

JUSTIFICATION OF COLISTIN ADMINISTRATION (COLISTIMETHATE SODIUM) IN CHILDREN WITH MUCOVISCIDOSIS.

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Colistin (INN- colistimethate sodium) is a cyclic polypeptide antibiotic, produced by *Bacillus polymyxa*, of *Colistin* subspecies. It belongs to the group of polymyxins including 5 chemically various components: polymyxin A, B, C, D and E. Colistin is a mix of the components of polymyxin E1 and E2, and it has bactericidal effect on gram-negative microorganisms, which are at the stage of division and resting stage, by modification of structure and function of an external and cytoplasmic membrane. Colistin destroys architecture of a cell wall of bacterium by close binding by liposaccharide residues and replacement of ions of magnesium necessary for stability of external membrane. It penetrates into the cell through a cytoplasmic membrane and causes irreversible leakage of cell content and its death. The preparation is registered and has been used since 1960th, but it was limited in administration in the early 1970th because of initial reports on its toxicity.

Today, considering the observed growth of frequency of isolation of *Pseudomonas aeruginosa* strains, multi-drug resistant to other antibiotics, administration of colistin in *pseudomonas* infection in children with mucoviscidosis is a reasonable and often the only decision.

Colistin has been used for more than 10 years in Denmark and England by inhalation and parenteral administration in respiratory diseases caused by *P. aeruginosa* during mucoviscidosis (1-2). Colistin has been circulated in Germany since 1960 and in Austria since 1962, including since 1993 for the indication "Aerosol therapy in infections of respiratory tracts caused by *Pseudomonas aeruginosa* in patients with mucoviscidosis". The preparation was specified in special literature even before its formal inclusion in this range of application as the preparation used in inhalation therapy for patients with mucoviscidosis. Many publications and leading professional societies (for example, the European working group on antibiotic therapy of mucoviscidosis, the German society of mucoviscidosis and Paul Ehrlich's Society on chemotherapy) recommend colistin for inhalations for patients with mucoviscidosis. Effectiveness of colistin is confirmed by placebo-controlled clinical trials (1-6). Experience of administration of colistin in Russia in the treatment of patients with mucoviscidosis is limited because of official lack of preparation in the country.

The antibiotic resistance problem of *Pseudomonas aeruginosa* during mucoviscidosis. Justification of colistin (colistimethate sodium) administration in children with mucoviscidosis.

The problem of antibiotic resistance of *P. aeruginosa* – a microorganism defining the progress of chronic bronchopulmonary infection in mucoviscidosis - is extremely actual.

In the Russian center of mucoviscidosis on the basis of RCCH MH of the Russian Federation and CCCH No. 13 n.a. N. F. Filatov of Moscow, together with laboratory of microbiology of CCH No. 15 n.a. O. M. Filatov of Moscow for more than 15 years, monitoring of microflora of the lower respiratory tracts in children with mucoviscidosis is carried out. The studies are carried out using "The automated workplace of microbiologist, epidemiologist and chemotherapeutist" on the basis of a tablet photometer iEMS-Reader ("TERMO-Electron company, Finland). Automation is provided by 2 programs: System of microbiological monitoring "MIKROB" (SMMM and updated version SMMM-2) and "MIKROB-Avtomat" (7-8). Input, statistical processing and analysis of data are carried out with the "System of microbiological monitoring "MIKROB" (8).

Determination of sensitivity to antibacterial preparations, quality control of determination of sensitivity is carried out according to the procedural guidelines of MUK 4.2.1890-04 "Determination of sensitivity of microorganisms to antibacterial preparations" (2004), guided by the standards of the National Committee on Clinical Laboratory Standards of the USA (NCCLS), since 2005 – the Clinical and Laboratory Standards Institute – (CLSI) (2000, 2001, 2002, 2003).

We carried out the analysis of the results of bacteriological analysis of bronchial mucous in children with MV during the period from 2000 to 2006. Identification of the isolated microorganisms was carried out taking into account morphological, tinctorial, cultural and enzymatic properties. The strains of *P. aeruginosa* producing mucus were described as *P. aeruginosa* muc., the strains which were not producing mucus – as *P. aeruginosa*.

The main microflora of the lower respiratory tract, causing chronic infectious bronchopulmonary process in children with MV, is presented in the fig. 1.

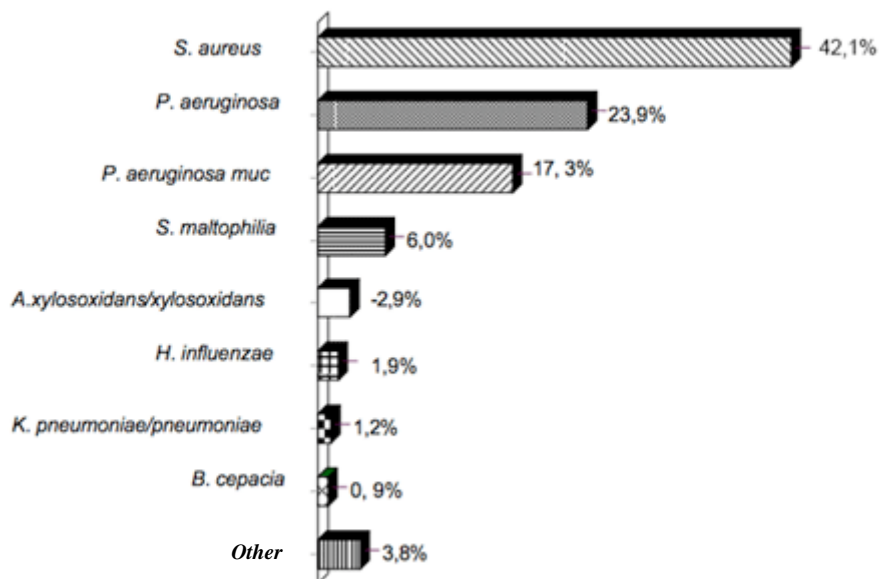


Fig. 1. Main microflora of lower respiratory tract in children with MV (% from analyzed strains).

Within bacteriological monitoring, the analysis of dynamics of antibiotic-sensitivity of priority pathogens, isolated from the lower respiratory tracts of children with MV, is carried out.

The data on resistance to antibiotics of strains *P. aeruginosa*, *P. aeruginosa muc.*, isolated from bronchial mucous in children with MV in 2000 - 2006, are presented in the tab. 1 - 2 .

Table 1. Dynamics of resistance to antibiotics of strains *P. aeruginosa*, isolated from bronchial mucous of children with MV in 2000 - 2006.

Antibiotics	Ratio of the number of resistant to the total number of microbial strains							
	2000-2001		2002-2003		2004-2005		2006	
	abs.	%	abs.	%	abs.	%	abs.	%
Polymyxin B	0/232	0	0/199	0	0/275	0	0/190	0
Amikacin	16/208	7.7	24/186	12.9	97/305.	31.8	61/189	32.3
Ciprofloxacin	10/217	4.6	28/196	14.3	55/278	19.8	32/179	17.9
Ceftazidime	31/232	13.3	36/199	18.1	98/287	34.1	56/203	27.6
Tobramycin	38/199	19.1	35/185	18.9	97/283	34.3	62/200	31
Gentamicin	48/224	21.4	42/199	21.1	119/287	41.5	68/176	38.6
Carbenecillin	58/228	25.4	35/190	18.4	83/257	32.3	53/187	28.3
Cefoperazone	53/235	22.5	60/206	29.1	98/287	34.1	54/189	28.6
Cefepime	33/193	17.1	46/218	21.1	113/292	38.7	60/192	31.3
Meropenem	5/63	7.9	18/86	20.9	38/87	43.7	44/145	30.3

Imipenem / cilastatin	3/61	4.9	17/83	20.5	16/26	61.5	15/47	31.9
Cefotaxime	59/232	25.4	73/208	35.1	178/283	62.9	79/160	49.4
Ceftriaxone	60/240	25.0	82/207	39.6	190/283	67.1	97/188	51.6

In regard to the strains *P. aeruginosa* (table 1), an accurate increase of resistance to the following was observed:

Aminoglycosides:

- amikacin from 7.7 -12.9% in 2000-2003 to 31.8-32.3% in 2004-06.
- tobramycin from 19.1-18.9% in 2000-2003 to 34.3-31% in 2004-06.
- gentamicin from 21.4% - in 2000-2003 to 41.5-38.6% in 2004-06.

Carbapenems:

- imipenem from 4.9% in 2000-01 to 20.5% в 2002-03, 31.9% in 2006
- meropenem: from 7.9% in 2000-2001 to 20.9% в 2002-03, 30.3 in 2006

Cephalosporin with antipseudomonal action:

- ceftazidime from 13.3-18.1% in 2000-03 to 34.1-27.6 % in 2004-06.
- cefepime from 17.1-21.1 % in 2000-03 to 38.7-31.3 % in 2004-06.
- cefotaxime from 25.4-35.1 % in 2000-03 to 62.9-49.4 % in 2004-06.

Also reliable increase of resistance to ciprofloxacin from 4.6% in 2000-2001 to 14.1% in 2002-2003 (p <0.05), with stabilization of resistance level at the level of 19.8-17.9% in 2004-2006 was traced.

Herewith there were no strains resistant to polymyxin B.

Similar data were obtained in the analysis of dynamics of resistance of strains *P. aeruginosa muc.* (tab. 2): reliable increase of resistance to the following was observed:

Aminoglycoside:

- amikacin from 14.7 -15% in 2000-2003 to 27.9-42.9% in 2004-06.
- tobramycin from 22.3-17.6% in 2000-2003 to 20.8-33.3% in 2004-06.
- gentamicin from 24.7% - in 2000-2003 to 28.9-49.3% in 2004-06.

Carbapenems:

- imipenem from 6.1% in 2000-01 to 16.7% - 43.5-25.8% in 2002-04-06.
- meropenem: from 10% in 2000-01 to 19.1% -26.2-18.5 in 2002-06.

Cephalosporins with antipseudomonal action:

- cefepime from 22.6-21.1% in 2000-03 to 30.4-37.9% in 2004-06.
- cefotaxime from 26% in 2000-01 to 38.8-68.2-65.5% in 2002-06.

Also, a reliable increase of resistance to ciprofloxacin from 7.6% in 2000-2001 to 11.2%-13.8-18.2 in 2002-2006 was traced. There was no reliable increase in the number of the strains resistant to ceftazidime.

There were no strains resistant to polymyxin B.

Table 2. Dynamics of resistance to antibiotics of strains *P. aeruginosa muc.*, isolated from bronchial mucous in children with MV in 2000 - 2006.

Antibiotics	Ratio of the number of resistant to the total number of microbial strains
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	2000-2001		2002-2003		2004-2005		2006	
	abs.	%	abs.	%	abs.	%	abs.	%
Polymyxin B	0/188	0	0/166	0	0/291	0	0/153	0
Amikacin	24/163	14.7	22/146	15.0	94/337	27.9	66/154	42.9
Ciprofloxacin	13/170	7.6	16/143	11.2	41/298	13.8	26/143	18.2
Ceftazidime	36/172	20.9	27/148	18.2	79/316	25	50/170	29.4
Tobramycin	33/148	22.3	24/136	17.6	66/317	20.8	56/168	33.3
Gentamicin	41/166	24.7	32/148	21.6	88/305	28.9	72/146	49.3
Carbenecillin	48/175	27.4	39/147	26.5	81/254	31.9	62/153	40.5
Cefepime	33/146	22.6	35/166	21.1	100/329	30.4	58/153	37.9
Meropenem	5/50	10.0	17/89	19.1	27/103	26.2	29/157	18.5
Imipenem / cilas- tatin	3/49	6.1	14/84	16.7	10/23	43.5	16/62	25.8
Cefotaxime	45/173	26.0	59/152	38.8	212/310	68.2	76/116	65.5
Ceftriaxone	44/188	23.4	52/158	32.9	180/300	60	82/151	54.3

Experience of colistin administration (colistimethate sodium) and treatment of children with mucoviscidosis in the Russian center of mucoviscidosis on the basis of RCCH MH of the Russian Federation and CCCH No. 13 of Moscow.

Unfortunately, on account of official lack of Colistin (colistimethate sodium) in our country, we have only a limited experience of its inhalation administration in chronic pseudomonal infection.

Considering the importance of prevention of chronic colonization development of *P. aeruginosa*, we administered colistin in inhalations in combination with per os ciprofloxacin for the purpose of *P. aeruginosa* eradication at its first seedings in 6 children. The scheme of antibiotic treatment for prevention of chronic colonization development of *Ps. aeruginosa* is presented in the table 3. Stable (1.5-2 years) sanitation of sputum in all 6 children was observed from *P. aeruginosa*. In 3 patients, colistin was administered in case of 2 seedings of *P. aeruginosa* within 6 months, however, sanitation of sputum, stable within 2 years, was received in 1 patient, unstable seeding of *Ps. aeruginosa* remained in 1 patient, a chronic pyocyanic infection developed in 1 patient. There were no effects from inhalations of colistin.

Table 3. Scheme of AT for prevention of *P. aeruginosa* chronic colonization development (1)

<i>P. Aeruginosa</i> seeding frequency	Colistin inhalation	Ciprofloxacin mg/kg/d per os	Course duration (in weeks)
1 st seeding	1 mln Un x bid	25-50	3
2 nd seeding	2 mln Un x tid	25-50	3
3 rd seeding for 6 months	2 mln Un x tid	25-50	12
The patients who earlier received i.v. courses of antipseudomonal therapy and	2 mln Un x tid	25-50	3

who had no seeding of P. Aeruginosa within several months			
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According to the Prescribing Information of Colistin

(Registration number: LS-002329 dd. 08.12.2006)

Indication for colistin administration is treatment of respiratory tract infections, caused by *Pseudomonas aeruginosa*, in case of mucoviscidosis.

Contraindications

- hypersensitivity to colistimethate sodium or polymyxin B.
- children under 6 years old.

Carefully: angina pectoris, renal impairment, blood spitting, pregnancy, lactation period.

Mode of administration and doses

- Inhalation. The daily dose of preparation for adults and children over 6 years is from 2 mln units to 6 mln units depending on disease severity. Doses of 1 mln units 2 times a day with a 12 o'clock interval are usually used.
- Duration of sanitation therapy in primary colonization / infection caused by *Pseudomonas aeruginosa* is from 3 weeks to 3 months. There are no temporary limitations of duration of inhalation therapy while chronic pseudomonas infection.
- There is no need to lower preparation dose for a patient with renal impairment.

The following relates to side effects:

- *Allergic reactions* - angioedema.
- *Nervous system disorders* - dizziness, paresthesia.
- *Respiratory system disorders* - bronchospasm (very often ($\geq 10\%$)), cough strengthening, sputum formation strengthening, mucositis (respiratory tract mucous membrane inflammation), pharyngitis, dyspnoea.
- *Gastrointestinal tract disorders*- nausea, heartburn.
- *Genitourinary system disorders* - acute renal impairment.

In connection with possible side effects in administration of colistin, it is necessary to follow some precautionary measures:

As inhalation medicinal preparations, including Colistin, can cause acute bronchoconstriction in sensitive patients, administration of the first dose of Colistin for inhalations should be carried out under supervision of the experienced medical personnel. Thus, administration of bronchial spasmolytic should precede inhalation, if it is included in the mode of therapy of this patient. Before inhalation of Colistin, it is necessary to measure the forced expiratory volume in 1 second (FOV1), to measure the peak expiratory flow rate by the PEF meter. If the patient, who is not receiving bronchial spasmolytics, has symptoms of medicamentally associated bronchial obstruction, at the next application of Colistin, it is necessary to repeat the test, adding the bronchial spasmolytic. Administration of Colistin should be carried out immediately after physiotherapeutic procedures on thorax. It is necessary to make a break between inhalations of dornase alfa and inhalation of the Colistin.

In the patients with renal dysfunction, it is necessary to pay close attention to a possibility of development of nervous system side effects and to control function of kidneys regularly.

Upon simultaneous application of Colistin with inhalation anesthetics (ether, halothane), neuromuscular relaxants or curariform preparations (tubocurarin, succinylcholine), it is necessary to pay close attention to a possibility of development of neurotoxic reactions.

The prepared solution of Colistin should not be mixed with other medicinal preparations.

Upon simultaneous application of potentially nephrotoxic preparations (aminoglycosides, cephalosporins, cyclosporine) and Colistin, the strengthening of nephrotoxicity is possible.

During the treatment with Colistin, in rare cases resistant strains of *Pseudomonas aeruginosa* are possible. After cancellation and/or modification of therapy, recovery of preparation effectiveness is possible.

Therefore, colistin (colistimethate sodium) can be successfully administered:

- for prevention of development of chronic pseudomonas infection, upon the first seedings of *Pseudomonas aeruginosa* – inhalant as monotherapy and in combination with oral administration of ciprofloxacin
- for chronic pseudomonas infection - long-term inhalation
- for pulmonary aggravation in patients with mucoviscidosis, caused by multi-drug resistant strains of *Pseudomonas aeruginosa* - intravenously

As colistin can cause acute bronchoconstriction in sensitive patients, application of the first dose should be carried out under the supervision of medical personnel under control of OFV1, values of peakflowmetry. If the patient, who is not receiving bronchial spasmolytics, has symptoms of medicamentally caused bronchial obstruction, at the next application of colistin it is necessary to repeat test, adding the bronchial spasmolytic.

Considering a possibility of neutralization of colistin by the action of DNA-containing bronchial mucous, before inhalation of colistin it is necessary to carry out a kinesitherapy of respiratory tracts. It is necessary to make a break between inhalations of dornase alpha and inhalation of colistin.

The rate of nephrotoxic and severe neurotoxic side effects in intravenous administration of colistimethate sodium is much lower, than it has been reported (9-10) earlier. On the basis of the conducted pharmacokinetic and pharmacodynamic researches, the new modes of intravenous dosage of colistin, allowing to increase its effectiveness and to minimize the frequency of toxic effects, are proposed. At the same time, in patients with kidney dysfunction, it is necessary to pay close attention to the development of side effects and to control regularly the function of kidneys. In inhalation administration of colistin, its undesirable side effects according to Lindemann, 2000 (11), were so small, that they could be neglected.

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