

Category: diseases of the upper respiratory tract

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Modern approach to the treatment of diseases of the upper respiratory tract and middle ear as a measure of hearing loss prevention

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The high prevalence of asymptomatic middle ear diseases in children is caused by frequent infections, inflammatory diseases of the upper respiratory tract and lack of appropriate pediatrician's caution. In this regard, the number of patients with mild conductive hearing loss, which is due primarily to otitis media with effusion, is growing steadily. The basis of the primary and secondary prevention of persistent hearing loss in this situation is the rational therapy of respiratory infections, as well as the timely diagnosis of productive inflammation in the cavities of the middle ear. The article reflects the current understanding of the complex topical treatment of acute and chronic respiratory diseases combined with the pathology of the middle ear, in particular the role and potential of mucolytic agents.

Keywords: *otitis media with effusion, children, mucolytic therapy, N-acetylcysteine.*

According to data provided in the newsletter of the World Health Organization (№ 300, April 2010) in 2005, about 278 million people on Earth have moderate or profound hearing loss [1]. And it is impossible to count individuals with light hearing loss. In Russia there are more than 13 million people with a socially significant hearing impairment, including more than 1 million children and adolescents [2]. It should be noted that the counted are only children registered in surd logical offices and centers.

The most constructive point of this bulletin is as follows: half of all cases of deafness and hearing impairment can be avoided through prevention, early diagnosis and treatment [1]. We mean both a conductive (sound conduction defect) and a sensorineural hearing (violation sound perception) forms of hearing loss. At the same time conductive hearing loss with timely prevention and therapeutic measures has a relatively favorable prognosis.

However, currently there is growth in the number of patients with asymptomatic, sluggish inflammatory process in the middle ear, whose inadequate diagnosis and treatment leads to the development of persistent conductive hearing loss [3]. This contributes to irrational and excessive antibiotic therapy, frequent refusal to perform tympanocentesis in acute inflammatory diseases of the middle ear and the neglect control over the restoration of auditory function and aeration of the middle ear cavity after acute otitis media.

Otitis media with effusion (OME) as the main cause of conductive hearing loss in pediatric

practice arises at least once for 90% of children under 3 years of age, while 50% of children suffer multiple episodes of illness [4]. The statistical accounting of this category of patients is considerably difficult, because there is a delayed diagnosis of middle ear disease, especially in infants and preschool children. It is caused by a number of objective and subjective reasons: age-related anatomical features of the auditory tube (length, width and angle of the lumen [5]), inability to use diagnostic techniques that are widely used in the adult ENT clinic, lack of implementation in routine outpatient practice of modern methods of examination, such as otomicroscopy, endoscopy of the nasal cavity and nasopharynx, acoustic tympanometry. And most importantly, in most cases the disease is practically asymptomatic when the only manifestation of disease (usually only at the bilateral process) is a slight hearing loss. This is often wrongly interpreted, not only by parents but also by pediatricians as a carelessness of a child.

As you know, one of the main starting points of a productive inflammation in the middle ear is an auditory tube dysfunction associated with its functional and / or mechanical obstruction. Prevalence of tube dysfunction in childhood is caused by high frequency of hyperplasia of lymphoid tissues of nasopharynx such as pharyngeal and tubal tonsils [5]; frequent respiratory infections. 70% of URTI, which every child has, is accompanied by the development of inflammatory disease of the middle ear [6]. In spite of the fact that in more than 50% of cases OME is resolved on its own within three months and in 95% of cases - within a year [7], having a chronic relapsing tube dysfunction and the recurrent OME in some cases potentially causes a chronic disease of the middle ear in the future and sometimes life-threatening intracranial complications. Thus, the chronic suppurative otitis media, cholesteatoma, adhesive otitis media in an adult patient are diseases come from childhood [8].

Rational treatment of acute and chronic inflammatory diseases of the upper respiratory tract and middle ear: rhinitis, rhinosinusitis, adenoiditis, acute otitis media etc. is the basis for the prevention of chronic OME. Thus, the primary prevention of conductive hearing loss in children primarily is the responsibility of the pediatrician, who must be well-oriented on this disease, and prescribe appropriate therapy upon disease indication in a timely manner to transfer the patient to the otolaryngologist or audiologist.

Knowledge of the pathogenesis of septic and non-purulent complications of paranasal sinuses and middle ear cavities of URTI should be the basis of therapeutic management.

The cause of these complications are inflammatory changes in the mucous membrane of the nasal cavity and nasopharynx, including its swelling in the "key" anatomical areas: ostiomeatal complex, the pharyngeal ostium of the auditory tube and its obstruction, impaired drainage of mucus and the emergence of transudate due to the reduction of intratympanic pressure, stagnation and infection with the same content, secondary mucociliary dysfunction, and goblet cell transformation of respiratory epithelium, changes in the characteristics of secretions in the form of displacement of pH, the violation ratio of gel / sol. Recently, much attention has been paid to the formation of reasonably bacterial films (or biofilms) - of highly communities bacteria formed on the surfaces due to their adhesion, growth, reproduction and formation of extracellular matrix. Bacteria in the biofilms differ considerably by higher resistance to environmental factors, including antimicrobial agents [9]. They play the special role in the development of chronic and resistant to therapy infectious and inflammatory processes in the upper respiratory tract. Thus, the biofilm-producing bacteria (BPB) in chronic adenoiditis and chronic OME stand out in 73.8% of cases [10].

Thus, the scheme of treatment of acute inflammatory diseases of the upper respiratory tract and

middle ear should be directed to the mechanical cleansing of the mucosa, the elimination of edema, decontamination, and the normalization of mucociliary transport system, including irrigation treatment, nasal decongestants, mucolytic agents and, in some cases, antibacterial or antiseptic agents.

It should be noted that topical therapy is the basis for treatment of uncomplicated respiratory infections. In most cases, a comprehensive local treatment is sufficient to prevent complications, including acute otitis media and otitis media with effusion, and on the other - to reduce drug load on the body and to avoid unnecessary use of systemic antibiotics.

Appointment of "nasal douche" isotonic saline to remove the discharge, reduces microbial contamination and improves the traffic of the mucous membrane is now regarded as an essential component of therapy. Recent systematic reviews indicate the efficiency of irrigation activities for therapeutic effects in children and adults (the grade of recommendations A) and antirecurrent prevention (grade of recommendations B) [11].

The data on the effectiveness of nasal decongestants in acute respiratory infections are highly contradictory. Several Meta-analyzes indicate no evidence of influence on the outcome of vasoconstrictors in acute rhinitis in children [12]. Nevertheless there is evidence of a statistically significant decrease in the incidence of "persistent" or longterm acute otitis media in children in the appointment of decongestants [13], which coincides with the opinion of most of domestic ENT schools. In our view, timely administration of drugs of this group for short course in acute respiratory infection eliminates the swelling of the pharyngeal ostium of the auditory tube, preventing or interrupting the exudation in the cavities of the middle ear.

Despite the high efficiency of "nasal douche", the transition to the stage of acute mucous-purulent discharge after second-third day of illness [14], dictates the need for joining a local mucolytic and sometimes antimicrobial therapy. In particular, this happens due to an increased risk of acute otitis media due to reflux of purulent discharge in the auditory tube and lengthening the term auditory tube dysfunction, i.e., starting the formation of the OME.

N-acetylcysteine is one of the most widely studied mucolytics in ENT practice [15]. The possibility of topical application (application to mucous membranes, an introduction to the sinuses and middle ear cavity, inhalation), both independently and in the form of chemical compounds with other drugs justifies its widespread use for diseases of ear, nose and throat. N-acetylcysteine is a direct mucolytic agent, whose action is related to the ability to break the intra- and intermolecular disulfide bonds of free sulfhydryl groups, acid mucopolysaccharides of the viscous secretions of any kind (slimy, putrid), thus damaging the biofilm. In addition, the drug reduces the adhesion of bacteria to the epithelial cells by stimulating production of sialomucines by viscous goblet cells, thus preventing the formation of biofilms.

The presence of SH-groups and intracellular glutathione metabolism of N-acetylcysteine explains the high level of antioxidant activity [16], which together with antiadhesive action may be directed to the prevention of chronic bacterial infection in the mucosa of the respiratory tract. The hypothesis about the devastating effect of direct mucolytics, in particular N-acetylcysteine is exerted by the composition of the biofilm and is confirmed by the work of S. Aslam with coauthors. The authors found that the use of N-acetylcysteine significantly reduces the thickness of the biofilm, significantly reduces the number of viable Gram-positive and gram-negative microorganisms and also has fungicidal activity against of *Candida* fungi. Thus, N-acetylcysteine has a mucolytic effect by destroying the biofilm and also potentially increases the effectiveness of antimicrobial agents [17].

A line of Zambon group products (Italy) on the basis of N-acetylcysteine, which was presented at the domestic pharmaceutical market, includes Fluimucil (N-acetylcysteine, ampoule form), Rinofluimucil (N-acetylcysteine + tuaminoheptane sulfate nasal spray) and Fluimutsil- antibiotic IT (Thiamphenicol glycinate acetylcysteinate), which allows to use a direct mucolytic by using different routes of administration according to the clinical situation, both in hospital and in out-patient practice (Table).

In acute stage of muco-purulent discharge in order to reduce the number of used drugs, combined nasal spray Rinofluimucil (including vasoconstrictor component tuaminoheptane sulfate) is used to improve compliance level.

Efficiency of a vasoconstrictor Tuaminoheptane was demonstrated in a research performed by A. Cogo et al. The results of a randomized double-blind comparative study, which were based on the performance active anterior rhinomanometry performed prior to the use of the drug and after 5, 10 and 20 minutes after its application, made it possible to state about fairly strength and speed-comparable vasoconstrictor's effect of tuaminoheptane and xylometasoline [18]. In this regard one must remember about the possibility of development of tachyphylaxis and the 'rebound' effect as the application of any nasal sympathomimetic, so therapy should not exceed 7 days. Given evident swelling of nasal cavity mucous membrane it is advisable to begin treatment of acute rhinitis with the appointment of a common vasoconstrictor (xylometasoline, oxymetazoline, phenylephrine, and others) with further change of the drug on Rinofluimucil 2-3 days, which reduces the risk of these adverse events.

If it is necessary to continue the topical mucolytic therapy (in the case of a prolonged course of rhinitis, rhinosinusitis, acute otitis media OME) of N-acetylcysteine 10% (in the form Fluimucil) can be inhaled via nebulizer.

When muco-purulent nasal discharge persists for more than 7 days in the absence of clinical symptoms of infection, that is systemic antibiotic therapy is not indicated, there is assigned a change of local antimicrobial therapy while continuing mucolytic therapy. Inhalation using Fluimucil-antibiotic IT is appropriate. Antibacterial activity of the drug is due to thiamphenicol (chloramphenicol derivative) which is bacteriostatic antimicrobial agent against most of the major bacterial pathogens of the upper tract and middle ear (*Staphylococcus* spp., *Streptococcus pyogenes*, *Haemophilus influenzae* and others). Thus the combination of acetylcysteine thiamphenicol facilitates the penetration of the N-acetylcysteine into tissues and secrets [16].

Until now, there were sporadic high quality clinical researches on the effectiveness of thiamphenicol inhalation in conjunction with acetylcysteine. One of the largest studies (817 patients), "Comparison of the effectiveness of inhaled thiamphenicol acetylcysteine glycinate", was presented by Italian authors in 2007 (in case of severe acute bacterial infections of the upper respiratory tract once the drug was injected intramuscularly with a subsequent transition to an aerosol form) carried out with standard systemic antibiotic therapy (beta-lactams). Clinical efficacy of the drug under study ranged from 87 to 94% depending on the nosological form and severity of infection; eradication of etiologically important microorganisms, according to the repeated microbiological studies; and was achieved in 86,2-96% of cases. The results of treatment on a group taking thiamphenicol with N-acetylcysteine were comparable to those using the standard protocols of systemic antibiotic therapy; and patients with rhinosinusitis had superior efficacy over beta-lactam therapy. No resistant strain of microorganism to thiamphenicol was discovered during a study [19].

The first literature review concerning the effectiveness of certain drugs for chronic ENT infections caused by biofilm formation was published in March 2011 [20].

An analysis of 30 articles allowed the authors to conclude that the relative ineffectiveness of antibiotics used in doses sufficient for eradication of planktonic forms of microorganisms. Among the tools that radically destroy the biofilm on the surface of the respiratory epithelium there were identified only gentian violet (used mainly in veterinary medicine), and mupirocin with Thiamphenicol glycinate acetylcysteinate (Fluimucil-antibiotic IT) [20]. "Sterile" formulations of N-acetylcysteine are proven in surgical otorhinolaryngology in addition to using these drugs for acute and chronic infectious and inflammatory diseases of ENT organs in pediatric practice or general practitioner.

Fluimucil and Fluimucil-antibiotic IT, are used in accordance with the instructions for medical use for the maxillary sinus in case of puncture and lavage of operational ear cavities; they are also used as ear drops for acute purulent otitis media with eardrum perforation and chronic suppurative otitis media. Experience of intraoperative intratympanic administration of N-acetylcysteine in case of tympanocentesis, myringotomy and tympanotomy in patients with chronic OME (more than 500 patients) in ENT department at Scientific Children's Health Center demonstrated the effectiveness of the drug for the drainage of the tympanic cavity given a viscous fluid and block of tympanic aeration pathways. The use of these drugs significantly reduces the time of normalization of the hearing, which allows widely recommend the drug in otosurgical practice.

Thus, the following treatment improves the effectiveness of therapy: a comprehensive and differentiated approach to the topical treatment of acute and chronic infectious and inflammatory diseases of the upper respiratory tract, as well as the combined pathology of the nasal cavity, nasopharynx and middle ear with the inclusion of direct-acting mucolytic drugs; it also measures primary and secondary prevention pathology of the middle ear. Pediatricians and general practitioners should be aware of high extension of asymptomatic disease of the middle ear; they should have a corresponding "surdological vigilance" and in case of failing to effect primary curative measures they should suggest otolaryngologist consultation.

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TABLE: Release forms and routes of administration of N-acetylcysteine

Medicine	MNN	Issue forms	Introduction forms
Rinofluimutsil	N-acetylcysteine Tuaminoheptane sulfate	Nasal spray	Intranasal
Fluimutsil	N-acetylcysteine	A solution for injections and inhalations, 3 ml ampullas (300 mg)	Intravenously Intramuscularly Inhalation Intratracheal Intranasal Transtympanic
Fluimutsil-antibiotic IT	Thiamphenicol glycinate acetylcysteinate	lyophilizate for solution for injection and inhalation, vials (500 mg thiamphenicol)	Intravenously Intramuscularly Inhalation Intratracheal Intranasal Intratympanic In sinuses with puncture/sensing In the post-operative cavity in the nose, paranasal sinuses, tympanic cavity, mastoid