UDC 616-001.17-085.246.8-053.2

DOI: 10.22141/2308-2097.4.62.2016.81095

PATSERA M.V., SKRYPNYKOVA YA.S., IVAN'KO O.H.
Zaporizhzhia State Medical University, Zaporizhzhia, Ukraine

USE OF *LACTOBACILLUS ACIDOPHILUS* R0052 AND *LACTOBACILLUS RHAMNOSUS* R0011 PROBIOTIC STRAINS IN CHILDREN WITH BURN INJURIES

Summary. *Today, burn injury is second most frequent diagnosis in all children hospitalized with injuries. The main cause of death in cases of extensive deep burns is burn infection that occurs in 23 to 82 % of all burn units' patients. Antibacterial treatment rationality is of great importance in fighting the generalized infections. This paper is aimed at scrutinizing the incidence and course characteristics of the antibiotic-associated diarrhea (AAD) in burn patients, as well as the possibility of its prevention in children receiving antibacterial treatment in the Regional Burn Unit of Zaporizhzhia. During 2012–2015, we have observed 438 children with burn injuries, who received antibiotics. We observed children receiving antibiotics and examined over hospitalization time by detection of the highly specific for antibiotic-associated diarrhea A + B Clostridium difficile toxins in stool, which allowed diagnosing the enterocolitis due to Clostridium difficile associated with antibiotics administration (A4.07, ICD-10). AAD prevention methods have been developed, among which preventive (from the first hours of hospitalization) administration of oral probiotic agent containing Lactobacillus acidophilus R0052 and Lactobacillus rhamnosus R0011 probiotic strains as a part of the Lacidofil® preparation dosed by age should be considered a major one. Prophylactic prescription of probiotic strains with antitoxic action against Clostridium difficile had reduced the incidence of antibiotic-associated diarrhea in children and the severity of its symptoms by 3.4 times.*

Key words: *children, burn injury, antibiotic-associated diarrhea, Lactobacillus acidophilus R0052 and Lactobacillus rhamnosus R0011 probiotic strains.*

Today, burn injury is second most frequent diagnosis in all children hospitalized with injuries. Burns remain among the most urgent and socially important issues of children's traumatism. According to global statistics, 18 to 42 % of people suffer from burns of varying severity during their life [1]. Patients' recovery and life prognosis depends on area and depth of the damaged skin. The development of burn disease is considered a dangerous condition for burned patients; the burn wound and resulting somatic changes cause adaptation mechanisms and body reactions stress, which might lead to death.

Burn shock, the first stage of the burn disease, can develop in children with burns of 5 to 10 % or more of the skin area, or with 3 to 5 % of damaged skin in cases of deep injuries. The peculiarity of children's burn injury is associated with age-related anatomical and physiological characteristics. Due to helplessness, the child is subject to longer exposure during the damaging factor action, which leads to deeper burns, as compared with adults.

Address for correspondence:
Patsera M.V.
Department of Propaedeutic Pediatrics,
Zaporizhzhia State Medical University, MOZ of Ukraine
Mayakovskiy ave., 26, Zaporizhzhia, 69035, Ukraine
E-mail: patsera1@rambler.ru

Loss of protective skin over a large area of the body surface creates conditions for microbial infestation on the one hand and disintegration of the major neurotrophic and metabolic functions of the organism on the other, which leads to disruption of anti-infective protection factors. The conditions for infectious process development and generalization are established in child's body. Necrotic tissue formed in the area of burn injury is a favorable environment for the invasion and multiplication of microorganisms. The main cause of death in cases of extensive deep burns is burn infection that occurs in 23 to 82 % of all burn units' patients [2, 3].

Prescription of antibiotics for patients with burns takes into account the surface area of damaged skin and stage of burn disease. For instance, if the area of burns is less than 10 %, the use of antibiotics is necessary with burdened premorbid background, specifically in patients with congenital heart disease, diabetes, hemoglobinopathy, renal diseases, or concurrent respiratory disease. In cases of burn area of 10 % or more, the antibiotic treatment is prescribed very frequently, usually on the background of thermal inhalation injury, in all cases of systemic inflammatory response, and against the threat of infection generalization. Any infectious process originating in the burn wound is able to trigger the development of severe complications, such as sepsis, pneumonia, septic arthritis, urinary tract infections, myocarditis, and lymphadenitis. In order to prevent the emergence of infectious complications, antibiotic treatment is initiated during the burn shock period and continued against the background of burn toxemia or septic toxemia. Antibacterial treatment rationality is of great importance in fighting the generalized infection. At present, the most commonly used antimicrobial preparations are cephalosporins of 2nd, 3rd and 4th generations and semisynthetic penicillins; aminoglycosides, carbapenems, imipenems, and glycopeptides are used less frequently. The average duration of antibiotic preparations administration, according to our data, is 15.8 days.

The lack of positive dynamics in the primary disease treatment and further development of complications, increase in systemic inflammatory response symptoms within 48 to 72 hours from the start of therapy, and the insensitivity of burn surface flora to administered antibacterial preparation requires antibiotic replacement. In severe disease course, combined antimicrobial treatment is used, which implies the simultaneous administration of two or even three preparations in their maximum therapeutic doses. It is clear that antibiotic treatment of many burn patients is characterized by high intensity and duration.

Under these conditions, the most important component of successful treatment is prevention of iatrogenic complications, particularly the antibiotic-associated diarrhea (AAD), which is unsafe for the patient's life and able to develop on the background of any antibiotic therapy [4, 5].

This paper is aimed at scrutinizing the incidence and course characteristics of the AAD in burn patients, as well as the possibility of its prevention in children receiving antibacterial treatment in the Regional Burn Unit of Zaporizhzhia.

During 2012–2015, we have observed 438 children with burn injuries who received antibiotics in the Regional Burn Unit of Zaporizhzhia. Observations were divided into two stages.

During the first stage, in 2012–2013, we have observed 120 children receiving antibiotics and being examined over hospitalization time by detection of the highly specific for AAD A + B *Clostridium difficile* toxins in stool [6]. AAD has occurred in 32 (27 %) of 120 observed patients and was characterized by liquid stool (at least 3 times a day, usually 6 to 16 times) in at least 3 days after hospitalization and antibiotic preparations prescription, and persisted for at least 48 hours [7]. The children had pain along their large intestine and decreased appetite; the onset of disease was not accompanied by fever response and vomiting. The most frequent viral and bacterial causes of diarrhea, such as gastroenteritis, nutrition mistakes, laxatives, etc. have been excluded in these patients.

Among 32 samples of liquid stool taken from the patients with the aforesaid clinical picture, in 25 (78 %) *Clostridium difficile* toxins have been found, which allowed diagnosing the enterocolitis due to *Clostridium difficile* associated with antibiotics administration (A4.07, ICD-10) [8]. According to the clinical course, 12 of 32 patients had mild diarrhea, 10 children had AAD of moderate severity, and 10 had severe diarrhea that required additional rehydration fluid therapy [9].

We were not able to identify the priority effect of specific antibiotics on severity and incidence of AAD; however, effects of age (younger age group mostly), the degree of burn injury, and administration of antibiotics in combination have been observed. The results obtained allow us to conclude that AAD caused by antibiotic therapy is a significant problem for the children treated in the burn unit that needs to be addressed.

AAD prevention methods have been developed, among which preventive (from the first hours of hospitalization) administration of oral probiotic agent containing *Lactobacillus acidophilus* R0052 and *Lactobacillus rhamnosus* R0011 probiotic strains as a part of Lacidofil® preparation dosed by age should be considered a major one. This probiotic agent had proved its effectiveness against antibiotic-associated diarrhea (including one associated with *Clostridium difficile* infection), being able to limit the pathogenic microorganisms' intestinal colonization and block the enteropathogenic (choleriform) and necrotic toxins [10–12]. In the subsequent period of 2014–2015, all 318 hospitalized patients have received antibiotics and their combinations similar to the previous ones in the same unit, which had not undergone any material or utility-related changes, except compulsory preventive therapy with *Lactobacillus acidophilus* R0052 and *Lactobacillus rhamnosus* R0011 probiotic strains. At the same time, AAD has been diagnosed in 25 children (7.9 %) over the observation period. In order to treat AAD, Enterol® probiotic preparation based on *Saccharomyces boulardii* strain [13] has been administered to 20 patients; another 6 children required metronidazole as a specific antimicrobial agent [14, 15] at a dose of 30 mg/kg per day in 3 divided oral doses for a 5-day period.

Only one patient required additional rehydration therapy. It should be emphasized that while using Enterol® preparation, we sought to take all necessary precautions in

order to avoid any contact between the powder and wound surface. Therefore, an aqueous suspension of Enterol® sachet contents had been prepared in a separate room and then brought to the patient room for per os administration. Lacidofil® preparation does not require such precautions, as it is packed into capsules [16, 17]. In addition, no cases of human infection by *Lactobacillus acidophilus* R0052 and *Lactobacillus rhamnosus* R0011 strains and occurrences of local or systemic infectious reactions have been registered over a long observation period [18–20].

It also should be noted that *Lactobacillus acidophilus* R0052 and *Lactobacillus rhamnosus* R0011 probiotic strains administered to 318 children have not caused any side effects, or extended the terms of wound healing process, or formed any unusual manifestation of wound healing.

Conclusions

1. During 2012–2015, 438 children have been receiving antibiotic therapy of varying intensity in the Burn Unit; antibiotic-associated diarrhea of varying severity had developed in different observation periods in 7.9 to 27 % of children.

2. The majority of children (73 %) had antibiotic-associated diarrhea accompanied by the release of enteropathogenic toxins *Clostridium difficile*, spores of which are likely to constitute a normal microbial component of the Burn Unit contamination.

3. Prophylactic prescription of *Lactobacillus acidophilus* R0052 and *Lactobacillus rhamnosus* R0011 probiotic strains with antitoxic action against Clostridium difficile as a part of Lacidofil® preparation in patients receiving antimicrobial treatment had reduced the incidence of antibiotic-associated diarrhea in children and the severity of its symptoms by 3.4 times.

References

1. Fistal E.Y., Kozinets G.P., Samoilenko G.E., Nosenko V.M. Pediatricheskaia kombustiologia: rukovodstvo dlia vrachei [Pediatric combustiology: the doctors' study guide]. — Donetsk: Veber, 2007. — P. 233.

2. Krutikov M.G., Bobrovnikov A.E. Preventive antibiotics in combustiology (literature review) // Combustiology journal (electronic version). — 2000. — № 4.

3. Krutikov M.G. Infection issues in burn patients (literature review) // Combustiology journal (electronic version). — 2002. — № 10.

4. Amsden G.W., Mandell G.L., Bennet J.E. Tables of antimicrobial agent pharmacology // Principles and Practice of Infectious Diseases. — 5th ed. — Philadelphia etc.: Churchill Livingstone, 2000. — P. 566-589.

5. Radutna O.A. Infektsionno-zavisimye mekhanizmy kishechnykh oslozhneniy, razvivaiushchikhsia vo vremia lechenia antibiotikami u detei [Infection-dependent mechanisms of intestinal complications development during antibiotic treatment in children] // Zaporozhskii Meditsinskii Zhurnal — Zaporizhzhia Medical Journal. — 2011. — Issue 13, № 4. — P. 40-43.

6. Ivanko O., Radutna H. Lacidofil® in prevention of antibiotic-associated diarrhea caused by Clostridium difficile infection // Annual Scientific Exchange. — 2005, Sept. 7–8. — Rome: Institut Rosell, 2005. — P. 32-34.

7. Lewis S.J., Heaton K.W. Stool form scale as a useful guide to intestinal transit time // Scand. J. of Gastroenter. — 1997. — Vol. 32. — P. 920-924.

8. Chernyshova L.I., Samarin D.V., Kramarev C.O. Gostri kyshkovi infektsii u ditey [Acute intestinal infections in children]. — Kyiv, 2006. — 163 p.

9. Ivanko O.H., Patsera M.V., Radutna O.A. Klinichna kharakterystyka ta mekanizmy formuvannia urazhen kishechnykhu pid chas terapii antybiotykamy u ditei. Proekt robochoi klasyfikatsii [Clinical characteristics and mechanisms of intestinal injuries formation during antibiotic treatment in children. Project of operating classification] // Pediatria, akusherstvo ta ginekologia — POG. — 2011. — Vol. 73, № 1. — P. 33-39.

10. Pelleschi M.E. Clostridium difficile-Associated Disease // Critical Care Nurse. — 2008. — Vol 28(1). — P. 27-35.

11. Johnston B.C., Supina A.L., Vohra S. Probiotics for pediatric antibiotic-associated diarrhea: a meta-analysis of randomized placebo-controlled trials // CMAJ. — 2006. — Vol. 175, № 4. — P. 377-383.

12. Chapman C.M., Gibson G.R., Rowland I. Health benefits of probiotics: are mixtures more effective than single strains? // European Journal of Nutrition. — 2011. — Vol. 50, № 1. — P. 1-17.

13. Kotowska M., Albrecht P., Szajewska H. Saccharomyces boulardii in the prevention of antibiotic-associated diarrhoea in children: a randomized double-blind placebo-controlled trial // Aliment. Pharmacol. Ther. — 2005. — Vol. 21, № 5. — P. 583-590.

14. Finegold S.M., Mathisen G.E. Metronidazole // Principles and Practice of infectious diseases / Mandell, Douglas, Bennett. — 3rd ed. — Edinburgh, London, Melbourne, 1990. — P. 303-308.

15. Hempel S. et al. Probiotics for the prevention and treatment of antibiotic-associated diarrhea: a systematic review and meta-analysis // Journal of the American Medical Association. — 2012. — Vol. 307, № 18. — P. 1959-1969.

16. Ivanko O.H., Patsera M.V., Shalmin A.S., Chernyshova L.I. Ispolzovanie probioticheskikh shtammov Lactobacillus acidophilus R0052 i Lactobacillus rhamnosus R0011 pri legochnom tuberkuleze u detei, oslozhnennom antibiotic-assotsiirovannoi Clostridium difficile kishechnoi infektsiei. [Lactobacillus acidophilus R0052 and Lactobacillus rhamnosus R0011 probiotic strains against pulmonary tuberculosis complicated by antibiotic-associated Clostridium difficile intestinal infection in children] // Zaporozhskii Meditsinskii Zhurnal — Zaporizhzhia Medical Journal. — 2010. — № 3. — P. 30-33.

17. Fisher M. Pseudomembranous Colitis: Nelson Textbook of Pediatrics. — 18th ed. — Kliegman, 2008. — www.mdconsult.com

18. Dial S., Jayaraman D., Tompkins T., Menzies D. Evaluation of the effectiveness of the probiotic lacidofil in the prevention of antibiotic associated diarrhea: pilot study for a randomized controlled trial. Annual Scientific Exchange 2003. Summary of probiotic Presentations&Poster abstracts, Institut Rosell — Lallemand Nutrition Group. — P. 31-33.

19. Del Piano M., et al. Is microencapsulation the future of probiotic preparations? The increased efficacy of gastro-protected probiotics // Gut Microbes. — 2011. — Vol. 2, № 2. — P. 120-123.

20. Foster L.M., Tompkins T.A., Dahl W.J. A comprehensive post-market review of studies on a probiotic product containing Lactobacillus helveticus R0052 and Lactobacillus rhamnosus R0011 // Beneficial Microbes. — 2011. — Vol. 2, № 4. — P. 319-334.

Отримано 21.09.16

Пацера М.В., Скрипникова Я.С., Іванько О.Г.
Запорізький державний медичний університет, м. Запоріжжя, Україна

ДОСВІД ВИКОРИСТАННЯ ПРОБІОТИЧНИХ ШТАМІВ *LACTOBACILLUS ACIDOPHILUS* R0052 ТА *LACTOBACILLUS RHAMNOSUS* R0011 У ДІТЕЙ З ОПІКОВОЮ ТРАВМОЮ

Резюме. На сьогодні опіки посідають друге місце серед усіх травм дітей. Основною причиною летальних наслідків у випадку виражених та глибоких опіків є інфекція, що виникає у 23–82 % усіх випадків опіків. Раціональна антибактеріальна терапія має велике значення в боротьбі з генералізованою інфекцією. Метою цього дослідження було ретельне вивчення епідеміології та характеристики антибіотик-асоційованої діареї (ААД) у хворих дітей з опіками, а також можливість запобігання цій діареї, що виникала внаслідок антибактеріальної терапії в пацієнтів Обласного опікового відділення м. Запоріжжя. Протягом 2012–2015 років ми спостерігали 438 дітей з опіковими травмами, які приймали антибіотики. У цих госпіталізованих дітей було знайдено специфічні для ААД *Clostridium difficile* токсини А + В у фекаліях. Це дозволило діагностувати *Clostridium difficile*-ентероколіт, пов'язаний з прийомом хворими антимікробних препаратів (А4.07, МКБ-10). Розроблено профілактичні методи ААД, а саме призначення з перших годин перебування в стаціонарі per os пробіотичного засобу *Lactobacillus acidophilus* R0052 і *Lactobacillus rhamnosus* R0011 у складі препарату Lacidofil®. Використання пробіотичних штамів з антитоксичною активністю щодо *Clostridium difficile* скорочує в 3,4 раза число випадків антибіотик-асоційованої діареї в дітей з опіками та зменшує тяжкість її симптомів.

Ключові слова: діти, опікова травма, антибактеріальна терапія, антибіотик-асоційована діарея, пробіотичні штами *Lactobacillus acidophilus* R0052 та *Lactobacillus rhamnosus* R0011.

Пацера М.В., Скрипникова Я.С., Иванько О.Г.
Запорожский государственный медицинский университет, г. Запорожье, Украина

ОПЫТ ИСПОЛЬЗОВАНИЯ ПРОБИОТИЧЕСКИХ ШТАММОВ *LACTOBACILLUS ACIDOPHILUS* R0052 И *LACTOBACILLUS RHAMNOSUS* R0011 У ДЕТЕЙ С ОЖОГОВОЙ ТРАВМОЙ

Резюме. Сегодня ожоговая травма занимает второе место среди всех травм детей. Основной причиной смерти в случае обширных глубоких ожогов является ожоговая инфекция, которая осложняет заболевание в 23–82 % случаев всех ожогов. Рациональная антибактериальная терапия имеет большое значение в борьбе с генерализованной инфекцией. Целью этого исследования было тщательное изучение распространенности и характеристики антибиотик-ассоциированной диареи (ААД) у больных с ожогами, а также возможность ее предотвращения у детей, получавших лечение антибактериальными препаратами в Областном ожоговом отделении города Запорожье. В течение 2012–2015 годов мы наблюдали 438 детей с ожоговыми травмами, получавших антимикробные препараты. У детей, находящихся на госпитализации и принимавших антибиотики различных групп, были обнаружены специфические для ААД *Clostridium difficile* токсины А + В в стуле. Это позволило диагностировать *Clostridium difficile*-энтероколит, связанный с назначением антибиотиков (А4.07, МКБ-10). Разработаны методы профилактики ААД, а именно назначение с первых часов пребывания в стационаре per os пробиотических штаммов *Lactobacillus acidophilus* R0052 и *Lactobacillus rhamnosus* R0011 в составе препарата Lacidofil®, дозированных по возрасту. Использование пробиотических штаммов с антитоксическим действием против *Clostridium difficile* сокращает в 3,4 раза число случаев антибиотик-ассоциированной диареи у детей с ожогами и уменьшает тяжесть ее симптомов.

Ключевые слова: дети, ожоговая травма, антибиотик-ассоциированная диарея, пробиотические штаммы *Lactobacillus acidophilus* R0052 и *Lactobacillus rhamnosus* R0011.