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PROSPECTS FOR THE USE OF INHALATION ANTIBACTERIAL DRUGS IN RESPIRATORY INFECTIONS (REVIEW)

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Abstract:

The need to find ways to improve the effectiveness of antibacterial therapy is due to the dramatic escalation of resistance to antibacterial drugs (ABD), while the growth rate of resistance to antibacterial drugs is outpacing the dynamics of the development of new drugs. The article presents up-to-date data on existing inhaled ABPs, allowing to evaluate their effectiveness and safety.

Keywords: antibacterial drug resistance, inhalation antibacterial drugs, lower respiratory tract infections, pper respiratory tract infections, pyocyanic infection.

The current state of therapy for infectious diseases is characterized by dramatic resistance to antibacterial drugs (ARs), while the growth of resistance of microorganisms to the effects of antibacterial drugs (ARs) exceeds the rate of development of new drugs. With the development of resistance to ABP, there are enormous socio-economic consequences - for example, in the United States, which accounts for about 46% of the global ABP market, the total cost of treating nosocomial infections of the most significant categories in 2013 amounted to 9.8 billion US dollars (95% confidence interval (CI) - 8.3-11.5 billion US dollars) [59], of which the costs of respiratory pathology amounted to 31.6%. Data from the Infectious Diseases Society of America (IDSA) [50] indicate that nosocomial infections caused by resistant microflora in the United States annually cause 99,000 deaths. The aggravation of the problem of resistance to ABP can provoke the development of a dramatic scenario, indicated in the work of B. Aslam et al. (2018) [3], according to which, by 2050, up to 444 million people in the global population will suffer from infections. From a modern point of view, the possibilities of resisting large-scale resistance to ABP include both the obligatory adherence to the principles of rational ABT and rethinking the value of systemic ABT with the search for alternative ways of targeted delivery of ABP to the focus of an infectious lesion.

Widely known factors of resistance to ABPs include their excessive use in agriculture, uncontrolled consumption by the population, and a high level of circulation of unmetabolized ABPs in the environment [4 7 , 4 8]. Close attention to the problem of uncontrolled consumption of ABP from the standpoint of clinical medicine has made it possible to identify additional negative factors of their systemic use. A. Langdon et al. (2016) [31] demonstrated that the systemic use of ABP can contribute not only to the formation of resistance, but also damage the human microbiome, while increasing the risk of developing infectious diseases. It has been demonstrated that microbiome dysbacteriosis is associated with metabolic, immunological and developmental disorders, while reducing the body's resistance to the effects of pathogens of infectious diseases, in particular respiratory ones [4,11]. The ability of normal microbiota to counteract systemic and respiratory infections was noted in the case of Escherichia coli [15], influenza viruses [27], Klebsiella pneumoniae [11], Listeria monocytogenes [28], Staphylococcus aureus [23] and Streptococcus pneumoniae [48]. The most pronounced changes in the microbiome of the human body are observed in the case of systemic use of ABP, while there are data indicating the maximum damaging effect of ABP when taken per os [60].

One of the main criteria for the effectiveness of ABT is the ability of the drug to create an effective inhibitory / bactericidal concentration in the focus of infection. With systemic routes of administration of ABP, such as per os, intravenous and intramuscular, the distribution of ABP over various organs and tissues of the body, including the focus of infection, is ensured. An important factor that hinders the effective treatment of infectious diseases of the lower respiratory tract is the introduction of microorganisms into the deep sections of the respiratory tract wall, where it is difficult to create the required concentration of ABP using traditional systemic therapy [55]. The criterion for the effectiveness of ABP in the treatment of respiratory tract infections caused by extracellular pathogens, we can consider a high concentration of ABP in the fluid lining the epithelium. The value of the ratio of the ABP concentration in the fluid lining the epithelium to the ABP concentration in the blood plasma, exceeding one, indicates a higher efficiency of the drug. Antibiotics with this ratio > 1 include macrolides, ketolides, new fluoroquinolones, and oxazolidinones. In turn, the ratio of drugs widely used in respiratory infections, such as β-lactams, aminoglycosides and glycopeptides is ≤ 1 [45]. On the ability of ABP to create effective

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concentrations in parenchyma with systemic administration, a change in hemodynamics in the lungs against the background of inflammation (a decrease in blood flow in the area affected by the infectious process and an increase in the area of adequate gas exchange in the area) can have a negative effect [51]. The condition for the effective action of systemically administered ABP in the respiratory tract is its ability to overcome the alveolar barrier and create high concentrations in the lung parenchyma. The function of the alveolar barrier is to activate the mechanisms of drug efflux (multidrug resistance protein-1), which further reduces the concentration of ABP in the lung parenchyma.

Thus, to increase the concentration of systemically administered antibiotics in the focus of infection, it is necessary to use high doses. In turn, high concentrations of ABP cause the development of dose-dependent toxic reactions. One of the most toxic groups of ABPs for systemic use are aminoglycosides. Among the negative reactions, ototoxicity, vestibulotoxicity, neuromuscular block, and most often nephrotoxicity should be distinguished. Excretion of aminoglycosides is carried out almost exclusively by glomerular filtration, while the drugs selectively act on the epithelial cells of the proximal tubules in the cortical substance of the kidney, accumulating in this zone (up to 5% of the administered dose). which explains the cellular and tissue specificity of aminoglycoside nephrotoxicity.

When exposed to systemic β-lactams, the following adverse reactions are noted: amoxicillin (aminopenicillin) can cause nephritis, eosinophilia, hemolytic anemia, as well as lesions of the oral mucosa and urogenital tract (candidiasis); frequent reactions after oral administration are nausea, vomiting, diarrhea and gastrointestinal problems; cephalosporins can cause side effects (morbilliform skin rashes, eosinophilia, gastrointestinal problems, hematological reactions, alcohol intolerance, nephrotoxicity, interstitial nephritis) in an average of 1-10% of cases; carbapenems can cause gastrointestinal disorders (vomiting, nausea (4%), diarrhea (3%), pseudomembranous colitis (0.16%), neurotoxic reactions (up to 3%), hematotoxic reactions (0.3%) [24] Also, gastrointestinal disorders (nausea, vomiting, diarrhea) associated with suppression of the normal intestinal flora and the growth of Pseudomonas, Proteus and Clostridium populations may occur with the use of tetracycline, with such adverse reactions as vaginal candidiasis, enamel damage teeth in the fetus, hepatotoxicity (when administered intravenously), nephrotoxicity (when taken together with diuretic drugs), photosensitivity [24]. three main drugs - azithromycin, clarithromycin, erythromycin Erythromycin and clarithromycin can have an indirect effect on kidney function, often not in case of drug interaction with CYP3A4 substrates, since they are its inhibitors (statins and calcium channel blockers) [35]. Fluoroquinolones are known primarily for their ability to provoke the development of tendonitis and tendon ruptures (0.08-0.2% of cases). Neurotoxic reactions include insomnia, restlessness, less often seizures and psychosis; development of chronic persistent peripheral neuropathy is possible [20]. Cases of hepato-, nephro- and cardiotoxicity (prolongation of the QT interval) have been described [36]. SJTelfer (2014) described the possibility of developing insulin resistance [53]. According to the results of a number of studies, it has been shown that for some ABP, systemic administration, even at high doses, does not allow reaching the BMD in the focus of infection. Thus, when taking the maximum oral doses of ciprofloxacin (750 mg 2 times a day) in patients with cystic fibrosis, the concentration of ABP in sputum was lower than the MIC for P. aeruginosa [16]. With intravenous infusion of tobramycin (7–10 mg/kg), its concentration in the fluids of the epithelial lining of the lungs remained minimal; target values were not achieved even when the dose was increased to 25–30 mg/kg [13].

The toxic effects of ABP during systemic use, the inability of a number of drugs to form effective MIC values against significant pathogens of respiratory tract infections, and the risks of drug-drug interactions, manifested in an additional burden of toxicity for the patient, were prerequisites for the introduction of such a method of targeted delivery of ABP to the respiratory tract as inhalation.

The inhalation route of administration of ABP implies the direct delivery of the drug to the site of infection and contributes to the achievement of high local concentrations without the risk of systemic toxic reactions. The first attempts to use antibiotics in the form of an aerosol for the treatment of infectious diseases of the respiratory tract were made since the 1940s; Until the 1990s, no significant progress was noted, which is due to the imperfection of the solutions used. The osmolarity of the inhaled tobramycin solution developed in the 1990s was close to that of the physiological fluids lining the lung epithelium, and this solution contained virtually no preservatives. Since the 2000s, the number of antibiotics intended for inhalation has increased, and the amount of reliable data on the effectiveness of their use has increased (see figure).

Levofloxacin was the first inhaled fluoroquinolone licensed for the treatment and maintenance of patients with cystic fibrosis and chronic Pseudomonas

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aeruginosa [34]. In an open-label, randomized, controlled, phase III study, the safety and efficacy of inhaled levofloxacin at 240 mg twice daily was compared with that of inhaled tobramycin (300 mg twice daily) over 3 consecutive 28-day cycles of inclusion/exclusion of the drug at therapy of patients older than 12 years with cystic fibrosis and chronic infection with P. aeruginosa. It was demonstrated that levofloxacin was not inferior to tobromycin in the relative change in predicted forced expiratory volume in 1 second (FEV 1) (1.86% in contrast to the change in predicted FEV 1 ; 95% CI - 0.66-4.39%), the safety profile of levofloxacin was comparable to that of tobramycin, with dysgeusia being the most frequently reported side effect [35].

A significant number of studies have been devoted to evaluating the effectiveness of inhaled forms of ciprofloxacin. When using inhaled ciprofloxacin, its sputum concentration was ≥ 50 times the MIC value for P. aeruginosa, and the serum concentration was significantly lower than values observed with oral administration, minimizing the possibility of systemic toxicity and side effects [14]. As part of a randomized, double-blind, multicenter phase II study, a statistically significant decrease in the total bacterial load was observed during the use of inhaled ciprofloxacin in patients with bronchiectasis on day 28 ($p < 0.001$) [24]. In the RESPIRE-1 study, treatment with inhaled ciprofloxacin significantly increased the period to the 1st exacerbation compared with placebo in patients with bronchiectasis (> 336 days and 186 days; adjusted odds ratio (OR) - 0.53; 97.5% - new CI - 0.36–0.80; $p = 0.0005$) and the frequency of exacerbations decreased according to compared with placebo (mean frequency of occurrence over a period of 48 weeks - 0.78 and 1.42; adjusted OR - 0.61; 97.5% CI - 0.40-0.91; $p = 0.0061$) [25]. In the RESPIRE-2 study, there was a trend towards an increase in the period to the 1st exacerbation and a decrease in the frequency of exacerbations, but without statistically significant values [16]. Improved efficacy of the liposomal form of inhaled ciprofloxacin (increased permeability through biofilms in the treatment of intracellular infections), tolerability and increased compliance due to a decrease in the frequency of administration were noted [16]. A pooled analysis of the Phase III ORBIT-3 and ORBIT-4 studies found that the formulation incorporating liposomal ciprofloxacin significantly increased the mean time to 1st flare requiring antibiotics compared to placebo, decreased the frequency of flare-ups, and decreased P density. aeruginosa in sputum during each treatment period [25].

The creation of an inhaled form of aztreonam monobactam is based on the substitution of lysine in the composition of arginine (arginine salt, a substrate for the production of nitric oxide in the lungs, contributes to increased inflammation in the airways) [26]. A. _ F. _ barker et al . (2014) analyzed data from 2 phase III trials (AIR-BX1 and AIR-BX2) to assess the effect of inhaled aztreonam on the quality of life of patients with bronchiectasis. AIR-BX1 was not significantly different from placebo; the AIR-BX2 study showed an improvement (4.6 (1.1-8.2); $p = 0.011$), although a difference of 4.6 points on the QOL-B-RSS scale after 4 weeks. The use of inhaled aztreonam was not clinically significant [6].

The inhalation route of administration allowed more active use of highly toxic ABPs, such as aminoglycosides. When using the inhaled form of gentamicin, eradication in the sputum of P. aeruginosa was 30.8%, and when infected with other pathogens - 92.8%; there was also a decrease in sputum virulence (8.7% vs 38.5%; $p < 0.0001$) and the number of exacerbations (0 [0-1] and 1.5 [1-2]; $p < 0.0001$) with an increase the period before the 1st exacerbation (120 [87-161.5] days and 61.5 [20.7-122.7] days; $p = 0.02$) [37]. The efficacy of inhaled amikacin has been demonstrated by MSNiederman et al. (2012) when used in patients on artificial lung ventilation (ALV) with pneumonia caused by gram-negative microflora. There was a high concentration of amikacin in the tracheal aspirate after inhalation (400 mg for 12 hours), the frequency of clinical cure in patients for ≥ 7 days of therapy was 15 (93.8%), 12 (75.0%) and 14 (87.5%) out of 16 patients in the inhalation groups once every 12, 24 hours and in the placebo group, respectively ($p = 0.467$) [42]. Inhaled tobramycin efficacy studies found that it significantly reduced P. aeruginosa density by 4.54 log10 cfu/g sputum compared with a mean increase of 0.02 log10 cfu/g sputum in patients treated with placebo ($p < 0$ 01), a clinical improvement in well-being was observed at the 6th week without an increase in resistance [44]. MEDrobnic et al. (2005) showed the effectiveness of inhaled tobramycin - when taking this drug, there was a lower rate of hospitalizations and their duration (0.15 ± 0.37 and 2.05 ± 5.03, respectively) compared with those in the placebo group (0. 75 ± 1.16 and 12.65 ± 21.8, respectively; $p<0.047$). There was also a decrease in the population of P. aeruginosa after 6 months. ($p = 0.038$). There were no significant differences in the number of exacerbations, the frequency of use of antibiotics, lung function and quality of life, as well as the phenomena of ototoxicity and nephrotoxicity [17]. In a review by M.Vendrell et al. (2015) presented the results of an analysis of

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publications on the use of inhaled tobramycin in patients with bronchiectasis, indicating the effectiveness of the drug in the treatment of chronic Pseudomonas aeruginosa infection of the bronchi [46].

The inhalation form is also available for the ABP of the polymyxin group - colistin, which has a pronounced bactericidal effect against gram-negative microflora, including P. aeruginosa. To date, for inhalation, a new encapsulated dry powder composition of micronized sodium colistimethate is used [49], with the use of which for 24 weeks. in patients with cystic fibrosis and chronic infection with P. aeruginosa, efficacy and safety were noted at a level comparable to those of inhaled tobramycin.

In general, the clinical efficacy of inhaled ABT for infectious diseases of the respiratory tract has been confirmed by the results of a sufficient number of published studies that included patients with severe chronic pathology (cystic fibrosis, bronchiectasis). JWYang et al. (2016) published the results of a meta-analysis of 8 randomized controlled trials (n = 539). Long-term use of inhaled antibiotics showed an obvious decrease in the density of bacteria in sputum (weighted mean difference - 2.85; 95% CI - 1.6–4.09; p < 0.00001) and an increase in the eradication of P. aeruginosa from sputum (OR - 6.6; 95% CI - 2.93-14.86; p < 0.00001), there was a decrease in the number of exacerbations (OR -0.46; 95% CI - 0.21-1.00 ; p = 0.05). Patients receiving inhaled antibiotics were more likely to suffer from shortness of breath (OR - 6.74; 95% CI - 2.22–20.52; p = 0.0008) and bronchospasm (OR - 2.84; 95% CI – 1.11–7.25, p = 0.03) [50]. According to a meta-analysis of I. F. _ Laska et al . (2019) 6 studies (n = 2597) [51], found an increase in bacterial eradication against the background of inhaled administration of ABP (OR - 3.36; 95% CI - 1.63-6.91; p = 0.0010) and a significant reduction in the frequency of exacerbations (OR, 0.81; 95% CI, 0.67–0.97; p = 0.020).

The considered inhaled ABPs are prescribed mainly for nosocomial infections caused by multidrug-resistant gram-negative microflora. Currently, an inhaled antibiotic thiamphenicol glycinate acetylcysteinate (Fluimucil-antibiotic IT) is proposed, the activity of which is aimed at community-acquired microflora that causes respiratory tract infections, including such typical pathogens as S. pneumoniae , Staphylococcus spp ., Klebsiella spp . and Haemophilus influenzae.

Thiamphenicol is a derivative of chloramphenicol, active against multi-resistant microflora (gram-positive and gram-negative). The safety and tolerability profile of this ABP is much higher compared to chloramphenicol, primarily due to the absence of hematotoxic effects. A. Marchese et al. (2002) [38] studied the in vitro activity of thiamphenicol and 11 other comparator ABPs against 397 ABP-resistant and/or invasive pneumococci and 52 multidrug-resistant MRSA; the bactericidal activity against H. influenzae and the aftereffect of the indicated ABP on S. pneumoniae , H. nfluenzae , S. _ aureus and E. _ coli . Among non-betalactam antibiotics, the maximum effect of thiamphenicol and chloramphenicol on invasive pneumococci was noted along with vancomycin and rifampin. In relation to strains highly resistant to penicillin, the activity of fenicols exceeded that of cefotaxime, ceftriaxone, and imipenem. In terms of effect on MRSA, thiamphenicol and chloramphenicol were second only to glycopeptides. A significant aftereffect of thiamphenicol (from 0.33 to 2.9 hours) was found for all studied pathogens and a powerful bactericidal effect against H. influenzae. The possibility of inhalation use of thiamphenicol is based on the ability of the drug to create high concentrations in the tissues of the respiratory tract. [42] The highest concentration of thiamphenicol in lung tissues compared to plasma was confirmed, which suggests biopharmaceutical advantages of the inhalation route of administration of this ABP.

An additional advantage of the considered inhalation drug is the presence of a mucolytic component - acetylcysteine. The benefits of acetylcysteine in respiratory tract infections are confirmed by data indicating its ability in vitro to effectively suppress the formation of new biofilms, destroy already formed biofilms of varying degrees of maturity, and reduce the viability of bacteria [8]. The formation of biofilms is a hallmark of the causative agents of ventilator-associated pneumonia, cystic fibrosis, chronic obstructive pulmonary disease, bronchiectasis, and bronchitis. Several studies have demonstrated the presence of biofilms in upper respiratory tract infections in 72% of patients with chronic rhinosinusitis [21]. F. Blasi et al. (2016) demonstrated the ability of N-acetylcysteine in vitro to inhibit biofilms of E. coli, K. pneumoniae, E. clo acae , Proteus spp . , P. aeruginosa , P. _ mendocina , A. _ baumannii , Prevotella intermedia [8]. Thus, a long history of the use of thiamphenicol glycinate acetylcysteinate, including pediatric practice, indicates the effectiveness of the drug and a high level of safety [46, 39].

Currently, the use of the inhaled route of administration of antibiotics is a rational choice in the treatment of patients with respiratory tract infections, such as cystic fibrosis and bronchiectasis. The inhaled ABPs considered in this article have a predominantly concentration-dependent effect; their ability to create high concentrations in the respiratory tract during

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inhalation, significantly exceeding the MIC, is an effective factor in overcoming bacterial resistance. Currently, existing recommendations for the treatment of patients with chronic Pseudomonas aeruginosa infection include the appointment of ABP in the inhaled form [41, 44].

A long-term positive experience with the use of thiamphenicol glycinate acetylcysteinate in the treatment of upper respiratory tract infections caused mainly by community-acquired microflora has been demonstrated. When exposed to acetylcysteine in the composition of this drug, not only a significant mucolytic effect is achieved, but the antibacterial effect of this ABP as a whole is also enhanced, which is confirmed by the ability of acetylcysteine to disrupt the formation of biofilms in the respiratory tract.

Thus, the existing arsenal of inhaled ABPs, along with the search for new drugs, can become one of the ways to combat global resistance to ABPs, which are characterized by a fairly high safety and tolerability profile on the part of patients.

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