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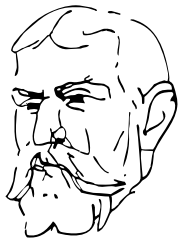

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REVIEW ARTICLE

MODERN APPROACHES TO TREATMENT OF *PSEUDOMONAS AERUGINOSA* VENTILATOR-ASSOCIATED PNEUMONIA (LITERATURE REVIEW)

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ABSTRACT

Introduction: Nowadays anti-microbial therapy of ventilator-associated pneumonia caused by is one of the most topical issue as a consequence of widespread multiresistant strains of causative agent and their biological peculiarity of actively formation of resistance to new antibacterial drugs.

The aim is to describe modern approaches to therapy of ventilator-associated pneumonia causative agent of which is presented by *Pseudomonas aureginosa* .

Materials and methods: An analysis and summing up of results of scientific investigations described in medical publications concerning the issues of therapy of ventilator-associated pneumonia caused by *Pseudomonas aureginosa* was done.

Conclusions: Despite the development of modern approaches to anti-microbial therapy of ventilator-associated pneumonia caused by *Pseudomonas aeruginosa,* which are also concerned with such controversial issues as correct choice of antibacterial drug, its optimal dose, and duration of this therapy, the problem of treatment of hospital-acquired infections of respiratory airways caused by *Pseudomonas aeruginosa* has been discussable yet and requires the further study.

KEY WORDS: ventilator-associated pneumonia, *Pseudomonas aeruginosa*, treatment

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INTRODUCTION

According to the existing definition of hospital-acquired pneumonia, it is considered to be pneumonia acquired in a medical institution 48 hours after the patient is hospitalized in case of the absence of any infectious disease during the incubation period and at the time of the patient's hospitalization. One of the varieties of hospital-acquired pneumonia is ventilator-associated pneumonia (VAP) – a special form of the disease which stands out, taking into account the severity of its course, the seriousness of the prognosis and the features of the management of reanimation patients. According to the results of the studies, the main pathogenic microorganisms in VAP are gram-negative bacteria (up to 74%), whose structure is dominated by *Pseudomonas aeruginosa*, as well as *Klebsiella* and E. coli. Among gram-positive microorganisms, VAP is most often caused by methicillin-resistant *golden Staphylococcus* (MRSA) [1,2].

Pseudomonas aeruginosa is a typical species of the genus *Pseudomonas*, gram-negative aerobic bacterium, widely known associative microorganism of various ecological niches in humans, animals and the environment, which is also widely used as a causative agent of opportunistic infections in medical practice. The presence of multiple molecular mechanisms of pathogenicity, the unique ability to adapt to different environmental conditions, as well as high resistance to various classes of antibacterial drugs, allows *Pseudomonas aeruginosa* to persist for a long time inside hospital wards. Hospital-acquired infections caused by *Pseudomonas aeruginosa* at the present stage are recognized as an urgent and acute problem and occupy one of the leading positions in the structure of hospital-acquired pneumonia in hospitals of various profiles [2,3,4]. The frequency of detection of *pseudomonas infection* in patients with hospital-acquired pneumonia is quite high and according to the results of foreign researchers it ranges from 10 to 35% [5]. A recent conducted study has shown that mortality from VAP associated with *Pseudomonas aeruginosa* has increased to 41.9% in recent years, and as independent predictors of increased mortality researchers consider an increase in patient age and initially inadequate antibiotic therapy in patient management [6].

Antimicrobial therapy of ventilator-associated pneumonia caused by *Pseudomonas aeruginosa* is today a very topical problem due to the widespread spread of multi-resistant strains and their biological peculiarity to actively form resistance to new antibacterial drugs. At the present stage, a large number of studies is devoted to the problem of ventilator-associated pneumonia therapy. At the same time, recommendations for the management of patients with VAP dynamically change and are regularly supplemented, which is facilitated by the development of innovative medical technologies and the appearance of new antibacterial drugs.

THE AIM

The aim of the research is to highlight the main modern therapeutic approaches and the prospects for further directions of treatment of ventilator-associated pneumonia, the causative agent of which is *Pseudomonas aeruginosa*.

MATERIALS AND METHODS

A thorough comprehensive analysis and synthesis of the results of conducted scientific researches, covered in fundamental medical publications concerning the treatment of ventilator-associated pneumonia caused by pseudomonas infection, was carried out.

REVIEW AND DISCUSSION

The latest recommendations for anti-bacterial therapy for ventilator-associated pneumonia (VAP) were developed in 2005 by the American Thoracic Society and the Society of Infectious Diseases of America, which recommend combination therapy of VAP with antipseudomonal cephalosporins (cefepime, ceftazidime) or carbapenems (iepenem, or by perennial venting tubes. β-lactamase inhibitor (piperacillin-tazobactam) plus antipseudomonal fluoroquinolones (ciprofloxacin or levofloxacin) or aminoglycosides (American Thoracic Society; Infectious Diseases Society of America, 2005). However, since the publication of these recommendations, many conclusions have been made in the field of antibiotic therapy in critically ill patients, including inadequate treatment for reasons of insufficient dosage and non-optimal antibiotic exposure, which, as a result, are associated with increased mortality and worse results [7,8]. In addition, the steady growth of multidrug-resistant bacteria strains against hospital-acquired pneumonia makes this approach obsolete.

According to the current general recommendations in the treatment of VAP, it is also necessary to avoid prescription of antibiotics to which the patient has been exposed for the last 30 days, since new episodes of the disease, as a rule, are relapses of a strain with different phenotypic variations, and not a consequence of reinfection. A study conducted in 2013 revealed the main risk factors for the ineffectiveness of VAP therapy, which included the patient's age, the presence of chronic pathologies, the severity of the disease, previous use in the treatment of fluoroquinolones and bacteraemia. Interestingly, neither the definition of antibiotic sensitivity nor the use of combination therapy influenced the frequency of ineffective cases of VAP therapy, while at the same time, treatment with fluoroquinolones significantly reduced it [9]. In our opinion, in order to avoid the irrational use of antibacterial drugs, it is necessary to adhere to an integrated approach, taking into account not only the classical microbiological paradigm, based only on the susceptibility to the drug and the minimum inhibitory concentration, but also having assessed certain risk factors for multidrug resistance.

Undoubtedly, timing is an important condition for successful treatment – effective therapy started timely and at the earliest possible time makes the difference between recovery and lethal outcome, especially in the presence of a patient's shock condition [10]. To date, there are already published data confirming the fact that the delay in effective therapy significantly increases the incidence and mortality rate among patients with VAP [11]. The empirical choice of the prescribed agent is also fundamental, which is based on taking into account the most likely pathogens and their perceived sensitivity to available antimicrobial agents. The results of a recent multicentre research on the study of potentially resistant microorganisms in patients with VAP have shown that late VAP (developing no earlier than the 6th day of hospitalization) is in most cases caused by aerobic gram-negative flora, 70% of which are *Pseudomonas aeruginosa*, *Acinetobacter baumannii* or MRSA [12]. When prescribing a starting antibiotic, we are obliged, first of all, to take into account its activity in relation to the most probable pathogens, the degree of effectiveness and timing of the use of previous antibiotics, the presence of comorbidities in a patient, the duration of hospitalization, and local epidemiology. In particular, the most reasonable approach is the use of a broad-spectrum antibiotic based on local microecology with subsequent re-evaluation of the clinical response and microbiological data after 48-72 hours [13].

Undoubtedly, patients with VAP need a special therapeutic approach, since its pathogens are characterized by multidrug resistance. According to the results of many studies and meta-analyzes, empirical combination therapy of VAP caused by pseudomonas infection with beta-lactams plus aminoglycosides proved to be more effective than monotherapy, making it possible to reduce mortality rates by 50%, mainly due to the corresponding initial therapy [13,14]. However, according to some researchers, there is no difference between using one or two effective antibiotics, which serves as a basis for de-escalation to monotherapy as soon as microbiological results are ready [13].

Another important point of the therapy is also the optimization of the choice of antimicrobial drugs in accordance with their pharmacokinetic and pharmacodynamic parameters. It is important to keep in mind that the antibiotic that we choose should reach therapeutic concentrations in the focus of infection, where bacteria interact with an antibacterial agent to obtain bacterial clearance as early as possible [15]. In addition, it should also be noted that the administration of a loading dose and the introduction of beta-lactams in the form of long-term and continuous infusions can increase the degree of exposure to the antibacterial drug, as well as the probability of reaching the target peak concentration, which plays an important role in the treatment of patients with septic shock, severe obesity, and burn lesions. The results of a recent multicentre research on the efficacy of VAP treatment in patients of the intensive care unit showed that about 16% of all patients did not respond to therapy with standard doses of β-lactams. While patients receiving antibiotics at a dose of 50% and 100% above the minimum inhibitory concentration, had much better clinical outcomes of the disease [16].

In addition to microbiological sensitivity, another equally important issue of antibacterial therapy of VAP, which

must be considered, is also the degree of pulmonary penetration of active substances. In recent years, methods of inhalation (nebulizer) administration of an antibiotic have been considered, which make it possible to achieve high concentrations in the bronchial tree and promote better alveolar penetration compared with injection administration. Colistin (polymyxin E) is an antibiotic belonging to the group of polymyxins, which has been successfully used for inhalation in patients with cystic fibrosis for a long time. In a small randomized retrospective study, the use of nebulized Colistin (in high doses) in the form of VAP monotherapy was studied. According to the results of the study, its therapeutic effect was not inferior to the combination therapy with injectable β-lactams in combination with aminoglycosides and quinolones in the treatment of VAP which was caused by susceptible strains of *Pseudomonas aeruginosa* and *A. Baumannii* [17]. This approach is of a considerable interest, as it provides a high concentration of antibiotic with minimal absorption at systemic levels, which could be a turning point of therapy in the presence of multidrug-resistant strains, where the available drugs are very toxic. To date, several antibacterial agents (colistin, tobramycin, aztreonam, ceftazidime and amikacin) are available for inhalation use, but should be subject to further study in randomized clinical trials to confirm their safety and the possibility of being adding to standard therapy.

The question of the optimal duration of antibiotic therapy remains controversial today. Until recently, the standard practice was the appointment of a 15-day course of antibiotic therapy for uncomplicated infections. At the present stage, the appointment of a 7-8-day course of antibiotic therapy has become more acceptable if the patient's response to the therapy is satisfactory [18]. Many studies have shown that the 8-day course of antibiotic use in VAP is considered safe. It reduces the likelihood of resistant strains of microorganisms, reduces the cost of treatment, and also avoids unnecessary toxicity [8,18]. However, it is also worth noting that with VAP caused by gram-negative bacilli, the use of an 8-day versus a 15-day antibiotic course is associated with an increased risk of recurrence of a pulmonary infection. According to some researchers, longer courses of antibiotics can be recommended for patients with an immunosuppressive state and initial inadequate empirical therapy of VAP caused by strains with extensive drug resistance without clinical resolution of the disease [8].

Today, it is known that cephalosporins are a group of antibacterial drugs with proven efficacy, a broad spectrum of action, and a well-studied pharmacodynamic profile, in addition to a favourable safety profile. These characteristics, undoubtedly, make this antimicrobial class of drugs one of the main ones in the treatment of hospital-acquired infections, including VAP caused by *Pseudomonas aeruginosa* [19]. In recent years, due to the emergence of hospital-acquired infections caused by β-lactam resistant gram-negative bacteria, two important strategies have been developed to improve the therapeutic efficacy of antibacterial agents: the development of new β-lactam drug molecules that can avoid the effects of some of the factors that form the mechanisms of bacteria resistance and addition of new compounds capable of inactivating bacterial β-lactamases [20]. Ceftobiprole medocaril, which has an increased activity against gram-negative pathogenic microorganisms, should be highlighted among the newest drugs in the latest developments in the field of the cephalosporin range of antibiotics. The activity of Ceftobiprole medocaril against strains of pathogens with multidrug resistance, the so-called ESKAPE pathogens (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumanii, Pseudomonas aeruginosa* and *Enterobacter species*) and its resistance to a wide range of β-lactamases make this drug a promising option for the treatment of hospital-acquired pneumonia [21]. Ceftazidime / avibactam (CAZ-AVI) is a fixed-dose combination of drugs that consists of cephalosporin antibiotic of III generation ceftazidime and a new non-standard β-lactam inhibitor of β-lactamase avibactam. The association of avibactam with ceftazidime protects the latter from degradation by β-lactamases, increasing its activity against various enterobacteria, including *Pseudomonas aeruginosa* [22]. Ceftolozane is a broad-spectrum cephalosporin antibiotic (similar to III generation cephalosporins). Its main difference is significantly higher activity against *Pseudomonas aeruginosa*, including ceftazidime resistant strains. According to some studies, ceftolozane exhibits increased affinity for penicillin-binding proteins as compared to other antisealtic β-lactams. The results of the study demonstrate that the combination of ceftolozane with tazobactam (β-lactamase inhibitor) is active against many strains of enterobacteria producing β-lactamase of extended-spectrum, but is inactive with respect to producers of metallo-β-lactamase [23].

Plasomicin (ACHN-490, Achaogen), an aminoglycoside of a new generation, which at the present stage is considered as a drug capable of reviving the class of aminoglycosides, is one of the modern drugs used in the treatment of pseudomonas infection. This drug has a fairly wide spectrum of activity, including both gram-negative (*Pseudomonas aeruginosa*, *A. baumanii, K. pneumoniae, E. coli*), and gram-positive microorganisms (MRSA). Conducted clinical studies on the assessment of the effectiveness of plasomicin against *Pseudomonas aeruginosa* revealed its synergistic effect with beta-lactam antibiotics. According to the obtained results, the drug also has no side effects in the form of nephrotoxicity and ototoxicity, which are characteristic of antibiotics of this group [24].

NXL104 (Novexel) is an injectable beta-lactamase inhibitor of a broad-spectrum from a completely new non-beta-lactam structural class, which, in combination with the ceftazopin antibiotic ceftazidime, demonstrated high activity against a wide range of gram-negative bacterial pathogens, including Enterobacteriaceae and *Pseudomonas*. According to the results of preclinical studies, the spectrum of activity of NXL104 is broader than the modern beta-lactamase inhibitors approved for clinical use (tazobactam, clavulanate and sulbactam). Adding NXL104 to ceftazidime restores susceptibility to gram-negative pathogens and, in case of further successful usage, the NXL104 / ceftazidime combination can be a

good alternative to carbapenems in the first-line treatment of serious gram-negative infections caused by pathogens with multidrug resistance [24].

Undoubtedly, the attention is also drawn by the drug *POL7080*, a new experimental peptidomimetic antibiotic developed specifically to combat *Pseudomonas aeruginosa*, which, according to published results, has already proved its effectiveness in experiments with mice [25]. At the present stage in Europe, I phase of clinical trials of this drug was successfully completed, which demonstrated clinical safety and tolerability of *POL7080.* To date, studies are ongoing on the evaluation of *POL7080* therapy of patients with VAP caused by *Pseudomonas aeruginosa*. One of the main problems with the use of this drug at the present stage is its nephrotoxicity [8].

At the present stage, one of the important directions in the treatment of infection caused by *Pseudomonas aeruginosa* is the creation of effective vaccines, the action of which will be aimed at blocking the main factors in the development of the infection process. It is worth noting that the development of these vaccines today is rather difficult due to the high variability between different types of *Pseudomonas*, the complexity of the infection process itself and the interaction of *Pseudomonas aeruginosa* with the immune system of the affected organism. In many of the studies conducted, the tested vaccines did not provide adequate "coverage" of different strains of *Pseudomonas aeruginosa*, showed low immunogenicity or had an insufficiently protected safety profile for use in clinical practice [8,26,27]. Currently, developments are being continued in this area of therapy.

CONCLUSIONS

A thorough analysis and synthesis of the results of scientific research on the treatment of VAP caused by *pseudomonas* infection has shown that despite ongoing research on the discovery and use of new antibacterial drugs, at the present stage *Pseudomonas aeruginosa* therapy remains an urgent and difficult task of medical practice. The presence of many molecular mechanisms of pathogenicity, as well as high resistance to various classes of antibacterial drugs, allows *Pseudomonas aeruginosa* to persist for a long time inside hospital wards, taking one of the leading positions in the structure of hospital-acquired pneumonia in hospitals of various profiles. Despite a long and in-depth study of the problems of hospital-acquired respiratory tract infections caused by *Pseudomonas aeruginosa* by domestic and foreign researchers, many issues of their treatment and prevention are still debatable and require further study.

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