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THE USE OF TIGECYCLINE IN COMBINATION THERAPY OF VENTILATOR-ASSOCIATED PNEUMONIA. CLINICAL CASE

Agil Novruzalievich Mirzoev[1*], Said-Magomed Suleymanovich Uzhakhov[1], Magomed-Salakh Khampashaevich Shamdarov[2], Valeria Alekseevna Vasilenko[1], Fatima Isaevna Evloyeva[1], Victoria Alexeevna Charkova[1]

1. ***Department of Therapy, Dental Faculty of Moscow State University of Medicine and Dentistry named after A.I. Evdokimov, Moscow, Russia***
2. ***Department of Therapy, Medical Faculty of Moscow State University of Medicine and Dentistry named after A.I. Evdokimov, Moscow, Russia.***

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ABSTRACT

In patients on artificial lung ventilation, the development of ventilator-associated pneumonia, the main causative agents of which are multi-resistant hospital strains of microorganisms, becomes a fairly frequent and formidable complication. Considering the case of initially community-acquired pneumonia in a patient with a rapid transfer to artificial lung ventilation, it should be noted that previous antibacterial therapy with broad-spectrum drugs significantly increased the risk of joining polyresistant nosocomial strains. This complicates the "starting" therapy of nosocomial pneumonia both in the absence of microbiological seeding and, sometimes, in its presence. While maintaining the relevance of the treatment of severe pneumonia caused by a multi-resistant hospital flora resistant to carbapenems, when selecting an alternative treatment, one of the drugs is a representative of the tetracycline series - tigecycline, from the group of glycylcyclines. This publication presents a case of treatment of nosocomial ventilator-associated pneumonia with tigecycline following the results of microbiological examination of sputum, blood, and urine.

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Introduction

Klebsiella pneumoniae microorganisms are among the group of the most common clinically significant pathogens with a high level of antibacterial resistance (ESKAPE) [1-3]. The rate of development of antibiotic resistance by *K. pneumoniae* strains has sharply increased and reached a pandemic scale. One of the main clinically significant mechanisms of their antimicrobial resistance is the production of B-lactamases, the groups of which vary depending on the region, country, and hospital. Currently, a significant part of the nosocomial *K. pneumoniae* is resistant to protected penicillins, cephalosporins of III-IV generations [4]. A serious threat to the healthcare system is the growing resistance of *Klebsiella* to carbapenems. First of all, these are cattle-, OXA-, NDM-, VIM-, and IMP-producing K. pneumoniac [5, 6]. The rapid spread of carbapenem-resistant *Klebsiella* in the world indicates the need for international cooperation in the control of antibiotic resistance. There is an increase in the frequency of acquired resistance of *K. pneumoniae* to non-B-lactam antibiotics (fluoroquinolones, aminoglycosides). *K. pneumoniae* isolates resistant to tigecycline and colistin are registered. In general, the problem of antibiotic resistance to pathogens of human infectious diseases, including pneumonia, continues to worsen. This is a serious threat to global public health, which requires action in all public sectors [7].

Klebsiella bacteria are a common cause of infections associated with medical care [8]. According to domestic and foreign studies, there is a real threat of the formation and spread of resistant strains of bacteria of the genus *Klebsiella* among patients of medical organizations, which leads to the development of serious complications and increases the risk of death [9].

Figure 1 shows the proportion of microorganisms producing carbapenemases.

Corresponding Author: Agil Novruzalievich Mirzoev; Department of Therapy, Dental Faculty of Moscow State University of Medicine and Dentistry named after A.I. Evdokimov, Moscow, Russia. E-mail: bucky99@ya.ru.

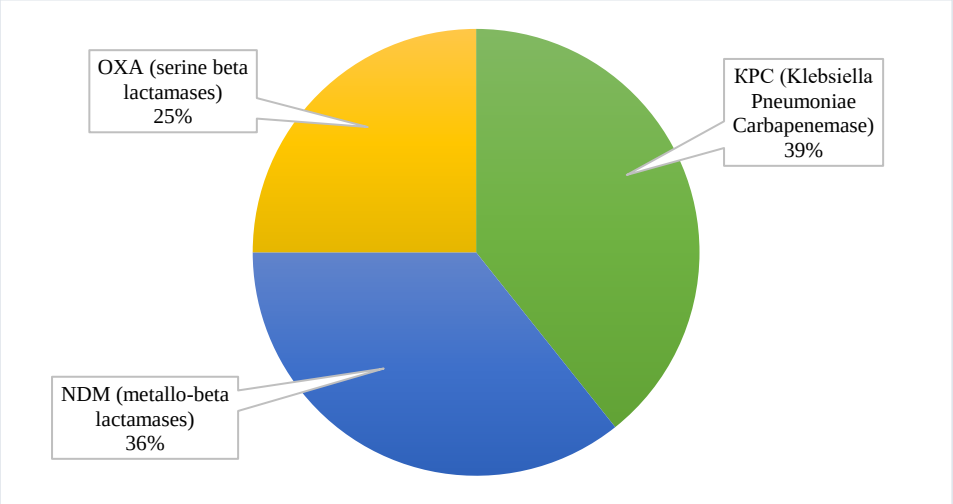

Figure 1. The proportion of microorganisms producing carbapenemases

The development of modern medical technologies leads to a change in the nature and intensity of the manifestations of the epidemic process, the constant use of antimicrobial agents is accompanied by the spread of resistant forms of bacteria. Metabolically inert microorganisms (persistors) can elude the effects of any antibiotics [10]. It is known that persistors can make up more than 10% of all microbial cells and maintain the preservation of the pathogen [11].

Monitoring and analysis of the hospital population of *Klebsiella pneumoniae* is the most important task of a hospital epidemiologist to assess the risk of nosocomial infection and the formation of hospital clones.

Clinical Case

The patient (female, 56 years old) was on inpatient treatment from 12/29/2021 to 01/13/2022. Initially, from 11/23/2021, she was hospitalized in Stavropol City Hospital No. 2 with suspected COVID-19. After receiving negative smears on 12/29/2021, she was transferred to the Stavropol Regional Clinical Hospital, first to the therapeutic department, and then to the department of anesthesiology and intensive care, where the study was conducted.

A clinical diagnosis was made: bilateral viral-bacterial poly segmental pneumonia, extremely severe course, degree of lung damage CT3, with the formation of fibrosis.

She was admitted on 01/01/2022 to the Department of Intensive Care and Intensive Care of the Stavropol Regional Clinical Hospital. It is known from the anamnesis that it has: arterial hypertension of the 3rd degree, ischemic heart disease, and atherosclerotic cardiosclerosis. Mitral valve insufficiency, prolapse of its valves of the 1st degree. Tricuspid valve insufficiency. Minor aortic insufficiency. Pulmonary artery valve dysfunction. Secondary cardiomyopathy (dysmetabolic, dishormonal). Hypercholesterolemia. Autoimmune polyendocrine syndrome: autoimmune thyroiditis, hypothyroidism, stage of drug compensation. Chronic adrenal insufficiency, the stage of drug compensation. Type 2 diabetes mellitus, on insulin. Diabetic polyneuropathy. Diabetic nephropathy.

Chronic pyelonephritis, remission. Cyst of the left kidney. Microliths in the kidneys. Chronic kidney disease of the 4th degree. In blood tests at admission anemia (HGB 91 g/l), decreased albumin (19.28 g/l), hypoproteinemia (total protein 36.4 g/l), increased creatinine (132.4 mmol/l), and urea (10.3 mmol/l), decreased prothrombin index (81%), increased INR (1.24 sec) and ACTV (59.8 sec). Auscultation breathing is carried out on both sides symmetrically, diffusely weakened. Crepitating wheezes in the middle, and lower lobes. There is a meager amount of sputum. The frequency of respiratory movements is 22-24 per minute. In atmospheric air, SpO_2 is 75%, with the supply of humidified oxygen at 8 l/min SpO_2 95%.

On the chest X-ray from 01/01/2022 R-signs of bilateral polysegmental pneumonia. Inhomogeneous infiltration sites are noted in all pulmonary fields, against the background of an enhanced pulmonary pattern. Later, namely 01/01/2022 R- signs of bilateral polysegmental pneumonia, stagnant changes in the small circle of blood circulation. The lungs are straightened, the pulmonary pattern is enhanced due to the peribronchial component, and a pronounced decrease in pneumatization in both pulmonary fields is poly segmental due to pneumonic infiltration. In comparison with the previous study, there is a negative trend.

CT scan of the thoracic cavity from 0/04/2022 shows signs of bilateral poly segmental pneumonia, and bilateral "small" hydrothorax. Manifestations of respiratory distress syndrome cannot be excluded. The lungs are straightened, poly segmentally, with areas of massive pneumonic infiltration of the "frosted glass" type in combination with areas of pronounced consolidation.

Taking into account the severity of pneumonia and the extent of the lesion, the increasing clinical symptoms, as well as the use of past antibiotics (cefoperazone/sulbactam and vancomycin), it was empirically prescribed: tigacil 50mg 2 times a day and broadleaf 1.5g 2 times a day.

Against the background of therapy initiated on 01/05/2022, the patient's condition did not improve, and respiratory failure and intoxication syndrome persisted. On the same day, the patient was transferred to invasive respiratory support in BIPAP mode

with an oxygen fraction of 60%, SpO_2 against this background of 94%. Auscultatively, the picture is the same. Hemodynamics is unstable, supported by the introduction of norepinephrine 4ml + a solution of 5% glucose 16ml at a rate of 7-10 ml/h.
In a microbiological study dated 01/05/2022, sputum–microflora growth was not detected. In the blood test for sterility, there is also no growth. But there is a growth of *Klebsiella pneumoniae* in the urine, resistant to almost all antibiotics, except for amikacin **(Table 1)**.
In blood tests from 01/06/2022, acute leukocytosis (WBC 17.4), thrombocytopenia (PLT 95), CRP (252 mg/L) rose, maximum body temperature 39.1°C, AsAT (52.6 units/L), bilirubin (23.7 mmol/L), creatinine (162 mmol/L) increased, urea (13.8 mmol/l). But by 01/08/2022, blood counts began to stabilize regarding the inflammatory process: WBC (7.1), CRP went down to (200 mg/l), AsAT (39 units/l). But signs of renal insufficiency began to prevail: creatinine (176 mmol/ L), urea (17 mmol/L), sodium (158.9 mmol/l). Hemodynamics is unchanged. The patient is out of sync with the respirator, pronounced tachypnea up to 28-33 per minute. To synchronize with the device, 1 ml of morphine and 2 ml of sibazone are injected 3 times a day. Auscultatively, the picture is the same. Outside of sedation, the level of consciousness is sopor.

Table 1. Antibioticogram (I-sensitive with increased antibiotic exposure, R-resistant, S-sensitive)

Amikacin	I
Amoxicillin+clavulanic acid	R
Ampicillin+sulbactam	R
Gentamicin	R
Imipenem	R
Meropenem	R
Piperacillin-tazobactam	R
Ticarcillin+ clavulanic acid	R
Cefepime	R
Cefotaxime	R
Ceftazidime	R
Ceftriaxone	R
Ciprofloxacin	R

On 01/07/2022, a tracheostomy was performed.
In a microbiological study from 01/08/2022 in the urine of candida albicans, resistant to all antifungal drugs.
On 01/08/2022, in blood tests WBC (7.1), CRP (209 mg/L), maximum body temperature 38.1°C, AsAT (39 units/L), bilirubin (28 mmol/L), creatinine (176 mmol/L), urea (16.8 mmol/L), sodium (158.9 mmol/l). Hemodynamics: norepinephrine at a rate of 5 ml/h. To synchronize with the device, 1 ml of morphine and 2 ml of sibazone are injected 3 times a day. Mucopurulent sputum is sanitized from the tracheobronchial tree in a moderate amount. Auscultatively, the picture is the same. Outside of sedation, the level of consciousness is sopor.
Bronchoscopy from 01/11/2022: there is an insignificant amount of mucosal sputum in the lumen of the segmental bronchi. Polysegmental sanitation with a physical solution was performed. The mucosa is hyperemic in all parts, there is no edema, and there is no fibrin plaque.

Results and Discussion

By 01/12/2022, against the background of the use of tigacil, the signs of the inflammatory process in the blood regressed: WBC (6,7), CRP (131 mg/ l), and the maximum body temperature of 38 °C. Determination of b-D-glucan – the result is 133.2 pg/ml. Fluconazole was added to therapy at a loading dose of 800 mg. But Acute respiratory distress syndrome took a more severe course, tachypnea up to 40 per minute. Parameters of artificial lung ventilation: Tinsp 0.90 sec, Pinsp 31 mbar, Pasb 25 mbar, f 21 per minute, FiO_2 90%, PEEP 9 mbar, against this background SpO_2 90%. Outside of sedation, the level of consciousness is a coma of the 2nd degree. There is no photoreaction, the sclera is icteric. Hemodynamics: norepinephrine at a rate of 12 ml/h. Absence of peripheral pulsation. The heart tones are deaf, rhythmic. The heart rate is 100 beats per minute. Diffuse microcirculation disorders appeared. Diuresis decreased to 550ml per day, edema of the upper extremities appeared, and the lower extremities were in elastic bandaging.
The main disease was complicated by respiratory insufficiency of the 3rd degree, of respiratory distress syndrome. Despite the positive effect of the use of tigecycline, the fatal outcome occurred on 01/13/2022 as a result of multiple organ failure: cerebral, pulmonary, renal, hepatic, and cardiovascular; as well as decompensation of chronic diseases.
Tigecycline is a representative of glycylcyclines with activity against multi-resistant bacteria, including those producing ESBL. Epidemiological monitoring of the dynamics of antibiotic resistance to tigecycline, conducted in the USA and European countries, showed that within two years after the introduction of this drug into clinical practice, the use of tigecycline was not accompanied by the spread of resistance to it among bacterial microorganisms, including *K. pneumoniae* [12]. V.A. Ageevets

[13] showed that polyresistant strains of *K. pneumoniae*, in which high values of the minimum suppressive concentration for cephalosporins, aminoglycosides, aztreonam, carbapenems were detected, retained sensitivity to tigecycline. Studies are being conducted on the use of combinations of tigecycline with other antibiotics, in particular, imipenem, and meropenem, to affect carbapenem-resistant microorganisms [14]. According to various authors, the number of nosocomial *K. pneumoniae* resistant to tigecycline varies significantly: from 12.5% and 16.3% to 21% [15]. In North America, 2.6% of isolated *K. pneumoniae* strains are resistant to tigecycline [16].

Conclusion

Antibacterial therapy of nosocomial pneumonia caused by polyresistant strains remains a serious problem. Encouraging in practical research is the obtaining of data on the optimal effectiveness of combination therapy, including tigecycline and other antibacterial drugs that affect non-fermenting gram-negative bacteria.

This clinical case shows the effectiveness of therapy in hospital ventilator-associated pneumonia caused by a polyresistant strain of *Klebsiella pneumonia*. One of the drugs that is active against the most virulent pathogen - the multi-resistant *Klebsiella pneumoniae*, is tigacil.

With the accumulation of a sufficient amount of material, it is necessary to correctly assess the possibility of using tigecycline in pneumonia and preserving it in clinical practice as an additional drug, the use of which must be strictly regulated taking into account the crops of the isolated microflora.

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