Editorial note. Dear colleagues! We continue publishing interesting lectures and reports presented at conferences and congresses organized by the Union of Pediatricians of Russia. We have traditionally minimized text content and present a considerable amount of information in the form of the slides demonstrated during presentations. In this issue we present to you a lecture by Professor J.P. Guggenbichler (pic. 1-2), head of the department of pediatric infectious diseases (University of Erlangen, Germany), which sparked much interest with Russian colleagues with as little as name and attracted a wide audience. Following the report, the lecturer continued answering questions of the interested colleagues regarding both the lecture subject and the issues of modern phytoneering.

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Effective prevention of a bacterial superinfection with phytopreparations in the event of a viral respiratory infection

It is widely known that the risk of a bacterial superinfection [dacryocystitis, otitis media (pic. 3), sinusitis] in infants and small children with acute respiratory viral infections (ARVI) is 20-25%. That is why prevention of bacterial superinfections is an important component of the complex therapy in this category of children; however, practicing physicians apply antibacterial drugs excessively often. According to the statistics, antibacterial drugs are prescribed to 70% of the patients with ARVIs. Improper and excessive use of antibiotics (detailed below) results in a dramatically high spread of multi-drug resistant microbes:
- prescription of antibiotics as means of preventing viral infections;
- unjustified use of wide spectrum antibiotics;
- local administration of antibiotics;
- improper daily dosage and dosage interval (ignorance of pharmacodynamics);
This results in an increase in the number of resistant microbes:
- methicillin-resistant staphylococcus aureus (MRSA);
- penicillin-resistant *Streptococcus pneumoniae* [mutations of the proteins encoding binding with penicillin];
- macrolide-resistant streptococci and pneumococci;
- fluoroquinolone- and aminoglycoside-resistant *Escherichia coli*;
- ESBL-genous *Haemophilus influenzae, Klebsiella, Enterobacter* in the event of urinary tract infections.
Moreover, antibiotics ought not to be used to prevent bacterial superinfections for the following reasons:
- limited prophylactic efficacy;
- impact on the normal human microflora:
● choice of resistant microbes (microflora of intestines, mouth cavity and skin);
● resistance development stimulation by employing subinhibitory concentrations etc.;
- no impact on biofilm microbes (chronic sinusitis, otitis media);
- side effects associated with gastrointestinal tract.
The pharmaceutical industry has been decreasing the effort regarding development of new anti-infectious drugs, especially of antibacterial and anti-parasitic agents and vaccines due to heavy expenses associated with research and clinical testing and regulatory complications. Given the increasing nature of antibiotic resistance, this tendency may acquire dramatic nature; such a discouraging situation is already observed in the USA and Japan; the issue has gained the most acute character in Europe.

At the same time, the forming antibiotic resistance continues to exhaust our supply of efficient antibiotics; this renders a worldwide infectious catastrophe possible. Alternative means of preventing bacterial superinfections in the event of an acute viral respiratory infection are required.

In order to propose an efficient protective technique, it is necessary to know the main pathological mechanisms of infection development. It ought to be noted that almost all viral infections start with affecting epithelial surface, whereas adhesion and colonization thereof are main virulence factors (pic. 4-5). That is why the natural body protection mechanisms are aimed against colonization of epithelial surfaces (pic. 6). The following antimicrobial agents are formed in the epithelial surface's liquid:

- lysozyme;
- β-defensin (pics. 7, 8);
- lactoferrin, siderophores;
- receptor-equivalent carbohydrates (pic. 9);
- secretory IgA.

In the event of mucosal local immunity decrease/malfunction there is a risk of development of such symptomatic pathological conditions (diseases) as:

- chronic polypous sinusitis;
- recurrent upper respiratory infections in children;
- recurrent urinary infections in patients with normal urodynamics;
- Crohn's disease;
- periodontitis.

Viral infections disturb the non-specific body protective mechanisms and contribute to the development of bacterial superinfections in the following ways:

- mucociliary clearance disturbance;
● secretion viscosity alteration;
● abnormal ciliary motility;
- intensified bacterial adhesion to the virally infected cells (pic. 10);
- inflammatory response: submucosal edema due to the generation of anti-inflammatory cytokines [leukotrienes, prostaglandins PGE2, PGD2, PGF2, prostacyclin, thromboxane, PAF (platelet activating factor), neurokinin A].

Anti-inflammatory cytokines cause:

- influenza-like condition, fever and arthralgia;
- bronchoconstriction, vasodilatation, heightened vascular permeability;
- reduced synthesis of antimicrobial peptides.

Many scientists believe that non-specific protective mechanisms may be activated by phytopreparations. In order to confirm this hypothesis it is necessary to remember the mechanism of action of phytopharmaceuticals (pic. 11-14). They feature anti-inflammatory effect due to antagonism of anti-inflammatory cytokines (triterpenes in many plants), COC2 expression reduction, PEG2 formation and spasmolytic activity (β2-symptomatic properties).

Let us examine efficacy of a phytopreparation for otitis media. Eustachian tube obstruction at ARVI leads to bacterial superinfection of the middle ear cavity and the primary symptom – earache. Early beginning of the treatment with anti-inflammatory agents (phytopreparations) "opens" Eustachian tubes and prevents the possibility of a bacterial superinfection in the middle ear cavity. In an animal model, Stiema et al. demonstrated efficacy of Sinupret for preventing bacterial infections (pic. 15). Before that there had been only observations to confirm clinical efficacy of the phytopreparation (pic. 16); now there are results of randomized prospective double blind studies of the required number of patients according to the European requirements (guideline) on the good clinical practice CPMP/ICH/135/95. pic. 17-19 feature stages of a multicenter double blind placebo-controlled randomized clinical study of a certain phytopreparation's (dry BNO-1016 extract) efficacy and safety in parallel groups of patients with acute rhinosinusitis. This study demonstrated that phytotherapy may well be used in the

modern medical practice (pic. 20). Only there ought to be a responsible attitude to drugs and understanding that their use may impose risks on the human body. Efficacy and safety of phytopreparations feature the same proof procedure as chemically synthesized drugs. Phytoneering – an actively developing relatively new sphere of medicine – contributes to this process.

Phytoneering (from Greek *phyto* – plant; from English *engineering*) is a scientific and technological concept, which appeared in Germany in the end of the XX century and became a link between classic naturopathy and modern pharmaceutical inventions. This new approach to manufacture and assessment of efficacy and safety of the manufacture drugs has contributed to the elimination of restrictions regarding prescription of phytopreparations. This is partly due to the standardized character of their composition, and also due to the fact that all the studies are evidence-based and that only the drugs associated with a high safety profile are permitted in the market. This allows practicing physicians to prescribe one polycomponent drug instead of several drugs, improving compliance and reducing therapy costs.

PIC. 1. Symposium chairmen: professors V.K. Tatochenko and M.D. Bakradze; lecturer — professor J.P. Guggenbichler

PIC. 2. Professor J.P. Guggenbichler

PIC. 3. Otitis media

PIC. 4. S. pneumoniae — adhesion on nasal epithelium cells

PIC. 5. Image of uropathogenic stock E. coli made by electron microscope

PIC. 6. Natural nocifensors against innidiation of mucous membranes
• Mechanical removal = mucociliary clearance
— Ciliary beats
— Requested liquid viscosity of epithelium (ELF)
— Free current of secretory liquids

PIC. 7. β-defensin (antimicrobial peptides). Epithelian cells form antimicrobial proteins (38–42 amino acids) upon contact with pathogenic germs

PIC. 8. β-defensin influence on P. aeruginosa (with Prof. Neuhuber, Univ. Erlangen)

PIC. 9. Interlocking of microbial adhesion

PIC.10. Intense nasal mucosa's epithelial cells innidiation *H. influenzae* under respiratory syncytial virus contamination (RSV)

PIC. 11. Effect of phyto- pharmaceuticals
• Improvement of mucociliary clearance
- Sekretoliticheskim properties: for example, primrose, gentian, elderflower, verbena, sorrel, thyme, ivy
- Sekretomotornym properties of lavender, myrtle, eucalyptus
• The direct antimicrobial effect

Pic. 12. Intensification of ciliary beats using essential oils

Substrate	Summary frequency	5 µg / ml	20 µg / ml

Eucalyptus	5/c	8/c	15 /c
Lavender	5 /c	6 /c	12 /c
Myrtus	5 /c	6 /c	12 /c
Camphor	5 /c	4 /c	2 /c
Menthol	5 /c	3 /c	2 /c

PIC. 13 Action of phyto-pharmaceuticals
• The antimicrobial properties when applied topically
(St. John's wort, thyme, chamomile, mountain pine, sage, various essential oils)
• Antiviral properties
• Stimulation β-defensins
• Blocking of adhesion using carbohydrates similar receptors contained in phyto-pharmaceuticals

PIC. 14 Antimicrobial activity of 0.1% extract oil mountain pine

PIC. 15 Studies in animals Sinupret

Модель синусита (кролик) Антибактериальная и противовоспалительная активность	Sinusitis model (rabbit) Antibacterial and anti-inflammatory activity
Снижение числа микроорганизмов в верхнечелюстной пазухе	Reducing the number of microorganisms in the maxillary sinus
Положительный бактериологический результат (%)	Positive bacteriological result (%)
Плацебо	Placebo
Экстракт	The extract
Длительность терапии (в неделях)	Duration of therapy (weeks)
Число КОЕ (верхнечел. синус, лево/право)	The number of CFU (supramaxillary sinus, left / right)
Компьютерная томограмма	CT scan
Снижение обструкции и затемнения	Reduction of obstruction and shading
Плацебо	Placebo
Закрытые пазухи евстахиевой трубы	Sinus closed eustachian tube
Экстракт	The extract
Свободные пазухи евстахиевой трубы	Free sinus eustachian tube
Сниженное воспаление слизистой оболочки	Reduced inflammation of mucosa
Общий гистопатологический балл	The total histopathologic score
Длительность терапии (в неделях)	Duration of therapy (weeks)

PIC. 16 Sinupret drops / pills in children. Observational study (rhinosinusitis)

Отделяемое из носа	Discharge from the nose
2–6 лет / 6–12 лет	2-6 years / 6-12 years
Частота ринита разной степени выраженности	The frequency of rhinitis of varying severity
До лечения / После лечения	Before treatment / after treatment
Нет	No

Тяжелый ринит	Severe rhinitis
Ринит средней степени выраженности	Rhinitis medium
Ринит слабовыраженный	Rhinitis ill-defined

PIC. 17 Sinupret drops / pills in children. Observational study (rhinosinusitis)

Болевой синдром (головная боль, боль в области лица)	Pain syndrome (headache, pain in the face)
2–6 лет / 6–12 лет	2-6 years / 6-12 years
Частота ринита разной степени выраженности	The frequency of rhinitis of varying severity
До лечения / После лечения	Before treatment / after treatment
Нет	No
Тяжелый ринит	Severe rhinitis
Ринит средней степени выраженности	Rhinitis medium
Ринит слабовыраженный	Rhinitis ill-defined

PIC. 18 Results: the primary endpoint

ARhiSi<2: Шкала основных симптомов (MSS) на 5<м визите (оценка врачом<исследователем), FAS, *n* = 380	ARhiSi <2: Scale of the major symptoms (MSS) for 5 <m visit (physician assessment <researcher), FAS, n = 380
Плацебо	Placebo
Достоверное различие в **1,03** балла между плацебо и активным препаратом	Significant difference of 1.03 between scores of placebo and active drug

PIC. 19 Results: Ultrasound sinuses

ARhiSi<2: Пациенты с симптомами синусита на 5<м визите, FAS, *n* = 371	ARhiSi <2: Patients with symptoms of sinusitis 5 <m visit, FAS, n = 371
[%] пациентов	[%] patients
Плацебо	Placebo
Подтверждение первичной конечной точки методом УЗИ	Confirmation of the primary endpoint by ultrasound

PIC. 20 Conclusion

• The emergence of micro-organisms with multiple stability in the society due to erratic the use of antibiotics for the prevention of bacterial superinfection

• Herbal preparations stimulate nonspecific mechanisms protecting the body against colonization by mucosal

• These products support the natural mechanisms protect the body