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Antibacterial Effect of Nitric Oxide on the Causative Agents of Hospital-Acquired Pneumonia (Experimental Study)

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Summary

The aim of the study was to evaluate the antimicrobial effect of single and repeated nitric oxide (NO) exposure on the major pathogens of nosocomial pneumonia isolated from the sputum of cardiac surgery patients.

Materials and Methods. A 24-hour culture of microorganisms from pan-resistant isolates of *Pseudomonas aeruginosa, Escherichia coli, Acinetobacter baumannii,* and *Klebsiella pneumoniae* from the sputum of inpatient cardiac surgery patients with nosocomial pneumonia, as well as strains of *P. aeruginosa* and *E. coli* from the American Type Culture Collection (ATCC), were exposed to 200 ppm NO (experimental sample) or medical air (control sample) in a sealed chamber for 30 minutes. After a single or 4 repeated gas exposure at 4 h intervals, Petri dishes were placed in a thermostat at 37°C and the results were evaluated at 24 and 48 h or at 12, 24, 36 and 48 h, respectively. Grown colonies were counted using an automated colony counter and recorded as CFU/mL.

Results. No growth of clinical isolates of *P. aeruginosa* and *E. coli* was observed 24 and 48 h after a single exposure to NO. Growth of *A. baumannii* was lower compared to controls at 24 h but continued at 48 h. No effect of a single exposure to 200 ppm NO on other microorganisms was observed. After 4 exposures to NO, the growth of ATCC *E. coli* was not detected, the growth of other experimental strains was significantly lower compared to the control ($P<0.05$).

Conclusion. Our results provide a rationale for the use of multiple intermittent inhalation of 220 ppm NO for the treatment of patients with hospital-acquired bacterial pneumonia.

Keywords: nitric oxide; NO; Acinetobacter baumannii; Pseudomonas aeruginosa; Escherichia coli; Klebsiella pneumoniae; hospital-acquired pneumonia

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Introduction

The global death toll from infections caused by multidrug-resistant bacteria is increasing every year. Today, resistant infections cause more than 700,000 deaths per year; by 2050, this number could rise to 10 million [1, 2]. Experts around the world are warning of the high risks of the post-antibiotic era [2]. In 2017, the World Health Organization published a list of pathogens that require new antimicrobials. Carbapenem-resistant *Enterobacteriaceae, Acinetobacter baumannii,* and *Pseudomonas aeruginosa* were identified as priorities [3, 4]. These pathogens are the leading causes of nosocomial pneumonia and represent a global public health threat [5]. However, the development of new antimicrobial drugs takes decades from molecule discovery to marketing approval. Resistance to an antibiotic develops concurrently with its introduction and use in clinical practice.

Researchers around the world are working to improve the efficacy of antibacterial therapy. From this perspective, the use of nitric oxide (NO) for medical purposes is highly promising, as evidence of its antimicrobial properties has emerged in recent years. This molecule's antiviral efficacy has been described [6–18], as well as its successful use in the treatment of infected wounds [19–23] and pulmonary infection in cystic fibrosis patients [24–27]. NO has

been shown to disrupt bacterial biofilms that cause antibiotic pseudoresistance [28–35]. The ability of NO to inhibit the growth of some microorganisms *in vitro* has been studied [36–39], and exposure to NO has been shown to reduce bacterial load in a rat model of Pseudomonas aeruginosa-induced pneumonia [40]. There have been reports of the use of NO as a rescue therapy in cystic fibrosis patients, with reduced microbial load and clinical improvement [41–44]. The use of NO is especially important in the treatment of infections caused by multidrug-resistant pathogens, because its antimicrobial mechanisms differ from those of traditional antibiotics [25, 45, 46].

For successful use of NO as an antimicrobial agent in clinical practice, it is necessary to determine the dose that is effective against a particular pathogen and at the same time safe for humans, as well as the necessary duration of exposure. Authors have reported heterogeneity in the susceptibility of different strains of microorganisms to NO [36, 38, 41]. Most studies show that the NO molecule exerts its antibacterial activity at high doses (⩾160 parts per million (ppm)) [23-25, 36, 39-47]. *in vitro*, continuous exposure to high doses of NO (⩾160 ppm) for 2–10 hours, depending on the pathogen, was found to be necessary for complete bacterial killing [36, 38, 46]. Continuous exposure of the human body to NO at this concentration is considered dangerous because it leads to methemoglobinemia [39].

Most of the Russian studies on the use of high doses of NO as an antimicrobial agent dealt with its local application in the treatment of wounds [48–53].

Studies of high-dose NO inhalation are scarce in the Russian literature [54, 55]. Currently, the clinical trials registry website Clinicaltrials. gov lists 3 Russian trials on the use of inhaled NO at 200 ppm, including RECORD Pilot NCT06162455 «High-dose Inhaled NO Therapy for the Prevention of Nosocomial Pneumonia after Cardiac Surgery with Cardiopulmonary Bypass», RECORD NCT06261827 «High-dose Inhaled NO Therapy for the pREvention of nosoCOmial Pneumonia after Cardiac Surgery with caRDiopulmonary Bypass» and NO PNEUMONIA NCT06170372 «High-dose Inhalations of Nitric Oxide in the Treatment of Pneumonia».

The COVID-19 pandemic has sparked renewed interest in inhaled NO therapy. Most studies highlight the efficacy and safety of intermittent, repeated high-dose (160–200 ppm) NO therapy with an average duration of 30 minutes per inhalation in humans [8, 24, 25, 40–44, 56, 57], including pregnant women [11] and neonates [58].

The current literature on the use of inhaled NO for bacterial respiratory infections focuses exclusively on the treatment of patients with cystic fibrosis [40–44]. Therefore, investigating the possibility of using NO as an antimicrobial agent in hospital-acquired bacterial pneumonia seems very relevant.

The aim of our study was to evaluate the antimicrobial effect of NO *in vitro* after single and multiple exposure to this gas of the major pathogens of nosocomial pneumonia isolated from the sputum of cardiac surgery patients.

Materials and Methods

A 24-hour microbial cultures of panresistant strains of *P. aeruginosa*, *Escherichia coli*, *A. baumannii*, and *Klebsiella pneumoniae* from sputum of inpatient cardiac surgery patients with nosocomial pneumonia and cultures of *P. aeruginosa* and *E. coli* from the American Type Culture Collection were grown on Endo agar. A bacterial suspension was prepared and adjusted to 108 colony forming units per mL (CFU/mL) by visual comparison with the appropriate McFarland standard (0.5) [36]. 0.1 mL of the suspension was diluted with sterile 1:1000 normal saline. 2 μL of each culture suspension was inoculated into ten Petri dishes with Endo agar using a calibrated bacteriological loop and spatula according to the «spot-on-the-lawn» method. All microorganisms were provided by the Department of Laboratory Diagnostics of Tomsk Regional Clinical Hospital.

In the first part of the experiment, according to 1:1 blind randomization, 5 out of 10 Petri dishes were exposed once to 200 ppm NO for 30 min in a closed chamber (experimental group). The second 5 Petri dishes were exposed once to medical air for 30 minutes (control group). Thus, a series of 10 interventions (N=5 in the experimental group and N=5 in the control group) was performed for each microorganism. NO produced by plasma chemical synthesis was passed through an NO supply line connected to a medical air supply circuit. The supply of synthesized NO was adjusted until a target concentration of 200 ppm was reached. The resulting gas-air mixture was passed through a viral-bacterial filter into a flow chamber containing Petri dishes with the tested microorganisms. The NO concentration was continuously monitored at the inlet and outlet of the flow chamber. Petri dishes with the tested microorganisms were kept in the gas-air mixture containing 200 ppm NO for 30 minutes.

After exposure to NO or medical air, Petri dishes were placed in a thermostat at 37°C. The result was evaluated after 24 and 48 hours.

In the second part of the experiment, the effect of repeated exposure to 200 ppm NO on microorganisms was evaluated using the same methodology. For this purpose, panresistant strains of *A. baumannii* and *K. pneumoniae* isolated from the sputum of patients with hospital-acquired pneumonia, as well as cultures of *P. aeruginosa* and *E. coli* from the American Type Culture Collection, were exposed

to NO (experimental samples) or medical air (control samples) for 30 minutes 4 times with an interval of 4 hours. For each microorganism, a series of 10 sessions (*N*=5 in the experimental group and *N*=5 in the control group) was performed. After each gas exposure, the Petri dishes were placed in a thermostat at 37°C until the end of the experiment.

The experiment was performed in 2 steps.

Step 1: 24-hour bacterial culture.

1. Preparation of Endo agar. 4 g of dry nutrient medium was added to 100 cm^3 of cold distilled water, mixed thoroughly and boiled for 3–5 minutes, avoiding burning. After cooling to 40–50°C, the nutrient medium was poured into sterile tubes and arranged at an angle to obtain agar slants.

2. Preparation of 24-hour bacterial culture. Six bacterial strains were inoculated onto the slanting Endo agar, including panresistant strains of *P. aeruginosa*, *E. coli*, *A. baumannii*, and *K. pneumoniae* from sputum of patients with hospital-acquired pneumonia, as well as cultures of *P. aeruginosa* and *E. coli* from the American Type Culture Collection. The bacterial strains were grown in a thermostat at 37°C for 24 hours.

Step 2: Preparation of bacterial suspension and exposure to NO

1. Preparation of bacterial suspension. 5 mL of sterile 0.9% NaCl solution was added to the tubes containing the grown 24-hour culture of microorganisms. To obtain a suspension, the tubes were placed on the platform of a PST-60HL thermoshaker and incubated at 30°C for 10 minutes.

2. Dilution of the bacterial suspension. Using sterile pipettes, 5 ml of bacterial suspension was removed from the tubes and transferred to borosilicate glass tubes. The optical density of the suspension was measured using a Biosan Den-1B densitometer and adjusted to 0.5 McFarland's standard (to 10^8 CFU/mL) using sterile 0.9% NaCl solution.

3. Seeding on Petri dishes. 0.1 mL of the suspension was diluted 1:1000 with sterile 0.9% NaCl solution. 2 μL of the suspension was inoculated into Petri dishes with dense Endo nutrient medium using the «spot-on-the-lawn» method with a calibrated bacteriological loop and spatula.

Each microbial culture was seeded on 2 Petri dishes.

The culture plates were treated with 200 ppm NO or medical air for 30 minutes once or 4 times at 4-hour intervals. After each exposure, the plates were placed in a thermostat at 37°C according to the 4-fold protocol. Results were evaluated after 12, 24, 36, 48 hours of incubation: colonies grown were counted using a Scan 1200 Interscience automated colony counter. Results were expressed in CFU/mL. In each case, microorganism identification was performed at the end of the incubation period.

Statistical analysis of data was performed using STATISTICA 10 and IBM SPSS Statistics 26 software. Quantitative parameters were reported as median and interquartile range, *Me [Q1; Q3]*. Quantitative parameters at 4 measurement stages for related samples were compared using the Friedman test. Quantitative parameters between groups at each step of the study were compared using the Mann–Whitney test. Differences were considered statistically significant at $P<0.05$.

Results and Discussion

No growth of clinical strains of *P. aeruginosa* and *E. coli* was observed 24 and 48 hours after a single exposure. Growth of *A. baumannii* was less than the control at 24 hours, but continued at 48 hours. This finding suggests that a single exposure to 200 ppm NO for 30 minutes had a bactericidal effect against panresistant strains of *P. aeruginosa* and *E. coli* and a bacteriostatic effect against panresistant strains of *A. baumannii*. As for the other microorganisms used in the experiment, no effect of a single exposure to 200 ppm NO was found. Therefore, it was decided to repeatedly expose these strains to NO at the same concentration.

After 4 exposures to NO with an interval of 4 h, the growth of the ATCC culture of *E. coli* was not detected, while the growth of other experimental strains was significantly reduced compared to the control (Table 1).

Meanwhile, significant differences in growth compared to control were observed for *P. aeruginosa* and *E. coli* at 36 and 48 hours after the first exposure to NO, for *A. baumannii* at 12, 24, 36 and 48 hours, and for *K. pneumoniae* at 12, 36 and 48 hours (Table).

The results of repeated exposure to NO compared to the control group at 24 and 48 hours are shown in Figure.

Thus, repeated exposure to NO caused death of the ATCC strain of *E. coli*, significantly inhibited the growth of *A. baumannii*, *K. pneumoniae*, and the ATCC culture of *P. aeruginosa*.

When comparing the number of CFU/mL at 12, 24, 36 and 48 hours for each microorganism, no significant differences were found (Table).

Our key finding is the demonstration of antimicrobial activity of NO against the major pathogens of nosocomial pneumonia in cardiac surgery patients, including multidrug-resistant strains. Furthermore, a single exposure to 200 ppm NO for 30 minutes completely inhibited the growth of clinical isolates of *P. aeruginosa* and *E. coli*. The effect remained stable even after 48 hours of observation. The growth of *A. baumannii* was reduced 24 hours after a single exposure to NO compared to control samples, but this effect disappeared after 48 hours. No growth of the ATCC strain of *E. coli* was observed after repeated exposure to NO, and the growth of other microorganisms tested was less intense than in the control.

Table. Results of repeated exposure of cultures under study to NO, *Me [25; 75]*.

Microorganism	Sample	CFU/mL after the last exposure to NO				*P*-value
		After 12 hours	After 24 hours	After 36 hours	After 48 hours	
ATCC *P. aeruginosa*	NO, *N*=5	23.5 [22; 24.5]	25 [24; 26]	23.5 [22; 24]	23 [22; 24.5]	0.059
	Control, *N*=5	38.5 [36; 39.5]	40 [37; 41]	39.5 [38; 43]	40 [38.5; 41;5]	0.061
	P	0.054	0.2	**0.0025**	**0.0015**	
ATCC *E. coli*	NO, *N*=5	0	0	0	0	—
	Control, *N*=5	12 [11.5; 13]	12 [11.5; 13]	13 [12.5; 13.5]	13 [12; 14]	0.054
	P	0.051	0.051	0.0048	0.0048	
A. baumannii (panresistant strain)	NO, *N*=5	13.5 [11; 14]	15 [12; 16.5]	15 [11; 16.5]	15 [13; 15.5]	0.061
	Control, *N*=5	54.5 [51.5; 59]	55 [53; 58.5]	55 [51.5; 56]	55.5 [54.5; 58]	0.059
	P	0.004	0.0195	0.044	0.018	
K. pneumoniae (panresistant strain)	NO, *N*=5	24 [23.5; 25]	27 [25.5; 28]	26.5 [25.5; 27]	27 [23; 30]	0.062
	Control, *N*=5	53 [49.5; 54]	54 [51; 57]	53 [52.5; 57.6]	53 [52.5; 54.5]	0.058
	P	0.0013	0.51	0.022	0.039	

Note. ATCC — American Type Culture Collection. Comparison between groups was done using the Mann–Whitney test, within groups — using the Friedman test.

Hospital-acquired pneumonia is one of the most common infectious complications in cardiac surgery patients. Its incidence ranges from 2 to 36% depending on the type of surgical procedure [59–66]. The major pathogens include *Enterobacteriaceae* (including *K. pneumoniae* and *E. coli*), *A. baumanii*, and *P. aeruginosa* [67]. Hospital-acquired strains of microorganisms are characterized by high levels of antimicrobial resistance, mainly due to the production of antibiotic-destroying enzymes such as broad-spectrum beta-lactamases and carbapenemases [5, 67–74].

The main dosing regimens for antimicrobial drugs are specified in the package insert, a legally binding document. These doses are calculated based on the drug's pharmacokinetics and pharmacodynamics, as well as the microorganism's susceptibility to the antibiotic, and are valid during the period of registration and authorization for use. Over time, the microorganism's sensitivity to antimicrobial drugs naturally decreases, resulting in an increase in the minimum inhibitory concentration (MIC). To successfully treat infectious diseases caused by resistant microorganisms, increasingly higher doses of antibacterial drugs must be prescribed, and the physician must strike a balance between therapeutic and toxic doses, which is a difficult task in clinical practice. For example, patients with renal or hepatic insufficiency require dose adjustments, and achieving the required therapeutic concentration at the site of inflammation is difficult. Combinations of two, three, or more antibiotics, as well as the simultaneous administration of antibacterial drugs from the same class, are becoming more common. This is associated with a higher risk of serious side effects and significant financial costs. Various antibiotic delivery methods, such as inhaled aminoglycosides and continuous infusion, are currently being tested. Superinfection, or the activation of another etiologic strain with a different susceptibility to antibiotics, could be one of the causes of antibiotic failure. The latter is frequently associated with changes in treatment regimens and duration, resulting in complications such as antibiotic-associated diarrhea (up to ulcerative colitis) and fungal infections. The clinician is frequently confronted with a discrepancy between the pathogen's susceptibility to antibiotics reported by the microbiology laboratory and the absence of clinical effect.

Hospital-acquired pneumonia is the most common infectious complication in patients undergoing cardiac surgery [63–66]. This is due to the impact of many damaging factors on the lungs of cardiac surgery patients. After cardiac surgery, the integrity and normal excursion of the thorax are compromised, and the cough reflex is impaired. Meanwhile, the main primary component in the pathogenesis of nosocomial pneumonia is aspiration of the patient's oropharyngeal secretions colonized with opportunistic microorganisms. In cardiac surgery patients, risk factors for antibiotic resistance include prior broad-spectrum antibiotic therapy, frequent occurrence of enzyme-producing strains, and severe comorbidities.

When choosing a NO therapy regimen, it is necessary to determine the single dose, the duration of each inhalation, and the total duration of therapy that are most effective and at the same time safe for the patient. The safety of repeated NO inhalations over 30 minutes has been demonstrated in viral pneumonia [7, 8, 11]. However, the intensity and duration of the antibacterial effect of 30-minute intermittent NO exposure has not been established.

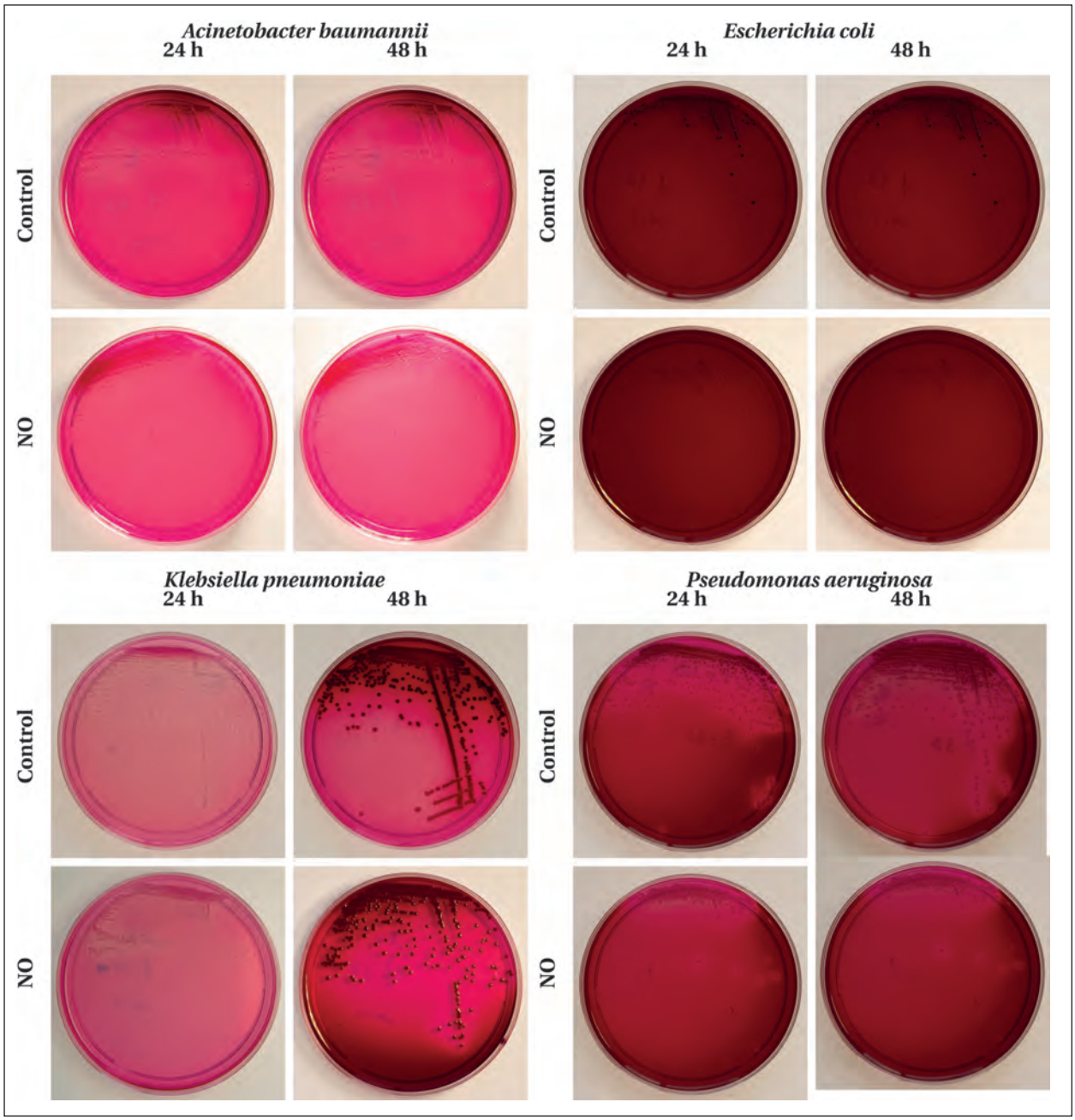

Fig. Visual evaluation of the result of repeated NO exposures to the major pathogens of hospital-acquired pneumonia *in vitro.*

The hypothesis of an antibacterial effect of repeated 30-minute exposure to 200 ppm NO on the major, including panresistant, pathogens of hospital-acquired pneumonia was tested as a clinically relevant model of NO therapy *in vitro*.

Our results show that the antimicrobial efficacy of NO persists after intermittent, repeated 30-min exposure. However, we observed a differential susceptibility of bacteria to NO action, which has been mentioned by other authors [36, 38, 41]. This is because microorganisms may have mechanisms for enzymatic inactivation of nitric oxide. One such enzyme is NO reductase, which converts NO to nitrous oxide and then to nitrogen. NO is also deactivated by oxidation by dioxygenase. In addition, some microbes can produce their own NO and use it to combat oxidative stress caused by external exposure to NO and its derivatives. As a result, microbes respond differently to NO. This has been demonstrated with common respiratory pathogens, whose susceptibility has been ranked from highest to lowest as follows *P. aeruginosa* > *Candida albicans* > *Staphylococcus aureus* > *Klebsiella pneumoniae* [75].

Our results highlight the importance of repeated NO exposure, as a significant decrease in *P. aeruginosa* and *E. coli* growth compared to the control was

only observed after 36 and 48 hours, i. e. after four NO exposures.

The use of NO is most relevant in the treatment of pneumonia caused by resistant organisms because the mechanisms of antimicrobial action of nitric oxide differ from those of traditional antibiotics [25, 45, 46]. In addition, there are observations describing the restoration of pathogen susceptibility to some antibiotics during NO therapy [43], including associations of pathogens with different antibiotic susceptibilities. NO appears to be a promising treatment for pseudoresistance caused by the ability of the pathogen to form biofilms, as it is an «anti-biofilm» agent [30]. Notably, NO therapy does not replace antibiotic therapy in pneumonia and should be used in combination with current antimicrobial agents.

Conclusion

We have demonstrated the antimicrobial effect of 200 ppm NO *in vitro* against the major pathogens of hospital-acquired pneumonia, which may provide a rationale for the use of multiple intermittent inhaled NO therapy in hospital-acquired pneumonia. This is particularly important in pneumonia caused by multidrug-resistant bacteria and in patients with risk factors for resistant microorganisms when the results of microbiological testing are pending.

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