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Risk Factors for the Development and Severe Course of Ventilator-Associated Tracheobronchitis in Patients with Prolonged Mechanical Ventilation

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Summary

Objective. Identification of risk factors for the development and severe course of ventilator-associated tracheobronchitis (VAT) in patients on prolonged mechanical ventilation (PMV).

Methods. VAT incidence rate in the intensive care unit of Academician V. Vakhidov Republican Scientific and Practical Medical Center for Surgery for the period 2018–2022 was evaluated retrospectively in 724 patients who were on PMV (more than 48 h). Patients' clinical and demographic characteristics were subjected to factor analysis. Mean age was 52.4±3.3 (18–81) years. VAT was diagnosed based on clinical signs (fever >38°C, leukocytosis >12 000 ctlls/ml, or leukopenia <4 000 cells/ml, purulent endotracheal secretions, or conversion to purulent), radiological (no progression of existing or emergence of new pulmonary infiltrates) and microbiological (polymorphonuclear lymphocytes with or without bacteria, moderate-to active growth of colonies of potentially pathogenic microorganisms) criteria. VAT prophylaxis was based on the use of bacterial filters and humidification of the respiratory gas; selective decontamination of the digestive tract; regulation of pressure in the tracheal cuff; sanitation of the oral cavity. Treatment of VAT included antimicrobial drugs administered i/v and/or inhalational, bronchodilators, expectorants and mucolytics.

Results. VAT incidence rate decreased over time from 24.7% to 10.1% (χ^2=9.52; *P*=0.003) with invariable practice of ventilator support. The incidence of the most severe VAT (hemorrhagic catarrhal purulent) also gradually decreased from 44.7% to 14.3% (χ^2=4.53; *P*=0.034).The duration of PMV and ICU stay in patients with VAT gradually decreased from 202.1±6.15 h to 125.3±7.81 h (*t*=7.73; *P*<0.0001), and from 9.7±0.25 days to 6.6±0.3 days (*t*=7.94; *P*<0.0001), respectively. In patients with VAT (*N*=122), in contrast to patients without VAT (*N*=602), the incidence of concomitant COPD was higher — 22.9% vs 10.6%, respectively (*P*<0.001). Gram-negative flora was the leading cause for development of severe tracheobronchitis, including *Acinetobacter* spp. — in 24% of cases, *Klebsiella pneumoniae* — in 11.6%, *Pseudomonas aeruginosa* — in 13.0%, *Esherichia coli* — 10.6%. Less frequently were isolated *Staphylococcus aureus* — in 5.3%, *Enterococcus* spp. — in 2.2% and *Candida fungi* — in 17.0%. The following predictors of severe VAT were identified: age over 60 years (OR=2.28; 95% CI 1.0–4.9), SAPS II > 40 scores (OR=5.9; 95% CI 2.6–13.8), duration of mechanical ventilation >144 h (OR=5.4; 95% CI 1.8–16.7) and the presence of malignant neoplasms (OR=2.83; 95% CI 1.2–6.9).

Conclusion. Decrease in VAT incidence rates, reduced duration of mechanical ventilation and ICU stay are indicative of adequate VAT prevention and treatment strategies within the analyzed period. Factors associated with VAT development and predictors of severe VAT can be used for identification of high risk patients.

Keywords: prolonged mechanical ventilation; ventilator-associated tracheobronchitis; risk factors

Conflict of interest. The authors declare no conflict of interest.

Introduction

Tracheobronchitis is one of the most common ventilator-associated complications. It is characterized by manifestations of respiratory infection without radiographic infiltrates in patients receiving prolonged mechanical ventilation for at least 48 h [1–4].

In the last decade, several epidemiological studies have shown that ventilator-associated tracheobronchitis (VAT) is a precursor of ventilator-associated pneumonia (VAP). VAT has an indirect effect on mortality, but once it develops, patient care costs increase in terms of ICU length of stay, antibiotic use, and duration of mechanical ventilation [5–8].

To date, many observational studies have shown an association between inadequate or no treatment of VAT and the subsequent development of VAP, but there are no randomized controlled trials demonstrating the benefits of VAT treatment [1, 7, 9, 10].

Meanwhile, the use of combined multi-zone decontamination of the upper airway, including the subglottic region, is known to reduce the risk of VAP development but does not affect the overall

incidence of various ventilator-associated infectious events [11].

The pathophysiological aspects and distinctive features of VAT as well as typical tracheobronchial morphogenetic patterns have been actively investigated worldwide [4, 5, 12–15].

The multicenter observational clinical study «Registry of Respiratory Therapy in Patients with Acute Cerebrovascular Accident (ACVA) (RETAS)», conducted under the auspices of the Russian Federation of Anesthesiologists and Reanimatologists, showed that in patients with acute cerebrovascular accident, the development of VAT and VAP is associated with increased duration of ventilatory support, delayed weaning time, prolonged stay in the intensive care unit, and poor outcomes. *Klebsiella pneumoniae, Acinetobacter baumannii,* and *Pseudomonas aeruginosa* are the most common causes of VAP in ACVA [16].

Studies conducted during the COVID-19 pandemic showed that ventilated patients with severe and critical COVID-19 were more likely to develop nosocomial infections, which negatively affected the outcome of the disease. In more than half of the cases, the infection was caused by resistant strains of gram-negative bacilli [17].

A comprehensive analysis of clinical data may help to understand the pathophysiological aspects of VAT development and contribute to the management of this complication.

The aim of this study was to identify risk factors for the development and severity of VAT in patients receiving prolonged mechanical ventilation.

Materials and methods

The characteristics and frequency of VAT were retrospectively analyzed according to the clinical reports of the Department of Surgical Intensive Care of the V. Vakhidov Republican Scientific and Practical Medical Center of Surgery from 2018 to 2022. The study included cases of VAT in patients who were on a ventilator for more than 48 h and met the diagnostic criteria for VAT.

The diagnosis of VAT was based on the following clinical, radiological and microbiological criteria:

— body temperature >38°C, leukocyte count >12000/μL or leukopenia (leukocyte count <4000/μL) combined with purulent endotracheal discharge or change in sputum character;

— absence of new or progressive infiltrates;

— detection of polymorphonuclear lymphocytes with or without bacteria on Gram staining of endotracheal aspirate and moderate or intense growth of potentially pathogenic microorganisms according to the semiquantitative analysis of endotracheal aspirate culture.

Patients were excluded from the study if they had

— severe immunosuppression (leukocyte count <1000/μL or neutrophil count <50/μL);

— VAP without preliminary criteria for VAT.

The morphology of the tracheal and bronchial mucosa was examined using a stationary video bronchoscope with subsequent digital processing and archiving of the data obtained. Video-assisted tracheobronchoscopy allowed to minimize the frequency of individual decision making, expand the possibilities of team visualization, and assess the severity of disease and the impact of bronchoscopic treatment on the efficacy of VAT treatment.

Treatment of VAT included intravenous and/or inhaled antimicrobials, bronchodilators, and broncho- and mucolytics. The inhaled route of administration was reserved for aminoglycosides and polymyxin.

VAT prophylaxis included the use of bacterial filters and humidification of respiratory gas, selective decontamination of the digestive tract (administration of antibacterial drugs into the naso-intestinal tube), regulation of pressure in the tracheal cuff and oral hygiene.

The collection, correction, and arrangement of the raw data and the obtained results were performed in Microsoft Office Excel 2016 spreadsheets. Statistical analysis was done with the STATISTICA 13.3 (StatSoft.Inc) software. Means of normally distributed quantitative data were compared using Student's *t*-test. Differences were considered significant at a significance level of $P<0.05$. Non-numerical data were compared using Pearson's χ^2 test. The odds ratio (OR) was used as the measure of effect when comparing relative parameters. The limits of the 95% confidence interval (95% CI) were calculated to extrapolate the OR values to the general population.

Results

A total of 8170 patients underwent mechanical ventilation during the study period (2018–2022), of which 724 patients required prolonged ventilation (more than 48 h), with VAT diagnosed in 16.9% (122 of 724) of cases (Table 1).

The incidence of VAT (Fig. 1) decreased significantly over time from 24.7% (38 of 154) to 10.1%

Table 1. Number of patients who underwent ventilation and VAT frequency during the study period from 2018 to 2022.

Study period, year	Number of patients			VAT frequency, %
	Mechanically ventilated	Mechanically ventilated for >48 h	With VAT	
2018	1814	154	38	24.7
2019	1752	158	30	19.0
2020	1202	118	19	16.1
2021	1722	156	21	13.5
2022	1680	138	14	10.1
2018–2022	8170	724	122	16.9

(14 of 138) over 4 years, while the incidence of ventilator use in ICU patients remained unchanged (χ^2=9.52; *P*=0.003).

The frequency of the most severe VAT with hemorrhagic, catarrhal and purulent morphology was assessed. This parameter also gradually decreased significantly from 44.7% (17 cases out of 38 of all VAT in 2018) to 14.3% (2 cases out of 14 of all VAT in 2022) (χ^2=4.53; *P*=0.034) (Fig. 2).

Severe VAT cases were identified based on bronchoscopy, clinical, laboratory, and microbiologic data. Bronchoscopic findings in early tracheobronchitis included tracheobronchial mucosal erosions and moderate amounts of mucopurulent sputum. As the inflammation progressed, erosive and hemorrhagic phenomena such as confluent hemorrhagic erosions of the tracheal wall, thrombi in the bronchial mucosa and hemorrhagic sputum were observed.

The major causative agents of VAT are listed in Table 2.

Gram-negative bacteria predominated among the causative agents of severe tracheobronchitis: *Acinetobacter* spp. was isolated in 24% of cases, *Klebsiella pneumoniae* in 11.6%, *Pseudomonas aeruginosa* in 13.0%, *Escherichia coli* in 10.6%, while *Staphylococcus aureus* was identified in 5.3%, *Enterococcus* spp. in 2.2%, and *Candida* spp. in 17.0%.

All strains isolated from the trachea were highly resistant to almost all groups of antibiotics except polymyxin, vancomycin and linezolid, and in some cases imipenem, meropenem and amikacin. *Candida* spp. were highly resistant to antifungal agents in 90% of cases.

During all periods of the study, the duration of mechanical ventilation was defined as the total time spent with intubation and tracheostomy tube (if the latter was used).

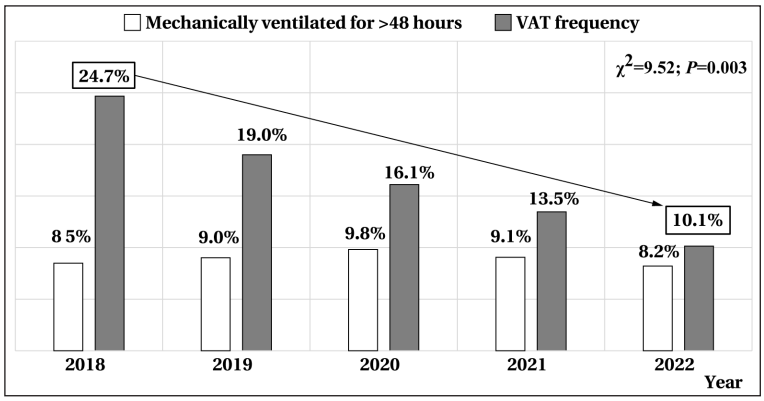

Fig. 1. Frequency of VAT during different periods of the study.

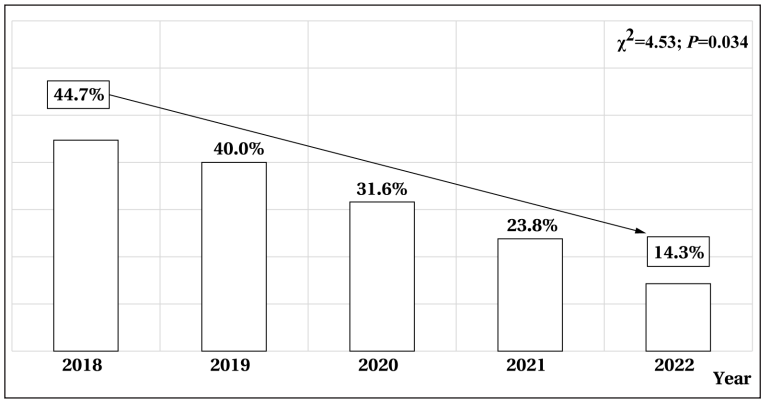

Fig. 2. Frequency of hemorrhagic catarrhal purulent VAT cases during the study period.

Table 2. Microorganisms isolated during 5 years.

Agent	Number of identifications per year				
	2018	2019	2020	2021	2022
Streptococcus spp.	1				
Enterococcus spp.		2		1	2
Staphylococcus aureus	1	2	1		1
Staphylococcus spp.	2	1		1	1
Acinetobacter spp.	10	6	11	4	8
Alcaligenes spp.		1			
Enterobacter cloacae			1		1
Esherichia coli	2	2	2	3	
Klebsiella pneumoniae		1	7		1
P. aeruginosa	1	2	2	2	3
Proteus mirabilis					
Proteus vulgaris					
Serratia marcesens	2			1	
Candida spp.					
Candida albicans	4	1	5	2	
Candida glabrata	2	1		2	
Candida kruseii	1			1	
Candida tropicalis					
Molds					
Total	24	23	29	17	17

The duration of mechanical ventilation in VAT patients gradually decreased from 202.1±6.15 h to 125.3±7.81 h between 2018 and 2022 (t=7.73; P<0.0001) (Fig. 3).

The minimum duration of mechanical ventilation during all 4 years of follow-up was 96 h and the maximum was 368 h.

As expected, the length of stay of patients with VAT in the ICU also decreased during this period from 9.7±0.25 days to 6.6±0.3 days (t=7.94; P<0.0001) (Fig. 4).

Clinical and demographic characteristics (Table 3) of patients receiving mechanical ventilation for more than 48 h (N=724) were analyzed. Patients with VAT (N=122) had a higher incidence of comorbid COPD compared to patients without VAT (N=602), 22.9% (28 of 122) vs. 10.6% (64 of 602) (P<0.001).

In addition, patients with VAT were found to have a higher mean SAPS II score (P<0.001), duration of ventilatory support (P<0.001), frequency of tracheostomy (P<0.001), and duration of ICU stay (P<0.001).

Several predictors of severe VAT were identified, including age greater than 60 years, male sex, severe comorbidities at baseline, and SAPS II score greater than 40 points (Fig. 5).

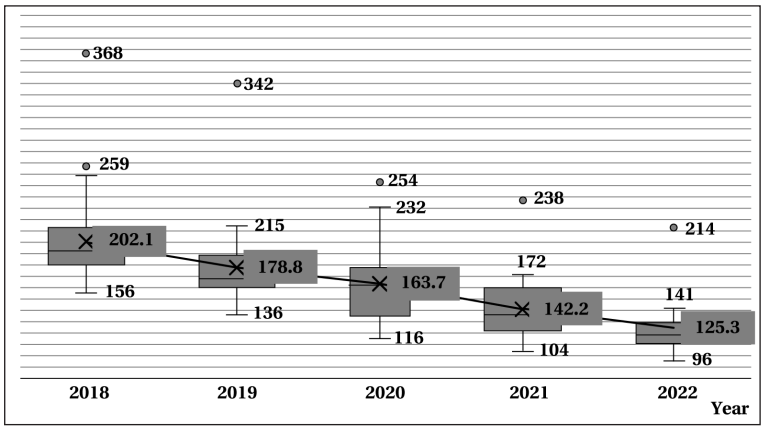

Fig. 3. Duration of mechanical ventilation in VAT, h.

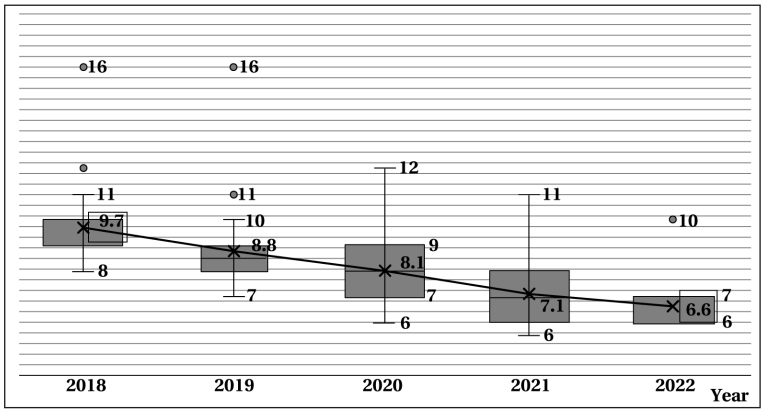

Fig. 4. Length of stay of patients with VAT in ICU, days.

Cardiac and vascular surgical procedures, which often require prolonged mechanical ventilation, and the presence of associated chronic lung disease did not significantly affect the development and progression of VAT.

The duration of mechanical ventilation over 144 h had a significant effect on the incidence of severe VAT.

The data obtained during the analysis of risk factors for severe VAT (Table 4) showed that such predictors as age over 60 years (OR=2.28; 95% CI 1.0–4.9), SAPS II over 40 points (OR=5.9; 95% CI 2.6–13.8), duration of ventilation more than 144 h (OR=5.4; 95% CI 1.8–16.7) and malignant surgical condition (OR=2.83; 95% CI 1.2–6.9) showed the most significant correlation between the factor and the outcome.

Discussion

In everyday clinical practice, hospital-acquired lower respiratory tract infections are commonly di-

Table 3. Clinical and demographic characteristics of patients with or without VAT who received ventilation for more than 48 h.

Parameters, units	Values		*P*
	Patients with VAT, *N*=122	Patients without VAT, *N*=602	
Mean age, *M*±*m* (range), years	52.4±3.3 (18–81)	54.8±3.6 (22–74)	0.623
Male sex, *n* (%)	76 (62.3)	398 (66.1)	0.482
Cardiovascular surgical conditions, *n* (%)	54 (44.3)	277 (46.0)	0.724
Pulmonary surgical conditions, *n* (%)	12 (9.8)	56 (9.3)	0.854
COPD, *n* (%)	28 (22.9)	64 (10.6)	<0.001
Malignancy, *n* (%)	26 (21.3)	107 (17.8)	0.429
Mean SAPS II score, *M*±*m* (range)	38.9±1.6 (11–81)	24.4±1.2 (11–56)	<0.001
Duration of ventilation, *M*±*m* (range), h	171.3±5.6 (96–368)	102.7±8.5 (56–172)	<0.001
Tracheostomy, *n* (%)	52 (42.6)	64 (10.6)	<0.001
Duration of ICU stay, *M*±*m* (range), day	8.4±0.4 (5–16)	4.7±0.3 (3–14)	<0.001

Table 4. Univariate factor analysis of the risk of severe VAT.

Parameter, *N* (%)	VAT severity		OR	95% CI
	Severe, *N*=42	Mild and moderate, *N*=80		
Age over 60 years	22 (52.4)	26 (32.5)	2.28	1.0–4.9
Malignancy	14 (33.3)	12 (15.0)	2.83	1.2–6.9
SAPS II more than 40 points	32 (76.2)	28 (35.0)	5.9	2.6–13.8
Ventilation time greater than 144 h	38 (90.5)	51 (63.8)	5.4	1.8–16.7

vided into intra-ICU and extra-ICU, often due to a conflict of interest in diagnosis. However, clinical studies in patients with such complications outside the ICU are limited due to bias in diagnostic approaches and limitations in microbiological identification [18, 19].

According to the literature, the incidence of VAT is estimated to be approximately 11.5%. The most common pathogens are *Pseudomonas aeruginosa, Acinetobacter* spp. and methicillin-resistant *Staphylococcus aureus*, although the infection may be polymicrobial [20].

Antimicrobial therapy in patients with VAT may not improve mortality, ICU length of stay, or duration of mechanical ventilation, but is usually associated with a reduction in the incidence of subsequent VAP [20].

Most clinicians believe that antibiotic therapy should be targeted and based on both combination and de-escalation approaches, as well as microbiological antibiotic susceptibility testing of the isolated agent. The results suggest that the prevalence of Gram-negative multidrug-resistant microflora among the pathogens and a high risk of fungal superinfection should be considered in the intensive care of patients with VAT.

The mean incidence of VAT over the 5-year study period was 16.9%, but decreased over time from 24.7% to 10.1%, despite an increase in high-tech major surgery, which often requires prolonged mechanical ventilation.

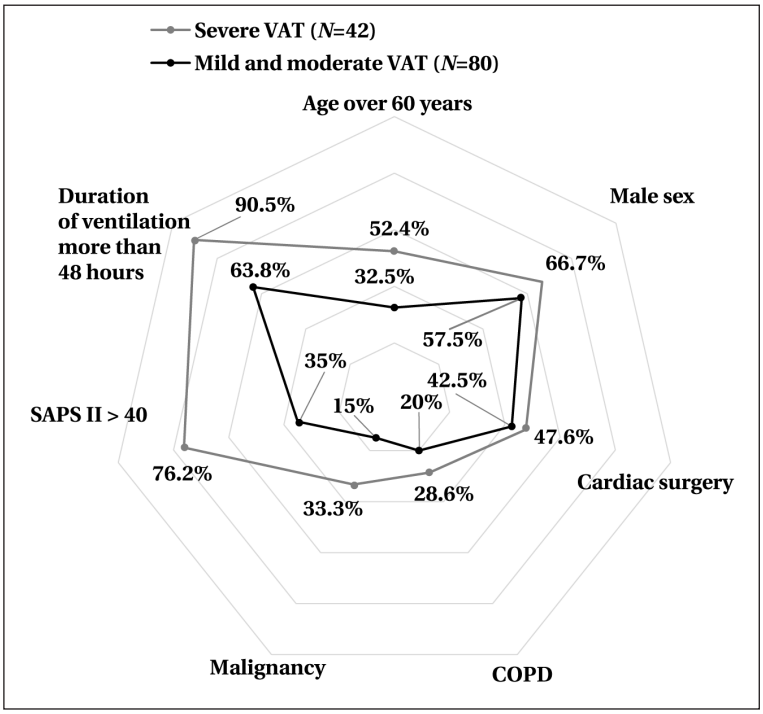

Fig. 5. Comparison of the frequency of identified risk factors for severe VAT.

Conclusion

Decrease in incidence of VAT, reduction in duration of mechanical ventilation and intensive care unit stay suggest adequate prevention and treatment of VAT during the study period. The identified factors associated with the development of VAT and predictors of severe VAT may provide a rationale for the identification of risk groups.

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