Case-control clinical and microbiological study of probiotic substantive approach to holiary therapy of seasonal influenza type A and B in adults

**Introduction.** Influenza-associated bacterial and viral infections are responsible for high levels of morbidity and death during pandemic and seasonal influenza episodes. Severe influenza-associated pneumonia is often bacterial and will necessitate antibiotic treatment. In spite of great quantity of modern medicines for a treatment of patients with influenza, there are still often development of bacterial complications. From one side it is determined by dysfunction of systemic immunity, especially cellular section, and from another it realized due to activation of opportunistic microorganisms which are present on the mucous membranes of nasal and tonsillar surfaces.

There are few experimental research dedicated to positive influence of bacillus contained bacterial preparations due to their antagonistic activity towards pathogenic strains. Recent scientific interest is increased in the field of infectology and microbiology as well as the place and role of probiotics in pharmacotherapy of infectious diseases.

The analysis of available literature data proved the absence of clinical and microbiological investigation in patients with seasonal influenza A and B in Ukraine and Eastern Europe.

**The research purpose** is to study the clinical peculiarities, microbiological efficacy of bacillus-contained probiotic “Biosporin” for prevention of bacterial complications in patients with seasonal influenza A and B.

**Material and methods.** This study enrolled 109 patients aged 18–25 had conducted in 2012–2013 (average 21.7 years old) infected mostly with seasonal influenza viruses. Gender allocation included 62 (56.9%) females and 47 (43.1%) — males. Investigated persons were belonging to Caucasian race. All enrolled persons having the same high risk to get influenza virus because of student activity based on the epidemiologic data being upon same exposure during communication and overcrowding.

One hundred and nine young patients with clinical features and laboratory findings (acute onset with hyperthermia more 38.5°C, scleritis, intoxication syndrome, etc., positive epidemiologic data) were investigated during October-March 2012–2013 at the Dept. of Droplet Respiratory Infections in the Municipal Clinical Hospital, Chernivtsi (South Western region of Ukraine, Eastern Europe).

Research material (smears from nasopharynx, tonsils) had delivered to Microbiological Clinical Laboratory of Municipal Clinical Hospital (Chernivtsi, Ukraine) with purpose to evaluate a species composition and populational level of nasal and tonsillar microflora. Cultures of facultative anaerobic and aerobic bacteria had cultured in an incubator (37°C) for 24–48 hours. Obligate anaerobic bacteria had grown in the anaerobic atmosphere. Bacteria isolation was done by microbiological methods: cultural, biochemical and serological tests.

**Results.** All enrolled patients were admitted to Infectious Department of Municipal Clinical Hospital (Chernivtsi, Bukovina) with purpose of stationary treatment. Influenza caused by A/H3N2 and A/H2N2/in investigated young patients characterized mostly by a moderate severity course. Influenza caused by B type virus had mild severity course.

The detailed characteristics of clinical course of influenza are described in the table 1.

Examined patients complained on moderate headache, dry persistent cough, general weakness, louse of appetite, pain in chest (98,17±1,28), pain in eyeballs (96,33±1,80), myalgia (88,99±3,00) and arthralgia — in 76,15±4,08 cases.

The diagnosis of influenza had proved by clinical data, epidemiologic anamnesis and serological tests (reaction of inhibition of hemmaglutination). The result of serological authentication proved: influenza A/N2N2 — in 46,78±4,78% cases, influenza A/N3N2 — in 40,36±4,70% and B — at 6,42±2,34% patients at Bukovina (Western Ukraine) during the epidemic season 2012–2013 years.

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Table 1. – The clinical characteristics of influenza course in young people (n=109)

<table>
<thead>
<tr>
<th>Clinical signs</th>
<th>Absolute quantity (N)</th>
<th>Relative quantity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intoxicative syndrome</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>– moderate headache</td>
<td>109</td>
<td>100,0±0</td>
</tr>
<tr>
<td>– general weakness</td>
<td>109</td>
<td>100,0±0</td>
</tr>
<tr>
<td>– louse of appetite</td>
<td>109</td>
<td>100,0±0</td>
</tr>
<tr>
<td>– pain in eyeballs</td>
<td>105</td>
<td>96,33±1,80</td>
</tr>
<tr>
<td>– myalgia</td>
<td>97</td>
<td>88,99±3,00</td>
</tr>
<tr>
<td>– arthralgia</td>
<td>83</td>
<td>76,15±4,08</td>
</tr>
<tr>
<td><strong>Catarrhal syndrome</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>– dry persistent cough</td>
<td>109</td>
<td>100,0±0</td>
</tr>
<tr>
<td>– pain in chest</td>
<td>107</td>
<td>98,17±1,28</td>
</tr>
<tr>
<td>– serous and mucosa nasal excretions</td>
<td>102</td>
<td>93,58±2,35</td>
</tr>
<tr>
<td>– stuffiness in nose</td>
<td>88</td>
<td>80,73±3,78</td>
</tr>
<tr>
<td><strong>Hypertermic syndrome</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>– chills</td>
<td>103</td>
<td>94,50±2,18</td>
</tr>
<tr>
<td>– febrile temperature (&gt;38 °C)</td>
<td>82</td>
<td>75,23±4,13</td>
</tr>
<tr>
<td>– high-grade fever (&gt;39 °C)</td>
<td>21</td>
<td>19,27±3,78</td>
</tr>
<tr>
<td>– subfebrile temperature (&gt;37,5° C)</td>
<td>6</td>
<td>5,50±2,18</td>
</tr>
</tbody>
</table>

Seasonal influenza usually characterized by typical clinical symptoms, with prevalence in certain cases of different syndromes (intoxication, catarrhal or hypertermia).

Species composition and populational level of nasal and tonsillar microbiota had evaluated following the microbiological research in this case-control study. The results of this case-control study of species composition and populational level of nasal and tonsillar microbiota in patients with seasonal influenza type A and B had described in the table 2.

Table 2. – Species composition and populational level of nasal and tonsillar microbiota in patients with seasonal influenza A and B subtypes (M±m)

<table>
<thead>
<tr>
<th>Microorganisms</th>
<th>Basic group (n=109)</th>
<th>Control group (n=67)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>C%</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>64</td>
<td>58,72±3,15</td>
</tr>
<tr>
<td>S. epidermidis</td>
<td>9</td>
<td>8,26±0,92</td>
</tr>
<tr>
<td>Streptococcus pyogenes</td>
<td>35</td>
<td>32,11±1,78</td>
</tr>
<tr>
<td>S. viridans</td>
<td>2</td>
<td>1,83±0,14</td>
</tr>
<tr>
<td>S. salivarius</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>S. pneumoniae</td>
<td>2</td>
<td>1,83±0,14</td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
<td>2</td>
<td>1,83±0,14</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>3</td>
<td>2,75±0,17</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>19</td>
<td>17,43±0,87</td>
</tr>
<tr>
<td>Klebsiella pneumoniae</td>
<td>3</td>
<td>2,75±0,17</td>
</tr>
<tr>
<td>Lactobacillus spp.</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Bifidobacterium spp.</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Fungi of Candida genus</td>
<td>14</td>
<td>12,84±0,89</td>
</tr>
</tbody>
</table>

Notes. N — number of obtained strains;  
C% — constancy index;  
Pi — frequency of occurrence;  
* — evident changes of parameters at р<0,05;  
** — evident changes of parameters at р<0,001.

As we can see from the table 2, several microorganisms persisted on nasal and tonsillar mucous membranes of infected patients with seasonal influenza subtype A with elevated constancy index: Staphylococcus aureus 58,72±3,15 vs 31,34±1,01 (р<0,001), Streptococcus pyogenes 32,11±1,78 vs 4,48±0,11 (р<0,001) and S. epidermidis 8,26±0,92 vs 13,43±1,14 (р<0,05).

The comparative mathematic analysis of microbial representatives proved the prevalence of Enterobacteria species — Klebsiella pneumoniae in 23% of patients and Pseudomonas aeruginosa — in 21% of examined cases (fig. 1).

In basic group against a background of deep deficiency of indigenous microorganisms it has been observed the contamination of stomatopharynx with Streptococcus pyogenes, Streptococcus pneumoniae, Enterobacter (Escherichia, Klebsiella pneumoniae), Staphylococcus aureus, Haemophilus influenzae, Candida. The foregoing bacteria were detected (in 60,55±4,68% patients) more often as monoculture, and also as associations which include two (in 35,78±4,59% cases) and three (in 2,75±1,46% patients) species of opportunistic microorganisms.

Their population level as quantitative figure mounted to high critical level that further to the influenza’s secondary complications in young people (bacterial lobar pneumonia, acute sinusitis, lacunar tonsillitis).
Fig. 1. Pathogenic and opportunistic pathogenic microorganisms obtained from nasal and tonsillar smears in patients with seasonal influenza A and B subtypes

The clinical investigation of the application of Biosporin should be based on the experimental positive data. Initially, the simultaneous 72 hrs cultivation of Staphylococcus and Streptococcus clinical strains with the Bacillus—contained probiotic was performed on selective medium (in vitro). Resulted this, “Biosporin” (includes Bacillus subtilis & Bacillus licheniformis) depressed the growth and reproduction of S. aureus and S. pneumoniae clinical strains: after 24 hrs for 24,15±0,17%, after 48 hrs — to 44,65±0,22% and percentage of strains’ inhibition depressed to 58,94±0,23 on the third day. In clinical condition we had suggested the new way of probiotic’s administration for great efficacy to elimination of pathogen organisms by the Biosporin’s application on palatine tonsils and drops into nose. As a consequence of the foregoing local using in the holiaty therapy of young patients with seasonal influenza we had testified the useful influence of bacterial antagonism. It was observed the decreasing of population level of pathogen and opportunistic organisms in nose cavity and stomatopharynx against a background of full elimination of the S. pyogenes, H. influenzae, S. pneumoniae, S. aureus, K. pneumoniae, E. coli, fungi of Candida genus (p<0.05). The medical observation during the one month after acute influenza proved the positive preventive application of probiotic-contained holiatry scheme in treatment of patients with seasonal influenza A and B subtypes in adults of Bukovina region (Western Ukraine).

Conclusions:
1. Seasonal influenza type A in young people is accompanied by elimination of indigenous oropharyngeal mucosa obligate anaerobic lactobacilli, bifidobacteria and salivary Streptococcus, and contamination of allochtonous pathogenic (pyogenic streptococci, pneumococci and haemophilic bacteria) and opportunistic (staphylococcus, streptococcus, enterobacteria, yeast-like fungi of Candida genus) microorganisms.
2. Persistence of these organisms are in the form of monoculture (in 60,6% of patients) and in association consisting of two (in 35,8%) and three species (2,8%) of opportunistic pathogens.
3. “Biosporin” initiates the reduce population levels of clinical strains of S. aureus and S. pyogenes, isolated from naso-, oropharynx of patients with influenza. The more effective inhibition of test strains of Staphylococcus aureus and pyogenic streptococci in the case of simultaneously cultivation of biosporin in liquid culture medium, resulting in the inhibition of growth had reached after 72 h of incubation, accounting for 58,94% S. aureus and 73,33% — S. pyogenes, respectively, from the initial population level of clinical strains.

Practical recommendations. In patients with influenza subtype A and B the significant violations of nasal and tonsillar mucosal microflora had suggested. For correction of this and prevention of bacterial complications we appointed to combined treatment with the inclusion of probiotic “Biosporin” (the content of the ampule with 2 doses should be diluted in 5 ml of 0,9% saline, followed by application of 2 drops into each nostril and simultaneous application of 3 drops on the surface of the tonsils).

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The theory of autoantigens genesis in detection of causal antigens for autoimmune responses while psoriasis

Теория происхождения аутоантигенов в обнаружении причинных для аутоиммунных реакций при псориазе антигенов

В основе современной терапии псориаза лежит иммunosупрессия, что обусловлено принадлежностью этого заболевания к аутоиммунной патологии, а реакция иммунитета против собственного эпидермиса в литературе гипотетически рассматриваются как генетически детерминированная ошибка иммунного ответа. Эта точка зрения во многом связана с тем, что псориатические аутоантитела и/или антигены остаются неустановленными до настоящего времени.

Однако на их существование косвенно указывают сообщения о случаях отрицательных последствий современной иммуносупрессивной терапии. Так, например, увеличивается количество больных псориазом, у которых наблюдается активация возбудителя туберкулеза при их лечении анти-TNF-моноклональными антителами (моноклональные антитела ингибирующие фактор некроза

Contents

Section 1. Biology ................................................................. 3
Koba Igor Sergeyevich, Reshetka Mikhail Borisovich, Novikova Elena Nikolaevna,
Luneva Albina Vladimirovna
Etiology and pathogenesis of acute postpartum bacterial and mycotic endometritis in cows ................ 3
Kutlymuratova Gulparshin Atamuratovna
Herbs the perspective for an introduction in the conditions of the republic of Karakalpakstan .......... 5
Polishchuk Ludmila Valilievna, Lukyanchuk Vitaliy Vladislavovich
Homology of primary structures of glycosyltransferases those involved in the landomycines synthesis in producing them Streptomyces ................................................................. 7
Sahabutdinova Dinara Irikovna
Assessment of the degree of anthropogenic impact on the ecosystems of rivers on development indicators of the plankton communities ................................................................. 11
Utemuratova Gulshirin Najimatdinovna
Dynamics of a biodiversity of small mammals in Southern Priaral's ecological conditions ............... 13

Section 2. Study of art ......................................................... 16
Prashchenko Svetlana Valerievna
Postmodernism image system in Advertising graphics ................................................................. 16

Section 3. History and archaeology ...................................... 18
Lupika Tatiana Alexandrovna
Socio-political processes in Ukraine in the postwar period: 1946–1953's (for example the Kharkiv) ..... 18
Priymak Viktoriia Viktorovna, Kovalenko Tatiana Sergeevna, Scherbyna Elena Viktorovna
Life and Creative Development of the Corresponding Member of the National Academy of Agrarian Sciences of Ukraine Vitaly P. Kovalenko (1940–2011) ................................................................. 21

Section 4. Medical science .................................................. 24
Baybakov Volodymyr Myhaylovich
Pathological changes in drainage vascular injury resulting testicular spermatic cord anastomosis in experiments on rats ................................................................. 24
Galimova Elmira Fanisovna, Abdullina Aigyl Zarifovna, Achmadullina Gulnur Chadaynovna,
Galimov Shamil Narimanovich
The role of Men and their health in the modern world ................................................................. 26
Digtyar Valeriy Andreevitch, Lukianenko Dmytro Mykolayovitch, Zharikov Nikolay Yurievich
The research of influence the octenidine dihydrochloride on the tissue joints of growing organism ..... 27
Kamalov Telman Tolyaganovich
Depressive and anxiety disorders in patients with diabetic foot syndrome ................................... 30
Moskaliiuk Vasyl Deoniziyovych, Sydorchuk Anitura Stepanivna
Case-control clinical and microbiological study of probiotic substantive approach to holiary therapy of seasonal influenza type A and B in adults ................................................................. 33
Sinitsyn Boris Fedorovich
The theory of autoantigens genesis in detection of causal antigens for autoimmune responses while psoriasis ................................................................. 35
Turdiyeva Shohida Tolkenovna, Taturova Nargiza Nuriddinovna, Shayhova Munira Ikramovna,
Nosirova Gulmira Ramzitdinovna
Results of the study of the physical development of children and teenagers with chronic gastroduodenal pathology ................................................................. 37
Khabibulla Aminov Djalalidinovich
MRI abnormalities and EEG patterns of symptomatic epilepsy in children with cerebral palsy ................................................................. 39
Khomko Oleh Yosiphovich, Svetlana Yurievna Karateieva, Igor Ivanovich Bilyk,
Khomko Bogdan Olegovich
Ozone application in multimodal treatment of pyoinflammatory complications in patients with diabetes mellitus ................................................................. 41

Section 5. Pedagogy ............................................................. 43
Angelova Marina Nikolaevna
Professionally oriented teaching of foreign language in non-linguistic colleges ................................ 43
Batyaeva Svetlana Vadimovna
Social-philosophical aspects of inclusive education ................................................................. 45
Garanina Reseda Muhtarrovna
Implementation of student-developing potential of independent work ......................................... 47
Georgiadis Alexandra Anatolevna
Application of media and educational technologies in an independent and individual work of students-philologists ................................................................. 49