Inhaled Antibiotics in the Treatment of Nosocomial Pneumonia

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Nosocomial pneumonia is the most common nosocomial infection in intensive care units. Rational antibiotic therapy is the basis for the treatment of nosocomial pneumonia. There is currently a challenge of the pathogens of nosocomial pneumonia being resistant to most of the antibiotics recommended for its treatment. Inhaled antibiotics used in combination with systemic drugs are an effective and safe treatment for nosocomial pneumonia. This review of literature characterizes the current possibilities of inhaled antibiotic therapy for nosocomial pneumonia in detail and describes medicaments and the advantages and disadvantages of this treatment option. Despite insufficient evidence in circumstances where the microorganisms are polyresistant and where the design of novel antibiotics shows no promise, the use of inhaled antibiotics is an important alternative in the treatment of severe nosocomial pneumonia caused by polyresistant gram-negative bacteria.
Key words: **nosocomial pneumonia, antibiotic therapy, inhaled antibiotics, resistance.**

Nosocomial pneumonia

Nosocomial pneumonia (NP) — is a disease associated with a 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-

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geal, 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 cassociations 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 bectericidial. Increasing daily doses of antibiotics is related to a risk of selection of multiresistant strains, side-effects and superinfection. Theferore inhaled 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 supressors, 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]

Antibiotic	Area of implementation	Dosage
AMINOGLYCOSIDES		
Amikacin	Exacerbation of bronchoectatic disease, mycobacterial infections.	500 mg BID
Gentamycin	Exacerbation of bronchoectatic disease.	80 mg BID
Tobramycin	Cystic fibrosis — prophylaxis and treatment of exacerbations.	300 mg BID
	Treatment of nosocomial pneumonia.	
	Continuous therapy of bronchoectatic disease.	80 mg BID
BETA-LACTAMES		
Aztreonam	Continuous therapy in cystic fibrosis.	75 mg TID for 28 days
Cefotaxim, caftazidim	**Treatment of nosocomial pneumonia.**	250 mg BID — 500 mg 4/day
	Continuous therapy of bronchoectatic disease.	
ANTIFUNGALS		
Amfotericin B	Prophylaxis of invasive aspergillosis in oncohematology and in solid organ transplantation.	20—25 mg/day For ventilated patients — 50 mg/day
Amfotericin B lipid complex	Prophylaxis of invasive aspergillosis in oncohematology.	50 mg/day For ventilated patients — 100 mg/day
Amfotericin B liposomal	Prophylaxis of invasive aspergillosis in oncohematology.	12,5 mg 2 times/week for 2 days
OTHERS		
Colistin	Cystic fibrosis — prophylaxis and treatment of exacerbations.	1—2 million IU BID
	Treatment of nosocomial pneumonia.	
	Continuous therapy of bronchoectatic disease	
Pentamidin	Prophylaxis of Pneumocystis spp. pneumonia in HIV patients	300 mg/month

Inhaled colistin, tobramycin, cephalosporins, amphotericin B, pentamydin have been used for prophylaxis and treatment of various infections for more than 50 years now. Modern nebulizers help to administer nearly 50—70% of IA dose directly into the infection focus. It is noteworthy that in this case the local sputum concentration of antibiotics is significantly higher that after the intravenous administration, which is important when treating multiresistant strains and preventing the formation of resistance. Inhaled administration of antibiotics is related to less systemic toxicity and a profound action on biolayers [17—22].

Inhaled colistin and inhaled aminoglycosides are the most frequently used IA in pulmonology and intensive care medicine [11—13, 23—39]. Aminoglycosides are the most suitable antibiotics for inhalation because they are bactericidial and concentration-dependant (high concentration for a short period of time) [29—32]. Also inhaled fluoroquinolones [40], cephalosporines [41], liposomal aminoglycosides [42]; aztreonam [43], combinations (fosfomycin/tobramycin, colitin/tobramycin, ciprofloxacin/colistin) [44—45] are used. Inhaled fosfomycin is active against both gram-negatives and gram-positives, but it is strongly recommended to combine it with other antibiotics to prevent a rapid resistance formation [46]. It is inexpedient to use inhaled beta-lactames, because they are concentration-dependant antibiotics, and therefore multiple inhalations will be required (e.g. every 3 hrs for ceftazidime). Carbapenems when inhaled induce allergic reaction: inhaled doripenem study was stopped at stage one due to this reason [20—21, 47]. Table deals with the currently used IA [22].

The majority of IA are used to treat acute and chronic pseudomonal infection in cystic fibrosis and bronchoectatic disease. Chronic preudomonal infection in cystic fibrosis increases mortality. Inhaled tobramycin (IT), colistin (50—75 mg BID-TID), aztreonam (75 mg TID within 28 days) and other antibiotics are used for continuous treatment of infectious complications of cystic fibrosis both in- and out-hospital. A 28-day course of IT is proved to be effective in eradication of Pseudomonas aeruginosa in cystic fibrosis (300 mg/day within 28 days, then 28-days break). But the recent meta-analysis shows that there are currently no evident data to support IA use in cystic fibrosis. Moreover, the increase of the prevalence of colistin and aminoglycoside resistant strains of *Pseudomonas aeruginosa* and gram-positive microbes is detected in cystic fibrosis patients [27—30, 32—33, 36, 48].

There were no randomized multicenter trials of IA use in NP. Several small trials proved that IA in combination with systemic antibiotics decrease the symptoms of NP, facilitate weaning from ventilator, decrease the sputum microbes titer. There are also some data on IA efficacy in nosocomial tracheobronchitis. Lu Q. et al. showed the same efficacy of systemic and inhaled ceftazidime and amikacin, but a lower rate of resistance formation in IA groups. It is noteworthy that IA in this study were used as a monotherapy (ceftazidime 15 mg/kg every 3 hrs., amikacin 25 mg/kg/day). Several cases of exhalation filter obstruction were detected [41]. The same group of authors proved later the same efficacy of inhaled colistin and combination of intravenous beta-lactames and aminoglycosides in NP patients caused by Pseudomonas aeruginosa and Acinetobacter baumanii [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^{3-4} 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 biolayers. 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 conservatives 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 tracheostomic tube is ineffective and must never be used [22].

Inhaled antibiotics are not used as a monotherapy without the systemic antibiotics, because their absorbtion 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 conservatives should be noted. The bronchospasm is mostly 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 pollution and resistance formation [22, 50].

Formation of microbial resistance is still a problem, but as it has been mentioned, the rate of resistance formation is lower in IA than in intravenous antibiotics. The informativity of sputum microbiology decreases in IA use: the absence of microbes in sputum does not mean their absence in distal parts of tracheobronchial tree and in alveoli. There are currently no inhaled anti-gram-positive antibiotics [22, 50].

Thus, the use of IA in combination with the intravenous administration is an efficient and safe treatment modality for severe NP caused by gram-negative strains. In spite of low evidence for this treatment method, the current situation of high microbial resistance and no perspectives of new antibiotics development rises the significance of this treatment modality.

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