or progressive infiltrates, which is the main differentiator between VAT and VAP. Hence, it is difficult to confirm that some VAT patients did not actually have VAP. Computed tomography was not routinely preformed to exclude occult infiltrations, and so many VAP cases could have been missed; this is a common feature between all the studies [4,6] conducted on VAT–VAP cases as computed tomography is not a routine investigation in ICU ventilated patients due to difficult transport and increased cost that limit such a practice.

The second limitation is that to confirm the progression from VAT to VAP, the same organism should be isolated, and because quantitative culture was used to identify VAT, any pathogen in low quantities could have been missed and separated analytically from the subsequent VAP episode. To verify such microbiological progression from VAT to VAP, molecular characterization techniques, for example 16S rRNA gene sequence analysis, may be needed for discrimination [24].

Another important limitation of our study is that the number and the method of selection of patients for this study could not be ideally provided and the number of included patients was lower than that initially expected. Potential reasons for this low recruitment include strict inclusion and exclusion criteria.

Conclusion

The incidence of VAT in the current study lies within the range reported in previous recent reports in the literature. VAT occurs less commonly than VAP. VAT does not appear to be a necessary precursor for all VAP cases as only 40% of VAT cases progressed to VAP. The

median time for the onset of VAT or VAP is almost similar. Patients diagnosed with VAT had outcomes similar to those with VAP.

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Conflicts of interest

None declared.

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