© Pediatr Med Rodz 2018, 14 (4), p. 412–415
DOI: 10.15557/PiMR.2018.0054

Khrystyna Ihorivna Vasylyshyn[1], Nadiya Volodymyrivna Gluschenko[1],
Ihor Yuriyovych Vysotsky[1], Oleksandr Ivanovich Smiyan[2],
Kateryna Oleksandrivna Smiian-Horbunova[2], Oksana Robertivna Gladchenko[3]

Received: 18.05.2018
Accepted: 27.09.2018
Published: 31.12.2018

Zastosowanie preparatu synbiotycznego w kompleksowej terapii pozaszpitalnego zapalenia płuc u dzieci w wieku przedszkolnym

The use of synbiotic preparation in complex therapy of community-acquired pneumonia in preschool children

[1] Department of Biophysics, Biochemistry, Pharmacology and Biomolecular Engineering, Sumy State University, Sumy, Ukraine
[2] Department of Paediatrics, Sumy State University, Sumy, Ukraine
[3] Department of Foreign Languages, Sumy State University, Sumy, Ukraine
Correspondence: Professor Oleksandr Ivanovich Smiyan, MD, PhD, Department of Paediatrics, Sumy State University, 28 Troytska Str., Sumy, Ukraine, tel.: +380506316005, e-mail: smiyana@ukr.net

Streszczenie

W artykule omówiono wpływ terapii synbiotycznej na zmiany jakościowe i ilościowe w mikroflorze jelita grubego u dzieci w wieku przedszkolnym chorujących na pozaszpitalne zapalenie płuc. Badaniem objęto 33 dzieci w wieku od 1 do 3 lat. Pacjentów podzielono na dwie grupy. Pierwsza liczyła 17 dzieci otrzymujących standardowe leczenie. Do drugiej grupy włączono 16 pacjentów, u których leczenie uzupełniono podawaniem preparatu synbiotycznego w dawce jedna saszetka na dobę. Ocenę mikroflory jelita grubego u 33 pacjentów przeprowadzono przed rozpoczęciem leczenia oraz w dniach 12.–14. terapii. Do grupy kontrolnej włączono 20 zdrowych dzieci dobranych pod względem wieku i płci. Badanie bakteriologiczne mikroflory jelitowej przeprowadzono metodą Epshtein-Lytvak. Ocena zmian w składzie mikroflory u dzieci z pozaszpitalnym zapaleniem płuc wykazała nasilenie zaburzeń równowagi mikroflory jelitowej u dzieci otrzymujących standardowe leczenie. W odniesieniu do skuteczności preparatu synbiotycznego u pacjentów z pozaszpitalnym zapaleniem płuc wykazano istotną poprawę mikrobiocenozy jelitowej u dzieci otrzymujących kompleksowe leczenie uzupełnione terapią synbiotyczną w porównaniu z dziećmi leczonymi według standardowego schematu. Zatem zastosowanie terapii synbiotycznej u dzieci z pozaszpitalnym zapaleniem płuc poprawia lub w pełni przywraca prawidłową mikroflorę jelitową w pewnych przypadkach. Preparat ten można stosować jako bezpieczny i dogodny sposób przywracania równowagi mikroflory jelitowej oraz zapobiegania patologiom przewodu pokarmowego.

Słowa kluczowe: pozaszpitalne zapalenie płuc, dzieci w wieku przedszkolnym, mikroflora jelitowa

Abstract

The article discusses the effect of synbiotic therapy on the qualitative and quantitative changes in colonic microbiota in preschool children with community-acquired pneumonia. A total of 33 children aged from 1 to 3 years were included in the study. All patients were divided into two groups. The first group consisted of 17 children who received standard therapy. The second group consisted of 16 patients, whose treatment was supplemented with a synbiotic preparation at a dose of one sachet per day. The assessment of colonic microbiota was conducted in 33 patients with community-acquired pneumonia before treatment and on treatment days 12–14. The control group consisted of 20 healthy age and sex-matched children. Bacteriological study of gut microflora was conducted using the Epshtein-Lytvak method. The evaluation of the microflora composition changes in children suffering from community-acquired pneumonia showed an intensification of gut microflora imbalance after standard therapy. When studying the effectiveness of the synbiotic preparation in patients with community-acquired pneumonia, it was found that the state of colon microbiocenosis in patients who received complex therapy with synbiotic drug significantly improved compared to children treated with standard regimen. Thus, of the use of synbiotic therapy in patients with community-acquired pneumonia improves or fully restores gut microflora in some cases. This preparation can serve as a safe and convenient way to restore gut microflora balance and prevent the development of gastrointestinal pathologies.

Keywords: community-acquired pneumonia, preschool children, gut microflora

INTRODUCTION

Community-acquired pneumonias (CAP) take top spot in the structure of general morbidity among children and remain one of the 10 key causes of mortality in economically developed countries. According to the World Health Organization statistics, 155 million cases of infant pneumonia are recorded annually. Cases of death due to pneumonia are observed mainly in infants (11,3 per 100,000 live births), but also in adolescents and children with immune defence disorders[1]. Despite advances in modern medicine, pneumonia still remains one of the most serious diseases. It is associated not only with high mortality risk and different complications, but also with a long recovery period with asthenic syndrome manifestations and vegetative regulation disorders. The degree of predisposition to different inflammatory reactions of the respiratory system and the peculiarities of their clinical course are connected with the state of immunological reactivity[2]. Typical large bowel microflora is known to play an important role in the maintenance of the immunological homeostasis. Eubiotic auto-microflora representatives can oppress the growth of various pathogenic and nonpathogenic microorganisms, intensify the phagocytic activity of macrophages, monocytes and granulocytes as well as increase cytokine, IgA and cytoimmunologic protection system synthesis[3–5]. The spectrum of diseases whose pathogenic mechanisms are related to qualitative and quantitative disorders of the gut microbiota is growing at present. The diseases of bronchopulmonary organs belong to this spectrum. The associated dysbiotic gut changes, having reached a certain level, worsen the clinical course of the underlying disease. As a result, the severity of clinical symptoms increases, and so does the disease duration, while the general condition, treatment parameters and patients' quality of life deteriorate. Once pneumonia is diagnosed, antibacterial therapy is prescribed immediately as a rule. At the same time, antibacterial therapy plays a key role in the gut biocenosis disorders. Antimicrobials are known to lead to microecological disorders even when used parenterally[2].

Unfortunately, modern medicine does not always take into account the need to maintain the symbiosis of the child's body with its microflora. Biotherapy, which includes mainly probiotic and prebiotic preparations, is considered the most optimal method for the prophylaxis and correction of microbiocenosis imbalance. According to some authors, probiotic and antibiotic co-administration prevents dysbiotic and immunological disorders, potentiates the effect of antibiotic therapy and reduces the duration of disease exacerbation[6].

Therapeutic and preventive effects of probiotics are associated with:

- activation of local macrophages to increase antigen presentation of B lymphocytes and increased local and systemic production of secretory immunoglobulin A (IgA);
- modulation of cytokine profiles;
- bacteriocin secretion to inhibit pathogens;
- participation in the regulation of biofilms functioning on the mucous membranes;
- food digestion and competition with pathogens for nutrients;
- local pH change to create unfavourable local environment for the development of pathogens;
- neutralisation of superoxide radicals;
- stimulation of epithelial mucin production;
- enhancing the gut barrier function;
- competitive interaction for the receptors on the colon mucous membrane[7–9].

Given the fact that populations of normal microflora representatives are able to grow rapidly in the presence of nourishing substrates, the use of synbiotic is appropriate as prebiotics perform a preparatory function for the development of probiotic culture. Symbiotic effect is based on the synergism between probiotics and prebiotics. As a result, not only microorganisms – probiotics are most effectively implanted in the gastrointestinal tract of the host, but also one's own microflora is stimulated. As a result, human metabolic processes normalise[10].

The aim of our research was to assess the effects of a synbiotic preparation on gut microflora in preschool children suffering from CAP.

The preparation contains the *Bifidobacterium* (BB-12) strain, which maintains and regulates gut microflora balance. It has a wide range of antagonistic activities against pathogenic and opportunistic bacteria (OB) as well as strong colonisation ability. *Bifidobacterium* BB-12 shows acid and gall tolerance, has predicted antibiotic resistance level, enhances the body's immunity and restores the natural protection of the child's organism. It is important that these bacteria have been awarded GRAS (generally recognised as safe) status, characterising them as definitely safe in use. The preparation is available in a sachet form, which contains more than 4 billion of lyophilised cells of *Bifidobacterium* BB-12 and a prebiotic component – fruitoligosaccharide. Acidolac Baby can be used in children aged from 1 to 3 years (1 sachet per day) and over 3 years (1 sachet 1–2 times a day). The presence of prebiotics (fruitoligosaccharide) in the formulation selectively stimulates and regulates the growth of probiotic components, allowing for more rapid and longer-lasting effects compared to preparations consisting of probiotics or prebiotics alone.

MATERIAL AND METHODS

The study included 33 children aged from 1 to 3 years, who underwent a course of CAP treatment in the infectious unit No. 1 of the Sumy Children's Clinical Hospital named after St. Zinaida. All patients were divided into two groups. The first group consisted of 17 children who received standard therapy according to the Ukrainian Ministry of Health Protocol No. 18 of health care for children with pneumonia

 DOI: 10.15557/PiMR.2018.0054

dated January 13th, 2015. The second group consisted of 16 patients with CAP, whose treatment course was supplemented with a synbiotic preparation at a dose of one sachet per day.

The characteristics of colon microbiota was conducted in 33 patients with CAP before treatment on day 1 of admission to hospital (groups I and II), in 17 patients on days 12–14 of standard treatment (group I) and in 16 patients on days 12–14 of the therapy supplemented with the synbiotic preparation (group II).

The control group consisted of 20 age and sex-matched healthy children.

Pneumonia diagnosis was verified based on complaints from the parents of affected children, medical history, objective symptoms as well as data obtained using laboratory and instrumental methods according to the children's care protocols of the "Children's pulmonology" approved by the Ukrainian Ministry of Health Order No. 18 dated January 13th, 2005.

The study of microflora structural peculiarities was performed using R.V. Epshtein-Lytvak method (1977). It is based on the calculation of bacteria quantity found in the dilution of 1 g of faeces seeded in selective nutrient media[11].

The indicator of microbial colonisation intensity (microbe count) was determined by counting the colonies with the help of colony forming units (CFU). Colonisation intensity was expressed as a decimal logarithm (1–12 lg CFU/g) in order to facilitate the calculation.

Statistical processing of final results was carried out using the standard statistical Microsoft Excel, adapted for biomedical research with Student criterion (t) used for the estimation of validity difference in absolute average values. If $t = 1.96$, $p < 0.05$, there is a significant difference between indicators.

The investigation was approved by the Institutional Bioethics Committee and conforms the principles outlined in the Declaration of Helsinki with subsequent amendments.

DISCUSSION OF RESULTS

The analysis of gut microflora in children with CAP showed considerable changes in qualitative and/or quantitative composition of aerobic and anaerobic bacteria in the first days of hospitalisation.

Evaluation of colonic dysbiotic changes in CAP patients at the beginning of the disease showed a reliable decrease of bifidobacteria [(5.97 ± 0.41) lg CFU/g ($p < 0.001$)] and lactobacteria quantity [(6.35 ± 0.44) lg CFU/g ($p < 0.001$)] compared to children from the control group (Tab. 1).

Evaluation of changes in the microflora composition in children suffering from CAP showed intensified gut microflora imbalance after standard therapy. The number of bifidobacteria [(4.27 ± 0.52) lg CFU/g ($p < 0.05$)] and lactobacteria [(4.63 ± 0.54) lg CFU/g ($p < 0.05$)], *Escherichia coli* [(5.25 ± 0.34) lg CFU/g ($p < 0.05$)] decreased, while the number of OB [(3.70 ± 0.41) lg CFU/g ($p < 0.05$)]

Bacteria	Control group, lg CFU/gr ($n = 20$)	Groups I and II at baseline, lg CFU/gr ($n = 33$)	Group I after treatment, lg CFU/gr ($n = 17$)	Group II after treatment, lg CFU/gr ($n = 16$)
Bifidobacteria	8.59 ± 0.33	5.97 ± 0.41 $p_{1-2} < 0.001$	4.27 ± 0.52 $p_{1-3} < 0.001$ $p_{2-3} < 0.05$	6.59 ± 0.89 $p_{1-4} > 0.05$ $p_{2-4} > 0.05$ $p_{3-4} < 0.05$
Lactobacteria	8.46 ± 0.25	6.35 ± 0.44 $p_{1-2} < 0.001$	4.63 ± 0.54 $p_{1-3} < 0.001$ $p_{2-3} < 0.05$	6.57 ± 0.65 $p_{1-4} < 0.05$ $p_{2-4} > 0.05$ $p_{3-4} < 0.05$
Total number of *Escherichia coli*	6.83 ± 0.19	6.21 ± 0.26 $p_{1-2} > 0.05$	5.25 ± 0.34 $p_{1-3} < 0.001$ $p_{2-3} < 0.05$	6.40 ± 0.39 $p_{1-4} > 0.05$ $p_{2-4} > 0.05$ $p_{3-4} < 0.05$
OB	1.88 ± 0.27	2.67 ± 0.27 $p_{1-2} > 0.05$	3.70 ± 0.41 $p_{1-3} < 0.01$ $p_{2-3} < 0.05$	2.14 ± 0.19 $p_{1-4} > 0.05$ $p_{2-4} > 0.05$ $p_{3-4} < 0.01$
Staphylococci	0.26 ± 0.14	0.90 ± 0.27 $p_{1-2} > 0.05$	1.67 ± 0.44 $p_{1-3} < 0.01$ $p_{2-3} > 0.05$	0.73 ± 0.25 $p_{1-4} > 0.05$ $p_{2-4} > 0.05$ $p_{3-4} > 0.05$
Fungi *Candida*	0.91 ± 0.27	1.85 ± 0.37 $p_{1-2} > 0.05$	3.16 ± 0.54 $p_{1-3} < 0.01$ $p_{2-3} > 0.05$	1.81 ± 0.27 $p_{1-4} > 0.05$ $p_{2-4} > 0.05$ $p_{3-4} > 0.05$

p_{1-2} – differentials between children at baseline and control group; p_{1-3}, p_{1-4} – differentials between control group and groups I and II; p_{2-3}, p_{2-4} – differentials between groups I and II at baseline and after treatment; p_{3-4} – differentials between groups I and II after treatment.

Tab. 1. Dynamics of gut microflora changes in preschool children suffering from CAP depending on therapy (M ± m; M – *arithmetic mean*, m – *mean error of arithmetic mean)*

DOI: 10.15557/PiMR.2018.0054

increased in children from group I compared to relevant indicators in the acute phase of disease. A significant decrease of bifidobacteria ($p < 0.001$), lactobacteria ($p < 0.001$), and *Escherichia coli* ($p < 0.001$) titres as well as increased OB, staphylococci and *Candida* titres ($p < 0.01$) were found compared to controls.

The obtained research data indicate that the use of standard therapy in children with CAP resulted in the absence of positive changes of the abovementioned indicators. Indigene microflora has a great stimulatory impact on local gut immunity; therefore, a decrease in lactobacteria and bifidobacteria reduced antagonistic and immunogenic properties of normal gut microflora. This, in turn, increased the number of pathogenic and opportunistic microorganisms as well as the imbalance in the ratio of obligate and facultative microorganisms in the normal gut microflora. This is in line with other authors[8,9]. Thus, the decrease in the composition of some microbiota representatives can cause an imbalance of the admirable system of local protection and even promote the development of pathological conditions.

When assessing the effectiveness of the synbiotic preparation in patients with CAP it was found that colonic microbiocenosis significantly improved in patients who received this preparation compared to children treated with standard regimen (Tab. 1).

The analysis of the composition of gut microbiota in children from group II revealed a significant increase of bifidobacteria [(6.59 ± 0.89) lg CFU/g ($p < 0.05$)], lactobacteria [(6.57 ± 0.65) lg CFU/g ($p < 0.05$)], and *Escherichia coli* [(6.40 ± 0.39) lg CFU/g ($p < 0.05$)] as well as a decrease of opportunistic microflora titres [(2.14 ± 0.19) lg CFU/g ($p < 0.01$)] compared to group I (Tab. 1). The composition of bifidobacteria, *Escherichia coli*, OB, staphylococci and fungi *Candida* normalised in children in group II.

Thus, the obtained research data prove the effectiveness of synbiotic preparation in patients suffering from CAP. The preparation improves or fully renews the state of gut microflora in some cases.

CONCLUSIONS

All preschool children included in the study showed a disbalance of gut microflora composition with decreased bifidobacteria and lactobacteria in the acute phase of CAP.

After standard therapy without the symbiotic preparation, a further significant decrease of bifidobacteria, lactobacteria, and *Escherichia coli* titres and an increase in the number of opportunistic bacteria were found in children with CAP.

Inclusion of synbiotic preparation in the therapy of patients with community acquired pneumonia promoted normalisation of bifidobacteria, *Escherichia coli*, *Staphylococcus*, *Candida* and opportunistic microflora.

This preparation can serve as a safe and convenient way to restore gut microflora balance and prevent the development of gastrointestinal tract pathological conditions.

Further research of the relationship between microbiota changes and immune system indicators is needed in children with CAP, who receive a synbiotic preparation to prevent complications of antibiotic therapy.

Conflict of interest

Authors do not report any financial or personal connections with other persons or organisations, which might negatively affect the contents of this publication and/or claim authorship rights to this publication.

Piśmiennictwo

1. le Roux DM, Myer L, Nicol MP et al.: Incidence and severity of childhood pneumonia in the first year of life in a South African birth cohort: the Drakenstein Child Health Study. Lancet Glob Health 2015; 3: e95–e103.
2. Agustina R, Kok FJ, van de Rest O et al.: Randomized trial of probiotics and calcium on diarrhea and respiratory tract infections in Indonesian children. Pediatrics 2012; 129: e1155–e1164.
3. Honda K, Littman DR: The microbiota in adaptive immune homeostasis and disease. Nature 2016; 535: 75–84.
4. Pickard JM, Zeng MY, Caruso R et. al.: Gut microbiota: role in pathogen colonization, immune responses, and inflammatory disease. Immunol Rev 2017; 279: 70–89.
5. Belkaid Y, Hand TW: Role of the microbiota in immunity and inflammation. Cell 2014; 157: 121–141.
6. Macfarlane S, Bahrami B, Macfarlane GT: Mucosal biofilm communities in the human intestinal tract. Adv Appl Microbiol 2011; 75: 111–143.
7. Holscher HD, Czerkies LA, Cekola P et al.: *Bifidobacterium lactis* Bb12 enhances intestinal antibody response in formula-fed infants: a randomized, double-blind, controlled trial. JPEN J Parenter Enteral Nutr 2012; 36 (Suppl): 106S–117S.
8. Meier R, Steuerwald M: Place of probiotics. Curr Opin Crit Care 2005; 11: 318–325.
9. Saavedra JM: Use of probiotics in pediatrics: rationale, mechanisms of action, and practical aspects. Nutr Clin Pract 2007; 22: 351–365.
10. Thomas DW, Greer FR; American Academy of Pediatrics Committee on Nutrition; American Academy of Pediatrics Section on Gastroenterology, Hepatology, and Nutrition: Probiotics and prebiotics in pediatrics. Pediatrics 2010; 126: 1217–1231.
11. Epshtein-Lytvak RV, Vylshanskaya FA: [Bacteriologytcheskaya diagnostika disbacteriosa kyshechnyka. Metod. Rekomendatsy] [Published in Russian]. Moscow 1977; 22.