

Morphometric and microbiological features of ventilator associated tracheobronchitis

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ABSTRACT: Changes in the composition of the microbiota of the tracheobronchial tree in patients on prolonged mechanical ventilation can contribute to various disorders of the immune defense of the respiratory tract, damaging mucociliary clearance, and cause a strong inflammatory response, including the formation of ventilator-associated tracheobronchitis (VAT). The aim was to study the specifics of changes in the microflora and histopathology of the tracheobronchial tree in VAT. Over a 10 year period 975 bacteriological analyzes were carried out in 355 patients who were on extended mechanical ventilation for more than 48 hours. VAT is accompanied by a pronounced lymphoid-neutrophilic infiltration of the mucosa of the trachea and bronchi, and in a complicated course with the presence of a purulent-inflammatory and erosive-hemorrhagic component leads to a violation of the integrity of tissues due to destruction and necrosis. The leading pathogens were representatives of gram-negative flora of 65.8% (47-76%), gram-positive flora was detected in 17.5% (10-30%) of cases, fungi of the genus *Candida* in 16.5 (4-42%) cases. Analysis of the antibiograms of isolated cultures in patients on prolonged mechanical ventilation shows high resistance to a wide range of antibiotics, namely: acinetobacter spp. - high resistance to all antibiotics, except for imipenem (0% resistant strains), polymyxin (0%) and tetracyclines (7-15.4%). Imipenem (10.5%), polymyxin (10.5%), amikacin (31.5%) and cefoperazone/sulbactam (31.5%) are active against *Escherichia coli*. *Klebsiella pneumoniae* was susceptible to imipenem, amikacin, ofloxacin and inhibitor-protected antibiotics-cefoperazone/sulbactam, piperacillin/tazobactam. *Staphylococcus aureus* was susceptible to III generation cephalosporins (cefotaxime, ceftriaxone, cefoperazone) and tetracyclines - 36.3% of resistant strains. Microbiological monitoring in patients with VAT over a 10-year period revealed a trend towards the prevalence of gram-negative microflora inoculation, and over the past two years, the range of isolated multi-resistant flora has been expanding.

KEYWORDS: Prolonged mechanical ventilation, Nosocomial infection, Ventilator associated tracheobronchitis, Microbiology, Histopathology

INTRODUCTION

To date, it has been proven that ventilator-associated infections of the upper and lower respiratory tract are one of the most common complications in patients on prolonged mechanical ventilation [1-4].

Most studies have shown that ventilator-associated tracheobronchitis (VAT) can be considered as an intermediate process leading to VAP, which has a limited effect on overall mortality, but shows a significant association with increased patient costs, length of stay in the hospital, use of antibiotics and the duration of mechanical ventilation [3, 5, 6].

As is known, VAT does not represent an impressive picture of clinical manifestations, which most of all depends on the duration of prolonged mechanical ventilation, the severity of multiple organ failure and the substrate of nosocomial infection. However, the features of morphological changes, for the most part associated with the development of a negative scenario, namely, the lightning-fast development of an erosive-hemorrhagic lesion, for the treatment of which there is currently no specific agent and technique, requires more thorough research and study [2, 7-10].

The lack of unity in understanding the pathophysiological aspects of the development of VAT and resuscitation tactics in the development of hemorrhagic syndrome allows us to study this problem on the basis of a

large clinical material already available, which, in our opinion, can make a significant contribution to the outcome of the treatment of this complication.

The aim of this study was to study the specifics of changes in the microflora and histopathology of the tracheobronchial tree in VAT.

MATERIAL AND METHODS

The study was based on the results of treatment of patients who were on prolonged mechanical ventilation in the intensive care unit of the RSSPMC for surgery named after academician V.Vakhidov. The study included cases with the development of VAT, selected from among patients who were on mechanical ventilation for more than 48 hours, and who met the diagnostic criteria for VAT.

The diagnosis of VAT was established on the basis of clinical signs, radiological and microbiological criteria.

- Clinical signs and symptoms include fever $>38^{\circ}\text{C}$, WBC count $> 12,000/\text{mL}$, or leukopenia (WBC count $<4,000/\text{mL}$) with new purulent endotracheal discharge or change in sputum pattern.

- Radiological criteria included the absence of new or progressive infiltrates.

- Morphological studies included a biopsy sample taken from the mucosa of the trachea and bronchi, which was fixed in a 10% solution of neutral formalin, followed by the manufacture of paraffin blocks. Histological preparations were stained with hematoxylin and eosin. For light microscopy, tissue samples were fixed in 10% formalin solution in phosphate buffer. Light-optical micrographs were taken on an Axioscop 40 – ZEISS microscope, coupled with a digital camera.

- Microbiological criteria included Gram stain of endotracheal aspirate demonstrating polymorphonuclear lymphocytes with or without bacteria, and semi-quantitative analysis of culture of endotracheal aspirate showing moderate or strong growth of potentially pathogenic microorganism.

Ethical approval

The review board and ethics committee of RSPMCS named after acad. V.Vakhidov approved the study protocol and informed consents were taken from all the participants.

RESULTS AND DISCUSSION

The morphometric picture in an uncomplicated course of VAT is characterized by the fact that signs of diffuse catarrhal inflammations of varying degrees and erosive deforming endobronchitis are verified on the mucous membranes of the bronchi, with severe lymphoid infiltration of the mucosa and its vascularization (Figure 1-A), as well as with metaplastic changes and violations of integrity epithelial lining (Figure 1-B). The microscopic picture of complicated forms of VAT, such as purulent-inflammatory and erosive-hemorrhagic ones, is characterized by inflammatory and degenerative changes in the surrounding tissues, in particular, ruptures of the bronchial wall (Figure 2).

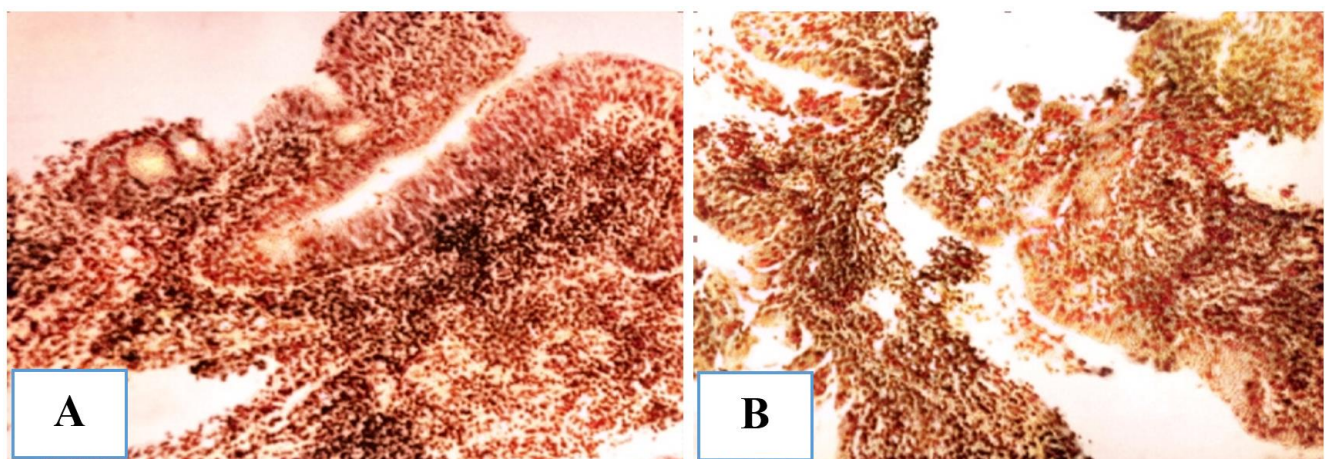


Figure 1. Histopathology of VAT. Hematoxylin and Eosin (H&E) Stain, original magnification 10×40 : A) bronchial mucosa with diffuse catarrhal inflammation of the 2nd degree, with severe lymphoid infiltration, vascularization; B) violation of the epithelial lining of the bronchial mucosa

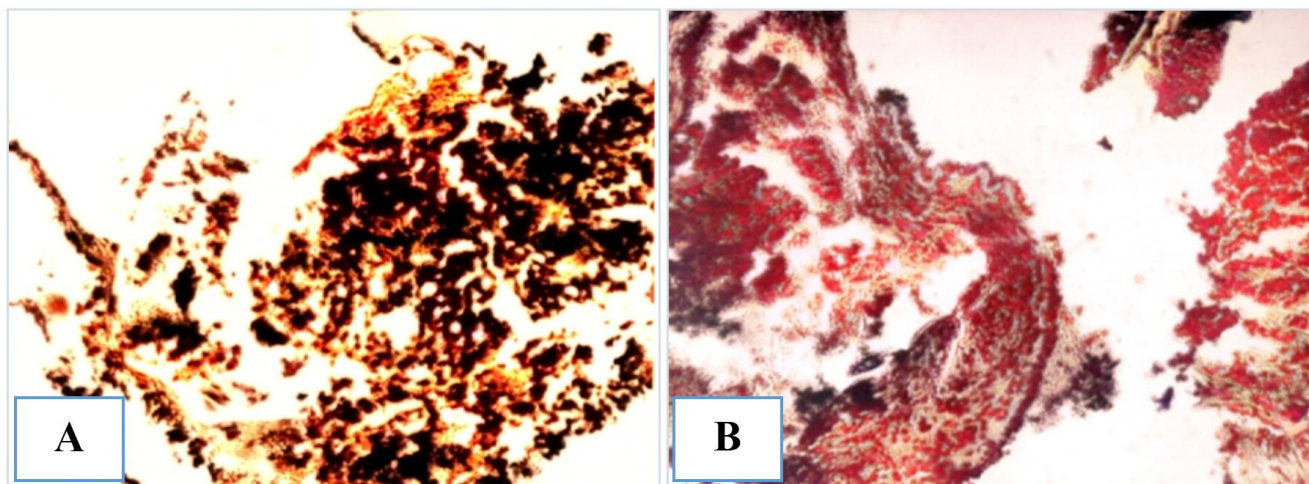


Figure 2. Histopathology of VAT. Hematoxylin and Eosin (H&E) Stain, original magnification 10×40: A) thinning of the bronchial mucosa with the presence of elements of inflammation in the area of erosive-hemorrhagic lesions; B) bronchial mucosa with edema.

Ventilator-associated tracheobronchitis (VAT) was characterized by a diverse morphological pattern of lesions of the mucosa of the trachea and bronchi, from catarrhal inflammation to pronounced erosive-hemorrhagic and purulent-necrotic lesions of the mucosa and deformation of the cartilaginous framework of the trachea. One of the predictors of the complicated course of VAT was the addition of a nosocomial infection to the ICU. The leading pathogens were representatives of gram-negative flora of 65.8+0.9%, gram-positive flora of 17.5+0.3%, fungi of the genus *Candida* of 16.5+0.9%. The prevalence of gram-negative bacteria in the ICU was observed throughout the study period (2011-2022) in 47-76% of cases, gram-positive flora was isolated on average in 10-30% of cases, and fungi of the genus *Candida* were isolated from 4% to 42% of cases (Table 1).

Analysis of the antibiograms of isolated cultures in patients on prolonged mechanical ventilation shows high resistance to a wide range of antibiotics, namely: *acinetobacter* spp. - high resistance to all antibiotics, except for imipenem (0% resistant strains), polymyxin (0% resistant strains) and tetracyclines (7-15.4% resistant strains). *Escherichia coli* - imipenem (10.5% resistant strains), polymyxin (10.5% resistant strains), amikacin (31.5% resistant strains) and cefoperazone / sulbactam (31.5% resistant strains) are active against it). *Klebsiella pneumoniae* was susceptible to imipenem (0% resistant strains), polymyxin (0% resistant strains), amikacin (0% resistant strains), ofloxacin (40.0% resistant strains) and inhibitor-protected antibiotics - cefoperazone/sulbactam (40.0% resistant strains), piperacillin/tazobactam (40.0% resistant strains).

Staphylococcus aureus was susceptible to III generation cephalosporins (cefotaxime, ceftriaxone, cefoperazone) and tetracyclines - 36.3% of resistant strains. There were no resistant strains to cefoperazone/sulbactam and vancomycin. *Staphylococcus* spp. showed good sensitivity to a wide range of antibiotics.

Analysis of the sensitivity of fungi r. *Candida* to antimycotics showed: nitroxoline - 11.4% of resistant strains, amphotericin and fluconazole (48.5%) of resistant strains, terbinafine - 51.4% of resistant strains (Table 2). Detailing the structure of the leading pathogens of tracheitis in patients on prolonged mechanical ventilation in the ICU is presented in Table. 3.

Table 1. Distribution of isolated microflora depending on the type of biomaterial

Pathogen	Swabs from throat		Bronchoalveolar lavage		From the trachea	
	n	%	n	%	n	%
<i>Acinetobacter</i> spp.	3	2.2%	2	1.5%	21	15.4%
<i>Escherichia coli</i>	2	1.5%	3	2.2%	15	11.0%
<i>Klebsiella pneumoniae</i>	3	2.2%	1	0.7%	11	8.0%
<i>Pseudomonas aeruginosa</i>	2	1.5%	4	3.0%	11	8.0%
<i>Staphylococcus aureus</i>	4	3.0%	2	1.5%	5	3.6%
<i>Staphylococcus</i> spp.	4	3.0%	1	0.7%	7	5.0%
Fungi of the genus <i>Candida</i>	19	14.0%	2	1.5%	14	10.3%

Table 2. The level of resistance of isolated pathogens to antimicrobial drugs

Antibiotic/Microorganism	<i>Acinetobacter</i> spp.	<i>Escherichia coli</i>	<i>Klebsiella pneumoniae</i>	<i>Pseudomonas aeruginosa</i>	<i>Staphylococcus aureus</i>	<i>Staphylococcus</i> spp.	Fungi of the genus <i>Candida</i>
Amikacin	92.3%	31.5%	0%	23.5%	63.6%	16.6%	*
Gentamicin	77%	79.0%	100.0%	23.5%	63.6%	33.3%	*
Imipenem	0	10.5%	0	0	-	-	*
Ofloxacin	92.3%	100.0%	40.0%	35.3%	63.6%	16.6%	*
Ciprofloxacin	100.0%	100.0%	100.0%	100.0%	72.7%	33.3%	*
Cefotaxime	100.0%	100.0%	100.0%	100.0%	36.3%	41.6%	*
Ceftazidime	100.0%	100.0%	100.0%	76.4%	100.0%	75.0%	*
Ceftriaxone	92.3%	100.0%	100.0%	100.0%	36.3%	16.6%	*
Cefoperazone	100.0%	100.0%	100.0%	100.0%	36.3%	25.0%	*
Cefoperazone/ Sulbactam	61.5%	31.5%	40.0%	35.3%	0	8.3%	*
Piperacillin/Tazobactam	92.3%	100.0%	40.0%	100.0%	-	-	*
Tetracycline	7.7%	100.0%	60.0%	100.0%	36.3%	33.3%	*
Doxycycline	15.4%	100.0%	100.0%	100.0%	36.3%	33.3%	*
Polymyxin	0.0%	10.5%	0	0.0%	*	*	*
Vancomycin	*	*	*	*	0	0	*
Nitroxoline	*	*	*	*	*	*	11.4%
Terbinafine	*	*	*	*	*	*	51.4%
Amphotericin	*	*	*	*	*	*	48.5%
Fluconazole	*	*	*	*	*	*	48.5%

*-natural resistance

Table 3. The structure of VAT pathogens in ICU patients for the period from 2011 to 2022

Microorganism/year	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
<i>Streptococcus</i> sp.			2		1			1				
<i>Enterococcus</i> sp.			2						2		1	2
<i>Staphylococcus aureus</i>	1	1	2	1	3	4		1	2	1		1
<i>Staphylococcus</i> sp.	5	2		2	2	1		2	1		1	1
<i>Acinetobacter</i> sp.	3	2	4	8	13	6	1	10	6	11	4	8
<i>Alcaligenes</i> sp.									1			
<i>Enterobacter cloacae</i>	14		1				1			1		1
<i>Escherichia coli</i>		6	6	6	5		2	2	2	2	3	
<i>Klebsiella pneumoniae</i>	10	8	4	2	3		1		1	7		1
<i>Ps. aeruginosa</i>	12	8	6	2	3		1	1	2	2	2	3
<i>Proteus mirabilis</i>				1								
<i>Proteus vulgaris</i>							1					
<i>Serratia marcescens</i>	1				2			2			1	
Fungi of the genus <i>Candida</i>	5	4										
<i>Candida albicans</i>				4	2	3	4	4	1	5	2	
<i>Candida glabrata</i>					4	2		2	1		2	
<i>Candida krusei</i>				1		1		1			1	
<i>Candida tropicalis</i>				1	4							
Mold fungi	1	1	1				1					
Total	64	31	33	28	38	21	14	24	23	29	17	17

The etiological structure of pathogens of tracheitis, mainly in patients on prolonged mechanical ventilation, consists of multiresistant strains of gr-flora: *Acinetobacter* spp., *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Escherichia coli*, as well as *Staphylococcus aureus* (in most cases - MRSA), *Enterococcus* spp. and fungi of the genus *Candida*. The spectrum of agents isolated from the trachea showed: *Acinetobacter* spp. (24.0%), *Klebsiella pneumoniae* (11.6%), *Pseudomonas aeruginosa* (13.0%), *Escherichia coli* (10.6%), and *Staphylococcus aureus* (5.3%),

Enterococcus spp. (2.2%) and fungi of the genus *Candida* (17.0%). Moreover, complications caused by the microbial association of pathogens (2 or more types of pathogens) were observed in 21.2% of cases.

CONCLUSION

The ventilator-associated lesion of the lower respiratory tract is accompanied by a pronounced lymphoid-neutrophilic infiltration of the mucosa of the trachea and bronchi, and in a complicated course with the presence of a purulent-inflammatory and erosive-hemorrhagic component; it leads to a violation of tissue integrity due to destruction and necrosis. In patients on prolonged artificial lung ventilation, a tendency was revealed for the prevalence of gram-negative microflora sowing, and over the past two years, the range of isolated multi-resistant flora has been expanding.

DECLARATIONS

Acknowledgements

This work was supported by State Institution "Republican Specialized Scientific and Practical Medical Center for Surgery named after academician V.Vakhidov", Uzbekistan.

Authors' contribution

All authors contributed equally to this work.

Funding support

None.

Competing interests

The authors declare that they have no competing interests.

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