RÉSUMÉ
Perspectives d'utilisation des antibiotiques inhalés en pédiatrie

La thérapie antibactérienne chez les enfants reste un problème complexe et non résolu de la médecine. Malgré le fait que les antibiotiques forment l’un des groupes de remèdes le plus répandu, chaque année de plus en plus de bactéries deviennent résistantes à ces médicaments. Un petit nombre de nouveaux antibactériens introduits en pratique restent également un moment négatif. Ce problème devient particulièrement actuel lors de maladies respiratoires. Cela est dû au fait que les antibiotiques systémiques pénètrent assez mal dans le tissu pulmonaire et ne créent pas de haute concentrations au site de l’inflammation. Avec l’accroissement du nombre de dosages des antibiotiques, leurs effets toxiques sur l’organisme du patient. Par conséquent, l’utilisation de ces médicaments par voie inhalée est de perspective et réduit le risque de développement.
noting that the inhaled antibiotics are practically not used as monotherapy, but only in combination with antibiotics with systemic action. They cannot be an alternative or a substitute for systemic drugs. The usage of this group of drugs makes it possible to improve the results of treatment of the respiratory diseases in children, especially with chronic inflammatory processes. The inhaled antibiotics can be one more important step in the fight against antibiotic resistance.

**Keywords:** antibacterial agents, inhaled antibiotics, inflammatory respiratory diseases, children, nebulizer therapy.

**INTRODUCTION**

The usage of the antibacterial drugs in pediatrics remains an actual and a complicated problem. The irrational usage of antibiotics leads to the increased resistance of pathogens and ineffectiveness of the already known drugs. According to the World Health Organization (WHO), less than 50% of patients receive adequate and rational antibacterial therapy. An extremely important issue is the development of antibiotic resistance in diseases of the respiratory system. The main problem of antibiotic therapy in these diseases is a poor penetration of intravenous and oral forms of antibiotics into the lungs. The traditional intravenous intake of antibiotics with a wide spectrum of action does not allow achieving their bactericidal concentration in the lungs, which leads to an increase in the resistance of microorganisms and the duration of the antibiotic therapy.

The perspective direction of the antibiotic therapy for respiratory diseases is the usage of inhaled antibiotics (IA). The inhalation route of intake is used for medicinal products of various groups: antibiotics, antifungal, antituberculous, immunosuppressors, vaccines, interferons, and others and has been known for a very long time. The inhaled antibiotics have a long history of usage in the treatment of infections of the lower respiratory tract. They have been used for over 50 years in different age groups of pulmonary patients. The usage of these drugs in patients with cystic fibrosis, chronic carriers of *Pseudomonas aeruginosa*, has been widespread.

Delivery of antibiotics through inhalations has significant benefits in the treatment of lower respiratory tract infections, compared with systemic (oral or intravenous) therapy. Among the main undoubted advantages of using IA are:

- Direct delivery of the antibiotic to the infection site. Usage of modern nebulizers allows to deliver 50-70% of the IA dose actually into the center of infection;
- Achieving high concentrations of antibiotic in the sputum, which is significantly higher than after intravenous intake, that is especially important in the treatment of infections caused by polyresistant strains and preventing the appearance of resistance;
- Reducing the risk of systemic toxic effect of antibiotics, due to the minimal systemic absorption of drugs;
- Possibility of usage in patients of any age;
- Aerosol intake of high concentrations of antibiotics (in particular, aminoglycosides) allows overcoming the antagonistic effect of the purulent sputum on the biological activity of the drug;
- Reduced number of hospitalizations;
- Positive effect on the quality of the patients’ life;
- Possibility of therapy at home.

Using modern nebulizers, the drug can be inhaled when the patient breathes in a relaxed state. So, no specific inhalation maneuver is required.

The effectiveness of the inhalation drug is also determined by many factors that influence the distribution of the drug in the respiratory tract (type of
nebulizer and compressor, size of the particles of the drug, rate of the aerosol delivery, age of the patient, severity of the underlying disease. It is important to note that the inhaled antibiotics are not used as a monotherapy without systemic drugs, because their degree of absorption into the blood is low (2-4%) and not sufficient for systemic effect and treatment of concomitant infections and secondary lesions.

Indications for the inhaled antibiotics usage for treating respiratory tract infections in children have not been defined until today. Further studies are needed to determine the significance of these drugs in infancy patients.

The largest domestic and foreign experience of using IA is accumulated in the treatment of acute and chronic infection in patients with cystic fibrosis, with exacerbation of bronchiectasis and severe pneumonias. In particular, the aerosolized antibiotics reduce the frequency of exacerbations, reduce the density of sputum in the respiratory tract, improve the function of the lungs, improve the quality of life in patients with cystic fibrosis. Therefore, these dosage forms are considered to be standard for a long-term treatment of lung deficiency with cystic fibrosis and are recommended by the American Thoracic Society (ATS) in the Clinical Pulmonary Guidelines. According to a large German study conducted by S. Ehrmann et al., 99% of physicians from resuscitation departments use an inhalation method of drugs intake, among them 43% use nebulizers (55% jet, 44% ultrasound, 14% nebulizers with a vibrating plate). 80% of the respondents use inhaled colistin, and 30% conduct inhaled antibiotic therapy at least once every 2 months.

Unfortunately, today, a small amount of antibiotics can be used by inhaling, and solutions for parenteral use have high osmolarity, acidity and contain preservatives, in particular phenols, that irritate the respiratory tract (cough, wheezing, chest pain). At present, special inhalation forms for the patients treatment exist only for colistin, tobramycin and aztreonam. Also, in recent years, the inhaled fluoroquinolones, amikacin, cephalosporins, phosphomycin, vancomycin and others began to be used in some countries. Perspective is the usage of the inhaled antibiotics combinations: phosphomycin/tobramycin, colistin/tobramycin.

**Colistin**

The antibiotic colistin (colistimethate sodium) belongs to the group of polymyxins. It was first detected in the middle of the 20th century, as a product of the bacteria *Bacillus colistinus* fermentation. Due to their cationic nature, polymyxin antibiotics are capable of damaging cell membranes of bacteria. Colistin is a bactericidal antibiotic and active against Gram-negative bacteria, including *P. aeruginosa*. Colistin is included into the clinical practice for the treatment of carbapenem resistant gram-negative bacteria. The inhaled colistin (50-75 mg, 2-3 times a day) is used for the long-term treatment of the cystic fibrosis infectious complications, both in hospital and in outpatients. In addition, colistin is used for the treatment of ventilated and associated pneumonias and severe infectious diseases of lungs caused by the Gram-negative flora, especially the *Pseudomonas aeruginosa*.

There are no specific requirements for inhalation devices of colistimethate sodium, so the drug can be taken with ultrasonic or jet nebulizers or devices with a pulse flap (mesh devices).

In 2011 a randomized, double-blind, phase III study on safety of a new form of colistimethate sodium in the form of powder that was used through the inhaler (Colobreathe, Forest Laboratories, UK) was completed and, after the drug registration by the European Medicines Agency in 2012, it began to be applied in Europe.

Colistin is the most complicated antibiotic for inhalation intake, because it is a pro-drug (colistimethate), which should be hydrolyzed for its activation. The latter process is too slow and is accompanied by a release of formaldehyde and bisulfites. Colistin is a mixture of cyclic cationic peptides, which can damage not only microbial cells, but also respiratory tract and pulmonary cells.

Patients generally tolerate colistimethate sodium good. The most important side effect is bronchospasm. Wheezing with a temporary decrease of forced expiratory volume (FEV 1) was registered in 17.7% of patients. Especially often, bronchial spasm is noted in patients with a bronchial asthma or hyperactivity of the respiratory tract. This side effect can be relieved by intake of short-acting agonists of beta2 adrenergic receptors before treatment.

Colistin is not approved for usage in the United States, because of a patient’s death after inhalation of the drug, by development of acute respiratory distress syndrome in a patient with a cystic fibrosis. After mixing colistin with sterile water, it turns into a biologically active form with the formation of active components of colistin A (polymyxin E1) and colistin B (polymyxin E2). In this case, the polymyxin E1 is toxic to the lung tissue. Mixing of colistin in an aqueous solution and storing it for more than 24 hours lead to an increase in the concentration of polymyxin E1 and an elevated toxicity potential. Despite this, colistin is used in centers of cystic fibrosis in the
United States for the treatment of chronic infection of *P. aeruginosa*.

**Aminoglycoside antibiotics**

Aminoglycosides are among the most effective and safe antibiotics for inhalation intake. These antibacterial drugs have several characteristics, which make them attractive options for the delivery of aerosol. First, their antibacterial effectiveness depends on the concentration, that is, the highest doses that can be used for intravenous intake result in low permeability into the lungs. Finally, aminoglycosides often maintain activity against the Gram-negative microorganisms, which are common pathogens for severe chronic infections of the respiratory tract. For these reasons, the main part of the literature concerning the delivery of antimicrobial substance with an inhalation method is concentrated on aminoglycosides.

**Tobramycin**

The aminoglycoside tobramycin is an antibacterial drug that inhibits the synthesis of protein, irreversibly binding to subunits of 30S bacterial ribosome.

Tobramycin, intended for intravenous intake, before the appearance of the inhalation form, was diluted with a physiological solution and used in intubations through a nebulizer. A specific formula of tobramycin for inhalation was developed in the 1980s. In studies published in the early 90’s, the effectiveness of this drug in chronic lung pathology, in particular for the elimination of *P. aeruginosa* in patients with cystic fibrosis, was established.

This antibacterial agent is effective against most Gram-negative microorganisms, but usually it does not exhibit significant effects against the strains of *Burkholderia cepacia* complex and *S. maltophilia*, although it affects the strains of *Enterococcus* and *Staphylococcus*. The bactericidal activity against most aerobic Gram-negative microorganisms, including against *P. aeruginosa*, depends on the concentration of the drug.

During the intravenous intake of tobramycin, its penetration into the lungs is small and constitutes 32%, the concentration in the sputum is less than 10% of the minimum inhibitory concentration (MIC), and the risk of toxic effects is quite high.

Since the bactericidal effect can be reliable only in concentrations containing 25-fold minimal inhibitory concentration, for achieving a concentration that inhibits *P. aeruginosa* in the respiratory tract, high doses of the drug are required that can only be achieved with inhalation intake.

Nowadays, inhalational tobramycin (IT) is one of the most common antibacterial drugs used to eliminate blue-purulent infection in patients with cystic fibrosis. This is due to many factors. In particular, it is known that the penetration through the wall of the bacterial cell is an energy-dependent process and it worsens in anaerobic conditions, therefore the low partial pressure of oxygen in purulent cork in cystic fibrosis (CF) can limit the effectiveness of aminoglycosides. In a solution of tobramycin for intubations, the drug particles are charged positively, and it is believed that with CF tobramycin is bound in the respiratory tracts to negatively charged DNA strands and membranes of *P. aeruginosa*. The choice of tobramycin for inhaled therapy is due to its high anti-pseudomonal activity, which exceeds such activity for gentamycin, with a low level of initial resistance of *P. aeruginosa* in patients with CF, a long-term aftereffect (suppression of a bacterial growth in vivo up to 10-12 hours after single usage), a chemical stability in different conditions, a lower toxicity than other aminoglycosides have, and acceptable flavoring properties.

When the inhalational tobramycin is used, the drug mainly stays in the respiratory tract, and it doesn’t penetrate through the respiratory epithelium. The bioavailability of tobramycin depends on the inhalation technique and on the state of the respiratory tract. The tobramycin is excreted mainly with sputum, a small part – with a glomerular filtration.

Against the background of an increase in frequency of the inhalational tobramycin in patients with CF in the last decade, there has been a progressive increase in the minimum inhibitory concentration (MIC) of this antibiotic for *P. aeruginosa*. The widespread CF causative agents, such as *Stenotrophomonas maltophilia* and *Burkholderia cepacia*, become resistant to tobramycin.

The use of the inhalational tobramycin in patients with CF is justified from the point of view of the evidence-based medicine (level of evidence A) and is recommended by national and international guidelines for treatment of pulmonary infection caused by *P. aeruginosa*. Currently, indications for inhaled intake of tobramycin in patients with bronchiectasis and nosocomial pneumonia are being expanded.

High efficiency and safety of the inhalational tobramycin usage in children – chronic carriers of a tracheotomy tube are shown.

Currently, in the world 3 drugs of tobramycin especially designed for intubations are widely used: tobramycin – a solution for intubations «Bramitob»,...
Amikacin

Amikacin is a semi-synthetic antibiotic from the group of aminoglycosides, which has a wide range of antibacterial effect. It is the most active against gram-negative microorganisms, including strains resistant to gentamicin. For the aerosol therapy the amikacin is used twice a day – 100 mg (2 ml), diluted in 2-3 ml of a physiological solution.

The inhaled intake of amikacin is a perspective addition to the standard therapy for pulmonary non-tuberculous mycobacterial (NTM) infections. The use of the aerosolized amikacin with a standard oral antibiotic therapy for pulmonary NTM infection can improve the effectiveness of treatment without increasing the risk of systemic toxicity.

It has been established that in comparison with the systematic use of amikacin, the aerosolized form of the drug has a lower amount of toxic side effects. So, according to data of K.N. Olivier et al (2013), only two patients (10%) stopped treatment due to hearing loss, and one of them could renew treatment at a lower dose without additional ototoxicity. The dysphonia was a relatively frequent symptom, but it could have been reduced by adjusting the dose practically in all patients. Side effects of the therapy also included sore throat (transient) and oral candidiasis.

Very perspective is usage of the inhalation form of liposomal amikacin. Thus, in an open long-term research, which studied the usage of the „Arikace” drug during cystic fibrosis at a dose of 560 mg per day by repeated courses of 28 days with intervals of 56 days, its apparent clinical effect was proved in the form of the improved pulmonary function and decreased bacterial insemination, which were stored even in the non-inhalation period.

Aztreonam

Aztreonam is a synthetic antibiotic of the monobactam range (monocyclic β-lactam) that is active against the Gram-positive aerobic microorganisms, with activity against P. aeruginosa and other Gram-negative pathogens, and resistant to most β-lactamases.

Aztreonam lysine is a new medical form that was certified in 2010 for aerosol treatment of infection caused by P. aeruginosa in patients with CF. In particular, the drug „AZLI” includes substances that are safe for inhalations, while Aztreonam arginine, which is used for intravenous intake, with a prolonged inhalational therapy, can cause inflammation in the respiratory tract in patients with CF.

Aztreonam lysine is intaken through the eFlow electronic nebulizer, providing deposition in the peripheral regions of the lungs after 2 minutes of inhalation. Clinically significant synergy of the inhaled aztreonam with aminoglycosides against P. aeruginosa has been proved in a double-blind placebo-controlled research, patients with CF over 12 years of age, in a stable state, independently took „AZLI” once a day with an increased dose from 75 to 150 and 225 mg, or
arthro- and chondrotoxicity38,26. These drugs are per-
is limited due to possible side effects, in particular
the lesion15,16.

In a 18-month research, the confirmation of safety
and efficacy of the drug in pediatric patients has been
confirmed37. As a rule, the inhaled aztreonam
is well tolerated15. The most commonly reported side
reactions include cough (32-35%), headache (6-11%),
bronchospasm (6-10%), nasal congestion (7-10%) and
rhinorrhea (7%)15,35. There are reports about patients
with the development of bronchospasm because of
the usage of this drug, so, it is necessary to take into
account the results of the usage of a controlled trial
dose under the supervision of a doctor, especially in
patients with severe pulmonary disease15.

**Fluoroquinolones**

Fluoroquinolones are important antibacterial
agents in the treatment of respiratory diseases, tak-
ing into account their high efficiency to a relatively
wide range of microorganisms, a special mechanism
of action and a good permeability into the pulmonary
tissue38. The usage of this group of drugs in pediatric
is limited due to possible side effects, in particular
arthro- and chondrotoxicity38,26. These drugs are per-
mitted to be used for the eradication of P. aeruginosa
in children with cystic fibrosis. That's why, in case
of cystic fibrosis and other severe chronic processes
in the lungs caused by Pseudomonas aeruginosa, the
usage of the inhaled forms of fluoroquinolones in
children is very promising, taking into account the
lower number of side effects and the possibility of us-
ing higher concentrations of the drug at the center of
the lesion15,16.

**Ciprofloxacin**

Ciprofloxacin is fluoroquinolone, which inhibits
the synthesis of bacterial DNA, blocking DNA-gyrase
and topoisomerase IV, which are required for DNA
replication38. The drug is widely used in oral form in
patients with CF and other diseases.

Ciprofloxacin is used for inhalations in the form
of dry powder39 and a liposomal form15,40. Taking into
account its adequate tolerability and a minimal sys-
temic action, this drug is used to treat patients with
chronic inflammatory diseases of the lungs caused by
P. aeruginosai14,19.

The liposomal form of the inhaled ciprofloxa-
cin has potential benefits, including controlled and
long-term effect release of the drug at the site of
action, protection against drug degradation, systemic
exposure and cellular uptake15,41.

The intake of ciprofloxacin in the form of an
aerosol (early known as BAY Q3939), with small par-
ticles or enclosed in liposomes to the guinea pigs in-
fected with Legionella pneumophila, or mice infected
with Francisella tularensis, prevented the death of ani-
malsthis indicates the delivery of aerosol into the
lower respiratory tract44. After the successful comple-
tions of Phase I and II of the studies on safety and
efficacy of the inhaled liposomal ciprofloxacin, the
possibility of the drug intake once a day was con-
firmed14,19. The most common side effects reported
while using the inhaled ciprofloxacin in powder form
are bitter taste in the mouth (14-94%), bronchospasm
(50-67%), headache (17-33%) and cough (3-17%)35,39,42.

**Levofloxicin**

The inhaled levofloxicin has been recently in-
troduced and is currently approved to be used in
Europe in patients with CF and chronic P. aeruginosai
infection15. The medical form of levofloxicin for aero-
sol intake was registered under the name „Aeroquins”
and specially prepared for intake via a nebulizer
eFlow4. Duration of inhalation of the drug does not
exceed 4-6 minutes19. The main way of eliminating
the drug from the lungs is systemic absorption44.

The conducted researches that compared differ-
ent doses of the inhaled levofloxicin (120, 240 mg a
day, 240 mg twice a day) with placebo in 151 patients
demonstrated a dose-dependent improvement in lung
function and a significant reduction exacerbations
frequency within 28 days15. The most commonly re-
ported side effects during the levofloxicin usage in-
clude cough, taste disturbance, general weakness43,44.

**Fosfomicin**

Fosfomicinis a bactericidal, antibacterial agent
of a wide spectrum of activity that is capable of in-
hibiting the initial stage of the peptidoglycan forma-
tion of the cell wall of bacteria. The drug also has
anti-adhesive properties that prevent bacteria sticking
to the epithelium (in particular, the urogenital tract).

The inhaled fosfomicin has an antimicrobial ac-
tivity against both gram-negative and gram-positive
microorganisms. The remedy is recommended to be
combined with other antibiotics to avoid the rapid
development of resistance to it14,27. A combination of
fosfomicin and tobramycint in a ratio of 4:1 was es-
pecially developed by Gilead Sciences (USA) for usa-
geviathe eFlow nebulizer to control P. aeruginosai14,19.
However, there is a high chance for some patients to
experience side effects such as local reactions, irrita-
tion of the respiratory tract mucous membrane, voice
obstruction, bronchial obstruction, bronchial hyper-responsiveness.

In recent years, cephalosporins, in particular ceftazidime, are more often used for inhalations. The drug is used most for the treatment of ventilatory-associated pneumonia and cystic fibrosis (in the presence of infection with Burkholderia cepacia). An injectable solution of ceftazidime is used, diluted with a physiological solution and injected into the respiratory tract using a jet spray. Nevertheless, the usage of the inhaled beta-lactam antibiotics is not entirely appropriate, since their antibacterial activity depends on the time of action that requires frequent inhalations. For example, for effective inhalation therapy with ceftazidime, inhalations are required every 3 hours (8 times a day), which is difficult to implement in practice.

**General side effects and disadvantages of the inhaled antibiotics usage.**

According to Quon B.S. et al (2014), known or potential adverse effects of the inhaled antibiotics are divided into three main categories: local, systemic, and emergence of antibiotic-resistant organisms.

Local effects include transient bronchial obstruction due to high osmolality and the presence of conservants in some solutions. Modified taste, dysphonia and throat irritation are also common side effects associated with the inhaled antibiotics. To avoid the development of these side effects, only special inhalational forms should be used and pre-inhalation of the bronchodilator should be made. The osmolality of the solution for inhalations should be 150-1200 mOsm/kg, sodium content 77-154 mEq/L, neutral pH, the content of chlorides should be at least 30 mEq for better penetration of the antibiotic into the cells and in order to avoid the development of cough and bronchospasm.

Modern knowledge about the systemic effects of the inhaled antibiotics remains limited, especially for forms of antibiotics specifically designed for usage in the respiratory tract. Usually systemic side effects are special for different groups of antibiotics and have been discussed above; however, it is worth noting some circumstances that increase systemic toxic effects of drugs. In particular, the systemic effect increases with abnormality of kidney and liver function, which reduces the efficiency of the antibiotic utilizing that has fallen into the blood stream. The development of systemic side effects may be associated with the absorption of antibiotics into the blood, which is significantly increased in pneumonia compared with healthy lungs.

The most common clinical problem with the use of the inhaled antibiotics is the emergence of resistant pathogens. This is especially actual for long-term aeration of *P. aeruginosa, Burkholderia cepacia*, Stenotrophomonas maltophilia and Achromobacter xylosoxidans in patients with cystic fibrosis.

Also, the disadvantages of the infusion antibiotic therapy associated with the drugs intake via the nebulizer are important:

1) **Duration of the procedure.** For patients, who use inhaled antibiotics, nebulizer therapy can take up to 2 hours a day. This time is required to prepare a nebulizer, inhale the drug and clean the nebulizer after its usage. For colistin and other drugs, it is necessary up to 10 minutes to dilute the appropriate dose in water for injections in order to produce the isotonic solution.

2) **The usage of nebulizers includes a risk of infection** if the device is not properly cleaned.

3) **Nebulizers are cumbersome and less portable than other devices.**

4) **Nebulizers require regular maintenance and replacement of components.**

In addition, the cost of the inhaled antibacterial drugs is not less important for patients as compared to the systemic drugs and the cost of a nebulizer with its components.

**Conclusions**

The usage of the inhaled antibiotics in children is a promising direction of the respiratory diseases treatment, taking into account the ability to use locally high concentrations of the drug with minimal systemic complications. These drugs have the most proven efficacy when treating chronic infections with *Pseudomonas aeruginosa* and other pathogens in patients with cystic fibrosis, where their usage is considered the most appropriate today. The inhaled antibiotics are practically not used as a monotherapy, but only in combination with systemic antibiotics. They cannot be an alternative or a substitute for systemic drugs. However, in severe pulmonary diseases, where the effectiveness of the traditional antibiotic therapy has bad results, the inhaled antibiotics are means of choice. That’s why the development of new inhalational forms of antibacterial drugs, the improvement of already existing dosage forms and ways of drugs intake into the respiratory tract is a perspective direction of modern pediatric pulmonology and medicine in general.

**Compliance with Ethics Requirements:**

"The authors declare no conflict of interest regarding this article."

"The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law."
REFERENCES

1. Kuzovlev AN, Moroz VV, Golubev AM. Inhaled antibiotics in treatment of nosocomial pneumonia. Anestesiologiya i reanimatologiya. 2015; 60 (4): 55-61[in Russian].

2. Izquierdo M, Gomez-Alamillo C, Ortiz F. Acute renal failure associated with use of inhaled tobramycin for treatment of chronic airway colonization with Pseudomonas aeruginosa. Clin. Nephrol. 2006; 66: 464-7.

3. Holloway KA. Promoting the rational use of antibiotics. Regional Health Forum – Volume 15, Number 1, 2011. 122-130.

4. Redko OK, Zahorodnii MF, Ponor OB. Antimicrobial resistance and the benefits of protected cephalosporins III generation in the treatment of children. Khimichy ta antybiotyky. 2011;205). Available from: http://www.mif-ua.com/archive/article/24853[in Ukrainian].

5. Sievert D, Ricks P, Edwards J. Antimicrobial-resistant pathogens associated with healthcare-associated infections: summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2009-2010. Infect Control Hosp. Epidemiol. 2013; 34 (1): 1-14.

6. Tiddens HAWM, Bos AC, Mouton JW. Inhaled antibiotics: dry or wet? Eur Respir J. 2014; 44: 1308-1318.

7. Wenzler E, Fraidenburg DR, Scardina T, Danziger LH. Inhaled antibiotics for Gram-negative respiratory infections Clin Microbiol Rev. 2006;19(3): 581-632.

8. Polonovnik SG, Kuzovlev AN, Ilyichev AN. An experience of administration of inhaled tobramycin in severe nosocomial pneumonia. Russian Pulmonology. 2011;12(3):109-112[in Russian].

9. Ioannidou E, Siempos I, Falagas M. Administration of antimicrobics via the respiratory tract for the treatment of patients with nosocomial pneumonia: a meta-analysis. J Antimicrob Chemother. 2007; 60 (6): 1216–26.

10. Chikina SYu. New inhalation form of tobramycin for chronic Pseudomonas aeruginosa infection in patients with cystic fibrosis. Lachebnoe delo. 2011; 4:105-112 [in Russian].

11. Pai VB, Nahata MC. Efficacy and safety of aerosolized tobramycin in cystic fibrosis. Pediatr Pulmonol. 2001;32:314–327.

12. Palmer LB. Aerosolized antibiotics in the intensive care unit. Clin Chest Med. 2011; 32 (3): 599-74.

13. Krasovskiy EA, Amelina EL, Kondrat’eva EI, Voronkova AVet. Drug treatment of cystic fibrosis patients in russian federation according to the national register, 2014. Russian Pulmonology. 2016;26(5):539-555[in Russian].

14. Kashirskaya NYu, Kapranov NI. Place inhalation forms of aerosolized tobramycin in the treatment of patients with cystic fibrosis and Pseudomonas aeruginosa infection carriage. Venstnik anestezioligii i teainmatologii. 2012;9(2):064-068 [in Russian].

15. Amelina EL, Krasovsky SA. Tobramycin inhalations in therapy of chronic infection Pseudomonas aeruginosa in cystic fibrosis. Russian Pulmonology. 2013;4(4):109-114[in Russian].

16. Chuchalin A, Csizer E, Gyurovics K, et al. A formulation of aerosolized tobramycin (Bramitob) in the treatment of patients with cystic fibrosis and Pseudomonas aeruginosa infection: a double-blind, placebo-controlled, multicenter study. Pulm. Drugs. 2007;9(1):21-31.

17. Geller DE, Weers J, Heuerding S. Development of an inhaled dry powder formulation of tobramycin using PulmoSphere technology. J Aerosol Med Pulm Drug Deliv. 2011; 24 (4): 175-182.

18. Murphy TD, Anbar RD, Lester LA, et al. Treatment with tobramycin solution for inhalation reduces hospitalizations in young CF subjects with mild lung disease. Pediatr Pulmonol. 2004;38:314–320.

19. Simonova O, Chistyakova V, Lazareva A, Katosova L. Inhalation antibiotics are essential for the control of infection in children with cystic fibrosis. Current pediatrics. 2011;10(3):119-123 [in Russian].

20. Sukhan VS. Nebulizer therapy in clinical practice: methodological recommendations. Uzhhorod, 2010 [in Ukrainian].

21. Pelouquin CA, Berning SE, Nitta AT, et al. Aminoglycoside toxicity: daily versus thrice-weekly dosing for treatment of mycobacterial diseases. Clin Infect Dis 2004;38:1538-1544.

22. McCoy KS, Quittner AL, Oermann CM, Gibson RL, Retsch-Bogart GZ. Tobramycin solution for inhalation reduces hospitalization of young CF subjects with mild lung disease. Pediatr Pulmonol. 2011;46:358-362.

23. Keller M et al. High efficiency pulmonary drug delivery of aerosolized tobramycin in chronic respiratory diseases. Expert Rev Respir. Med. 2011; 5(5):609-622.

24. Ballmann M, Smyth A, Geller DE. Therapeutic approaches to chronic cystic fibrosis respiratory infections with available, emerging aerosolized antibiotics. Respir Med. 2011;105(Suppl 2):S2–S8.

25. Le J, Ashley ED, Neuhauser MM, et al. Consensus summary of aerosolized antimicrobial agents: application of guideline criteria. Insights from the Society of Infectious Diseases Pharmacists. Pharmacotherapy. 2010; 30 (6): 562–84.

26. Hodson ME, Gallagher CG, Govan JR. A randomised clinical trial of nebulised tobramycin or colistin in cystic fibrosis. Eur Respir J 2002, 20, 658–664.

27. Davis KK, Kao PN, Jacobs SS, Ruoss SJ. Aerosolized amikacin for treatment of pulmonary Mycobacterium avium infections: an observational case series. BMC Pulmonary Medicine.2007;7:2.

28. Geller DE, Pitlick WH, Nardella PA et al. Pharmacokinetics and bioavailability of aerosolized tobramycin in cystic fibrosis. Chest 2002; 122: 219–226.

29. Olivier KN, Shaw PA, Glaser TS, et al. Inhaled amikacin for treatment of refractory pulmonary nontuberculous mycobacterial disease. Ann Am Thorac Soc. 2014;11(1):30-5.

30. Kapranov NI, Pharmacotherapy of cystic fibrosis: inhaled antibiotics. Meditsinskiy sovet. 2013;11:62-69 [in Russian].

31. Principi N, Esposito S. Appropriate use of fluorourquinolones in children. International Journal of Antimicrobial Agents. 2015;6:1-6.

32. Petrova SI, Panyutina YaV, Peshekhonova YuV, Tsvetkov EA, Galustyan AN, Kondrashova EM. Use of inhaled tobramycin in children with chronic airways diseases and Pseudomonas aeruginosa infection carriage. Vestnik anestezioligii i reanimatologii – BOYARCHUK et al. 2011;2(05). Available from: http:/ /www.mif-ua.com/Reference/Media/24853/in Russian].

33. Sukhan VS. Nebulizer therapy in clinical practice: methodological recommendations. Uzhhorod, 2010 [in Ukrainian].

34. Peloquin CA, Berning SE, Nitta AT, et al. Aminoglycoside toxicity: daily versus thrice-weekly dosing for treatment of mycobacterial diseases. Clin Infect Dis 2004;38:1538-1544.

35. McCoy KS, Quittner AL, Oermann CM, Gibson RL, Retsch-Bogart GZ. Tobramycin solution for inhalation reduces hospitalization of young CF subjects with mild lung disease. Pediatr Pulmonol. 2004;38:314–320.

36. Simonova O, Chistyakova V, Lazareva A, Katosova L. Inhalation antibiotics are essential for the control of infection in children with cystic fibrosis. Current pediatrics. 2011;10(3):119-123 [in Russian].

37. Sukhan VS. Nebulizer therapy in clinical practice: methodological recommendations. Uzhhorod, 2010 [in Ukrainian].

38. Pelouquin CA, Berning SE, Nitta AT, et al. Aminoglycoside toxicity: daily versus thrice-weekly dosing for treatment of mycobacterial diseases. Clin Infect Dis 2004;38:1538-1544.
030 // Congress of the International Society for Aerosols in Medicine. Baltimore, 2003.

37. Oermann CM, Retsch-Bogart GZ, Quittner AL, et al. An 18-month study of the safety and efficacy of repeated courses of inhaled aztreonam lysine in cystic fibrosis. Pediatr Pulmonol. 2010;45:1121-1134.

38. Choi S-H, Kim EY, Kim Y-J. Systemic use of fluoroquinolone in children. Korean J Pediatr. 2013; 56(5): 196–201.

39. Stass H, Nagelschmitz J, Willmann S, Delesen H, Gupta A, Baumann S. Inhalation of a dry powder ciprofloxacin formulation in healthy subjects: A phase I study. Clin Drug Investig. 2013;33:419–427.

40. Bruinenberg P, Blanchard JD, Cipolla DC, Dayton F, Mudumba S, Gonda I. Inhaled liposomal ciprofloxacin: once a day management of respiratory infections. Respir Drug Deliv. 2010;1:73–81.

41. Haworth C, Wanner A, Foehlich J, et al. Inhaled liposomal ciprofloxacin in patients with bronchiectasis and chronic pseudomonas aeruginosa infection: Results from two parallel phase III trials (ORBIT-3 and -4). Am J Respir Crit Care Med. 2017

42. Dorkin HL, Staab D, Operschall E, Alder J, Criollo M. Ciprofloxacin DPI: A randomised, placebo-controlled, phase IIIb efficacy and safety study on cystic fibrosis. BMJ Open Respir Res. 2015;2:e000100.

43. Flume PA, VanDevanter DR, Morgan EE, et al. A phase 3, multi-center, multinational, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of levofloxacin inhalation solution (APT-1026) in stable cystic fibrosis patients. J Cyst Fibros. 2016;15:495–502.

44. Geller DE, Flume PA, Staab D, Fischer R, Loutit JS, Conrad DJ. Levofloxacin inhalation solution (MP-376) in patients with cystic fibrosis with Pseudomonas aeruginosa. Am J Respir Crit Care Med. 2011;183:1510–1516.

45. Lu Q, Yang J, Liu Z, et al. Nebulized ceftazidime and amikacin in ventilator associated pneumonia caused by Pseudomonas aeruginosa. Am J Respir Crit Care Med. 2011;184(1):106-115.

46. Quon BS, Goss CH, Ramsey BW. Inhaled antibiotics for lower airway infections. Ann Am Thorac Soc. 2014; 11(3): 425–434.

47. Izquierdo M, Gomez-Alamillo C, Ortiz F. Acute renal failure associated with use of inhaled tobramycin for treatment of chronic airway colonization with Pseudomonas aeruginosa. Clin Nephrol. 2006; 66: 464–7.

48. Patatanian L. Inhaled tobramycin-associated hearing loss in an adolescent with renal failure. Pediatr Infect Dis J. 2006; 25 (3): 276–8.

49. Sawicki GS, Tiddens H. Managing treatment complexity in cystic fibrosis: challenges and opportunities. Pediatr Pulmonol 2012; 47: 523–533.

50. Blau H, Mussaffi H, Mei Zahav M, et al. Microbial contamination of nebulizers in the home treatment of cystic fibrosis. Child Care Health Dev 2007; 33: 491–5.