Nosocomial pneumonia — is a disease associated with the formation of new focal and infiltrative changes on the chest X-ray 48 hrs after the hospitalization along with the clinical data confirming their infectious nature (fever, purulent sputum or purulent discharge from the tracheobronchial tree, leukocytosis, etc.), excluding infections which were incubated on the admission [1].

Nosocomial pneumonia — is the most prevalent intensive care unit infection. The high prevalence of NP is due to the widespread and irrational use of antibiotics and artificial pulmonary ventilation. The Russian National data confirm that NP incidence in surgical patients is 6% after elective surgery and 15% after emergency surgery. The incidence of ventilator-associated pneumonia is 22% after elective surgery in ventilation longer than 2 days and 34.5% after emergency abdominal surgery; up to 55% in acute respiratory distress syndrome. Every day in intensive care unit stay increases the risk of NP by 3%. Nosocomial pneumonia significantly deteriorates the course of any disease, increase the duration of intensive care unit stay by 4.3—6.1 days and mortality. The attributable mortality of NP is between 5.8 to 27% [2—5].

The pathogenesis of NP in critically ill patients is based on an imbalance between the lung protective mechanisms and microbial aggression. The lung can be infected either exogenously or endogenously. Aspiration of pharyn-
gastric, esophageal and stomach contents is the leading factor in NP pathogenesis. The risk of aspiration significantly increases in conscious impairment, dysphagia, deterioration of pharyngeal reflexes and intestinal peristalsis, in intubated patients. Tracheal intubation makes a way for bacterial migration into lungs. Bacterial biofilms formation occurs inside the tracheal tubes. Microbes in the biofilms are protected against antibiotics and immune system. Translocation of opportunistic microbes from the intestines is the other important pathogenetic factor of NP. Exogenous acquisition of NP may occur from the air, medical gases, respiratory devices, microbiota of medical personnel and other patients etc. [6—8]

The proved methods of NP prophylaxis in the intensive care unit include the 300 elevation of head, an early removal of nasogastric tubes, a continuous subglottic aspiration and a regular oral cleaning with watery chlorhexidine [8].

The key etiological agents of NP are associations of multiresistant gram-negative (Pseudomonas aeruginosa, Acinetobacter spp., Klebsiella pneumonia) and gram-positive (Staphylococcus aureus) strains. The spectrum of NP agents differs among the intensive care units. Associations of 3—4 multiresistant strains of Pseudomonas aeruginosa (70—80%), Acinetobacter baumanii/calcoaceticus (70—90%), Klebsilella pneumonia (30—40%), Proteus mirabilis (20—25%) were detected in our investigation; gram-positive strains were detected in 10—15% of patients (Staphylococcus aureus MRSA, Enterococcus faecalis, Enterococcus faecium) [9—13].

Rational antibiotic therapy is the background of NP treatment. Intravenous carbapenems, cephalosporins III—IV generations, protected anti-pseudomonal penicillines, aminoglycosides, fluoroquinolones, glycopeptides and their combinations are recommended for NP treatment [9]. Early start of antibiotics improves outcomes, but the mortality and microbial resistance still remain extremely high. The problem of microbial resistance to the majority of antibiotics is of great significance. Pseudomonas aeruginosa, Acinetobacter spp., Burkholderia spp., Stenotrophomonas spp., have a natural property to form biolayers, which protect them against the immune system and antibiotics. There are currently no perspectives of producing new classes of antibiotics [8—9].

In view of the abovementioned special regimens of antibiotic therapy are recommended: increase of doses, continuous infusions, etc. Randomized controlled trial shows that continuous infusion of piperacillin/tazobactam and carbapenems decreases the mortality in NP. The main pitfall of intravenously administered antibiotics is their bad penetration into the lungs, which leads to the sputum concentrations lower than bactericidal. Increasing daily doses of antibiotics is related to a risk of selection of multiresistant strains, side-effects and superinfection. Therefore inhalaed antibiotics (IA) as an adjunct to systemic ones present a good treatment modality [7, 9, 14—15].

**Inhaled antibiotics**

The inhaled root has long been used to administer various medicines: antibiotics, antifungals, antimycobacterials, immune suppressors, insulin, vaccines, nitrous oxide, interferones, furosemide, in genotherapy of some diseases. Ehrmann S. et al. showed that 99% of German doctors use some inhaled preparations, 43% of them use nebulizers (55% — jet, 44% — ultrasound, 14% — mesh nebulizers). Eighty percent of them use inhaled colistin in their daily practice, and 30% use inhaled antibiotics minimum 2 times a year [16].

### Inhaled antibiotics in modern medicine [22]

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Area of implementation</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AMINOGLYCOSIDES</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amikacin</td>
<td>Exacerbation of bronchoectatic disease, mycobacterial infections.</td>
<td>500 mg BID</td>
</tr>
<tr>
<td>Gentamycin</td>
<td>Exacerbation of bronchoectatic disease.</td>
<td>80 mg BID</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>Cystic fibrosis — prophylaxis and treatment of exacerbations.</td>
<td>300 mg BID</td>
</tr>
<tr>
<td></td>
<td>Treatment of nosocomial pneumonia.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Continuous therapy of bronchoectatic disease.</td>
<td>80 mg BID</td>
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<tr>
<td><strong>BETA-LACTAMES</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aztreonam</td>
<td>Continuous therapy in cystic fibrosis.</td>
<td>75 mg TID for 28 days</td>
</tr>
<tr>
<td>Cefotaxim, caftazidim</td>
<td><strong>Treatment of nosocomial pneumonia.</strong></td>
<td>250 mg BID — 500 mg 4/day</td>
</tr>
<tr>
<td></td>
<td>Continuous therapy of bronchoectatic disease.</td>
<td></td>
</tr>
<tr>
<td><strong>ANTIFUNGALS</strong></td>
<td></td>
<td></td>
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<tr>
<td>Amfotericin B</td>
<td>Prophylaxis of invasive aspergillosis in oncohematology and in solid organ transplantation.</td>
<td>20—25 mg/day</td>
</tr>
<tr>
<td>Amfotericin B lipid complex</td>
<td>Prophylaxis of invasive aspergillosis in oncohematology.</td>
<td>50 mg/day</td>
</tr>
<tr>
<td>Amfotericin B</td>
<td>Prophylaxis of invasive aspergillosis in oncohematology.</td>
<td>For ventilated patients — 50 mg/day</td>
</tr>
<tr>
<td>Liposomal</td>
<td>12.5 mg</td>
<td>For ventilated patients — 100 mg/day</td>
</tr>
<tr>
<td></td>
<td>2 times/week for 2 days</td>
<td></td>
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<tr>
<td><strong>OTHERS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colistin</td>
<td>Cystic fibrosis — prophylaxis and treatment of exacerbations.</td>
<td>1—2 million IU BID</td>
</tr>
<tr>
<td></td>
<td>Treatment of nosocomial pneumonia.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Continuous therapy of bronchoectatic disease.</td>
<td></td>
</tr>
<tr>
<td>Pentamidin</td>
<td>Prophylaxis of Pneumocystis spp. pneumonia in HIV patients</td>
<td>300 mg/month</td>
</tr>
</tbody>
</table>

**Inhaled antibiotics in modern medicine [22]**
Inhaled colistin, tobramycin, cephalosporins, aminoglycoside resistant strains of Pseudomonas aeruginosa. Moreover, the increase of the prevalence of colistin and currently no evident data to support IA use in cystic fibrosis (CF) patients caused by Pseudomonas aeruginosa and Acinetobacter baumannii [49]. Korbila I. et al. showed more rapid NP resolution in combination of inhaled and intravenous forms of colistin [23]. Arnold H. et al. in the retrospective trial showed a higher survival in NP patients treated with IT [31]. All the abovementioned trials showed a low threshold of resistance emergence and low incidence of side effects in IA use.

Our data on the inhaled tobramycin use in septic patients with NP proved its efficacy and safety: decrease of systemic inflammation and acute respiratory insufficiency signs 2.3±1.2 after the treatment onset. Eradication of microbes in sputum was detected in 28% of patients, in other patients a decrease of microbial titer to 10^{+4} CFU/ml was detected. Deescalation of antibiotic therapy was possible in 20% of patients treated with IT. It is noteworthy that 20% of patients were in vitro resistant to tobramycin, but it was clinically effective, probably due to a local superconcentration. Treatment with IT was associated with an increase of sensitivity of microbes to antibiotics they were prior resistant to (40% of patients). This is probably due to IT effects on sputum. Positive chest X-ray dynamics was detected in 60% of patients 9.0±2.5 days after the treatment onset. The treatment with IT made it possible to wean 30% of patients on the day 5.2±1.7. Hearing loss and tinnitus was detected only in 2 patients in our study. There were no cases of bronchospasm or kidney dysfunction in our study, which is in accordance with the other trials [11—13].

Only special preparations for inhalation and modern nebulizers must be used for an effective treatment with IA. The preparation for inhalation use should not contain some conservitives and should not be hyperosmolar, should be pH neutral and contain chlorides to prevent bronchospasm and cough [22]. Mesh nebulizers are most suitable for IA administration. This type of nebulizers forms 2.1 μm particles and provides a delivery of 5—70% of drug dose into the lungs; temperature of preparation remains constant during the aerosol formation; the air flow minimally affects the ventilation parameters; constant humidification of air can be continued. Instillation of antibiotics through the intubation or tracheostomie tube is ineffective and must never be used [22].

Inhaled antibiotics are not used as a monotherapy without the systemic antibiotics, because their absorption into the blood is low (2—4%) and not sufficient to treat the concomitant extrapulmonary infections and moreover insufficient to reach the alveoli [19—22, 50]. But we have a clinical experience of an effective monotherapy with IT in a patient with severe allergic reaction to systemic antibiotics. Currently it is not recommended to use IA for the NP prophylaxis [22, 50—51].

Use of IA is related to some problems. The penetration of IA into the obstructed airways is deteriorated. A possible inactivation of IA in sputum should be taken into account. This effect is mostly profound in aminoglycosides.
A 25-fold increase over the minimal inhibitory concentration is required to overcome this inactivation. Changes of physico-chemical properties of IA during the aerosol formation due to heating, cooling, vibration, etc. (more profound in jet nebulizers), local and systemic toxic effects, bronchoconstrictive effects of conservaties should be noted. The bronchospsam is mainly induced by the inhaled colistin. Only special preparations for inhalation must be used to prevent these complications. Inhaled antibiotics and nebulizers are expensive, their use is associated with the environment due to heating, cooling, vibration, etc. (more profound absorption).


Chuchalin A.G., Gembitskaya T.E. Isolation of Pseudomonas aeruginosa from patients with cystic fibrosis. Use of inhaled tobramycin in patients with cystic fibrosis. Terapevticheskii Arkhiv. 2010; 82 (8): 76—78. [In Russ.]


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