Clinical Trial/Experimental Study

Medicine

OPEN

Oral *Lactobacillus fermentum* CECT5716 in the patients with lactational abscess treated by needle aspiration

The late follow-up of a randomized controlled trial

Yi Zhang, MM[a], Yajun Gao, MBBS[a,*], Xiangping He, MM[a], Songtao Ding, MM[a], Haifeng Gao, MM[a]

Abstract

Background: Lactational mastitis and breast abscess cause trouble for women. It has been shown that oral probiotics can improve breast microecology, thus alleviating inflammatory responses. Our study aims to understand the long-term effect of *Lactobacillus fermentum* CECT5716 on patients with lactational breast abscess after needle aspiration.

Methods: Data continued in a randomized controlled study of 101 subjects with lactational abscess from 12 hospitals were included. They were randomly divided into an experimental group and a control group. After needle aspiration treatment, the experimental group was orally administrated with *L fermentum* CECT5716 for 4 consecutive weeks, while the control group was treated with maltodextrin in the same way). In the third month after randomized controlled trial, the subjects were followed up by an online questionnaire investigation. The observation indexes included the relief of breast pain, recurrence of mastitis from the end of oral administration to the follow-up, and the effect on continuing breastfeeding.

Results: A total of 101 patients were enrolled and 83 valid questionnaires were received during follow-up, including 40 in the experimental group and 43 in the control group. The rate of stop breastfeeding due to recurrence of mastitis was 2.5% (1/40) in the experimental group and 18.6% (8/43) in the control group, with a statistically significant difference (odds ratio = 0.112, 95% confidence interval: 0.013–0.942, $P < .05$). The rate of stop breastfeeding was 10% (4/40) in the experimental group and 25.6% (11/43) in the control group, without significant difference. The pain relief rate in the experimental group was 80% (32/40), which showed no significant difference from that in the control group, that is, 72.1% (31/43). The recurrence rate of mastitis in the experimental group was 20% (8/40), which was not significantly different from that in the control group, that is, 16.3% (7/43).

Conclusions: In lactating women with a history of breast abscess, oral *L fermentum* CECT5716 may reduce the risk of stop breastfeeding due to recurrence of mastitis.

Abbreviations: CI = confidence interval, *L. fermentum* = *Lactobacillus fermentum*, *S. aureus* = *Staphylococcus aureus*, WHO = World Health Organization.

Keywords: lactational breast abscesses, *Lactobacillus fermentumi*, stop breastfeeding

1. Introduction

The World Health Organization recommends exclusive breastfeeding for newborns in the first 6 months after birth and to continue breastfeeding until the age of ≥2 years.[1] Breast milk can not only provide irreplaceable nutrients for infants' growth and development but also prevent respiratory tract infection and diarrhea to a certain extent and reduce the probability of obesity in infants.[2] Studies in developing countries have shown that nonbreastfed infants are 6 to 10 times more likely to die in the first months after birth than breastfed infants.[3,4] Li et al.[5,6] have reported that in the recent 15 years, the exclusive

The project was funded by Nanjing Yuheming Medical Nutrition Co., Ltd and Elife Technology Co., Ltd. The funding body was not involved in the study design; the collection, analysis, and interpretation of data; or writing of the article.

The dataset supporting the conclusions of this article is included within the article.

This clinical study is a retrospective study. Only the clinical data of patients are collected, and there is no intervention in the treatment plan of patients, which will not bring physiological risks to patients. The researchers will do their best to protect the information provided by patients from disclosure of personal privacy. For this kind of research, the Principles of the Declaration of Helsinki should be complied with, and all the studies are approved by the ethics committee of Haidian Maternal and Child Health Hospital without discussion and reply by the members of ethics committee.

The authors declare that they have no competing interests.

The authors have no conflicts of interest to disclose.

[a] *Department of Breast Surgery, Maternal and Child, Center for Prevention and Cure of Breast Diseases, Haidian Maternal and Child Health Hospital, Haidian District, Beijing, China.*

**Correspondence: Yajun Gao, MBBS, Department of Breast Surgery, Maternal and Child, Center for Prevention and Cure of Breast Diseases, Haidian Maternal and Child Health Hospital, Haidian District, Beijing 100080, China (e-mail: gaoyajunzi@sina.com).*

How to cite this article: Zhang Y, Gao Y, He X, Ding S, Gao H. Oral Lactobacillus fermentum CECT5716 in the patients with lactational abscess treated by needle aspiration: The late follow-up of a randomized controlled trial. Medicine 2022;101:26(e29761).

Received: 18 September 2021 / Received in final form: 21 April 2022 / Accepted: 23 May 2022

http://dx.doi.org/10.1097/MD.0000000000029761

breastfeeding rate of infants in the first 6 months in major cities in China has been far lower than the international average. Previous studies have found that about 30% of women suffer from mastitis during lactation.[7,8] Moreover, it has been confirmed that lactational mastitis is one of the causes of early weaning in lactating women.[9,10] About 3% of women suffering from mastitis develop breast abscess,[11,12] which always requires subsequent puncture, pus aspiration, and even surgical incision, further aggravating the pain of lactating mothers. Oral *Lactobacillus fermentum (L. fermentum)* CECT5716 has been found to improve breast microecology to treat lactational mastitis,[13] but there is a lack of efficacy verification in abscess to adjuvant therapy. On this basis, the preliminary randomized controlled trial (RCT) was to verify the effect of *L. fermentum* CECT5716 in the treatment of patients with breast abscesses during lactation. From May 2020 to August 2020, 12 hospitals across the country were organized to conduct a randomized, controlled, and double-blind trial, which revealed that oral *L. fermentum* CECT5716 might improve the cure rate of breast abscess on the fifth day of the trial (preprint doi:10.21203/rs.3.rs-280421/v1). In the third month after the trial, a follow-up investigation was carried out to understand the long-term effect of *L. fermentum* CECT5716 on the patients.

2. Materials and methods

2.1. Selection of participants

The inclusion criteria for completed RCT were as follows: patients aged 20 to 45 years with breast abscess diagnosed during lactation (diagnostic criteria: painful breast mass and mass fluctuation, which may be accompanied by skin redness, elevated skin temperature and edema, and is accompanied with or without fever, and pus that can be removed by needle aspiration[14]); patients with single-cavity abscess in unilateral breast, with the maximum diameter measured by ultrasound of ≥3 cm and ≤6 cm, and no epidermal rupture; and patients willing to be treated with needle aspiration. The exclusion criteria included: patients who had previously presented with a breast abscess during the current pregnancy and lactation period; patients in whom a medical examination revealed comorbid infections of other organs, such as puerperal infection; patients with severe comorbid organ dysfunction (e.g., diabetes or hepatic, renal, or immune insufficiency); patients who did not maintain milk production in the affected breast through breastfeeding, breast pumping, or manual expression; patients with body temperature >37.5°C within 24 hours. The flow chart representing the selection of study participants is shown in Figure 1.

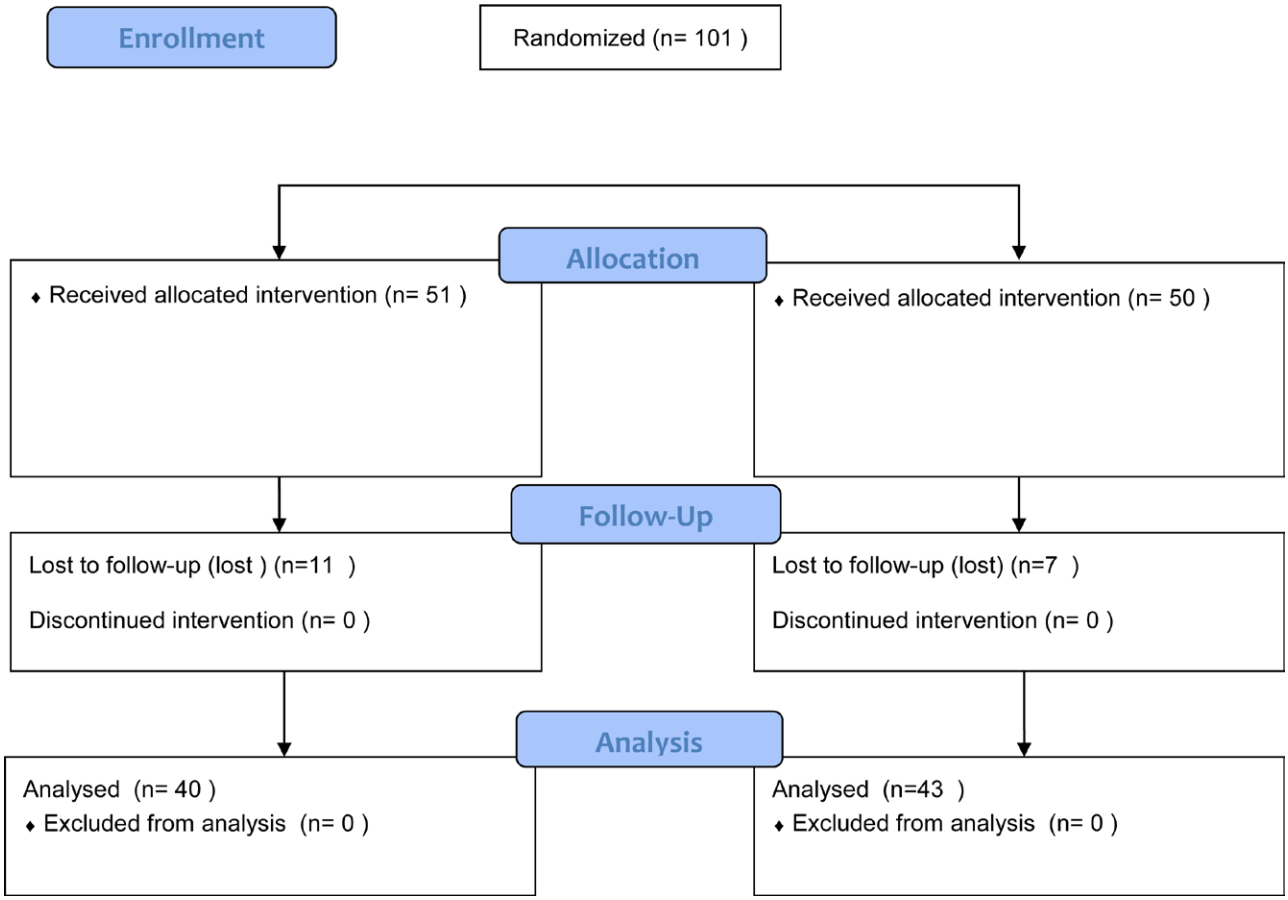

Figure 1. Flowchart for the selection of study participants.

The completed trial was a multicenter, randomized, double-blind, and controlled clinical trial. A total of 12 centers participated in this study, and the random distribution ratio between the experimental group and the control group was 1:1. Both groups were treated with a routine needle aspiration for breast abscess. Based on needle aspiration treatment, the experimental group took 1 sachet with 2 g of a freeze-dried probiotic containing 3×10^9 CFU of *L. fermentum* CECT5716 once a day for 4 weeks continuously from the first needle aspiration treatment session. L. fermentum CECT5716 was manufactured by Biosearch Life (Granada, Spain). During the trial, breastfeeding was continued, and the frequency of needle aspiration was performed according to the condition. The control group was treated with maltodextrin in the same way. According to the above criteria, a total of 101 patients completed the clinical trial from May 2020 to August 2020.

The preliminary RCT was registered in the Chinese Clinical Trial Registry (http://www.chictr.org.cn), registration number: ChiCTR2000032682, registration date: May 6, 2020. The ethics document for the previous study has been supplemented in the Chinese Clinical Trial Registry (2020XLA025-1).

2.2. Methods.

In November 2020, the 101 enrolled patients were investigated and followed up using a questionnaire on the Gold Data System through the WeChat group, and the informed consent was obtained online.

2.3. Outcomes/measurements

The main observation indexes included whether mastitis recurred after the preliminary trial, the relief of breast pain during lactation, and the continuation of breastfeeding. Recurrence of mastitis was defined as "lactational mastitis," definitely diagnosed in the hospital.[14] The pain was evaluated using the visual analog scale, with a score of 1 to 3 as mild pain and 4 to 7 as moderate–severe pain. The degree of breast pain during the last milk removal in the 2 groups was compared with that before the study. Pain relief was defined as relief from moderate to severe pain to mild pain and below, and from mild pain to no pain.

Table 1

Basic information of the 2 groups.

Variables	Assignment	Experimental group n (%)	Control group n (%)	*P* value
Pregnancy	Singleton	33 (82.5)	35 (81.4)	.896
	Twins	7 (17.5)	8 (18.6)	
Production	Eutocia	29 (72.5)	30 (69.8)	.784
	Cesarean delivery	11 (27.5)	13 (30.2)	
Breastfeeding situation	Breastfeeding	24 (60.0)	24 (55.8)	.700
	Mixed and artificial feeding	16 (40.0)	19 (44.2)	

2.4. Statistical methods

SPSS 23.0 (IBM Corp., Armonk, NY) was used for statistical analysis, and the medians were described for the measurement data and the percentages for the count data, and the chi-square test was used for comparison between groups.

3. Results

3.1. Basic information

In the preliminary RCT, a total of 101 patients were enrolled. During the follow-up of this study, 83 patients completed successfully and 18 were lost. Among them, there were 40 patients in the experimental group (median age, 31 years; age range, 21–39 years), and 43 patients in the control group (median age, 30 years; age range, 23–41 years). The other general data are shown in Table 1.

3.2. Comparison of weaning

As shown in Table 2, the rate of stop breastfeeding at follow-up was 10% (4/40), during the follow-up was 10% (4/40) in the experimental group, and 25.6% (11/43) in the control group. The intergroup difference in the rate of stop breastfeeding was 15.6%, without statistical significance (Pearson chi-square = 3.398, $P = .065$). After excluding the patients with weaning for work personal reasons, the patients with weaning due to recurrence of mastitis were further counted (Table 3), revealing that the rate of stop breastfeeding was 2.5% (1/40) in the experimental group and 18.6% (8/43) in the control group. The intergroup difference in the rate of stop breastfeeding was 16.1%, with statistical significance (odds ratio = 0.112, 95% confidence interval: 0.013–0.942, $P = .045$).

3.3. Comparison of the pain relief rate between the 2 groups

The relief rate of breast pain was 20% (8/40) in the probiotic group and 27.9% (12/43) in the control group, without a statistically significant difference (Pearson chi-square = 0.708, $P = .400$). For details, see Table 4.

3.4. Comparison of recurrence of mastitis between the 2 groups

The recurrence rate of mastitis was 20% (8/40) in the experimental group and 16.3% (7/43) in the control group. The intergroup difference was 3.7%, which was not statistically significant (Pearson chi-square = 0.194, $P = .660$). For details, see Table 5.

4. Discussion

Previous studies have found that about 3% to 20% of breastfeeding women suffer from acute mastitis during lactation.[15,16] In addition, after suffering from mastitis, a considerable number of women are suggested by health professionals to suspend breastfeeding on the affected side or stop breastfeeding completely.[17] There is also a study showing that women who have

Table 2

Comparison of the 2 groups for weaning.

Variables	Experimental group n	Experimental group %	Control group n	Control group %	Pearson's chi-square	*P* value
Weaning	4	10	11	25.6	3.398	.065
Continue breastfeeding	36	90	32	74.4		

Table 3

Comparison of the 2 groups for weaning due to mastitis.

	Experimental group		Control group			
Variables	**n**	**%**	**n**	**%**	**OR (95% CI)**	***P* value**
Weaning	1	2.5	8	18.6	0.112 (0.013–0.942)	.045
Continue breastfeeding	39	97.5	35	81.4		

CI = confidence interval, OR = odds ratio.

Table 4

Comparison of pain relief rate between 2 groups.

	Experimental group		Control group			
Variables	**n**	**%**	**n**	**%**	**Pearson's chi-square**	***P* value**
No relief	8	20	12	27.9	0.708	.400
Relief	32	80	31	72.1		

Table 5

Comparison of recurrence of mastitis between 2 groups.

	Experimental group		Control group			
Variables	**n**	**%**	**n**	**%**	**Pearson's chi-square**	***P* value**
Recurrence	8	20	7	16.3	0.194	.660
No recurrence	32	80	36	83.7		

suffered from mastitis and share a bed with their babies may breastfeed longer, indicating that mastitis may be positively correlated with breastfeeding duration.[18] Nevertheless, mastitis and even local redness and swelling, pain and other infectious symptoms of breast abscess will still Stop the mother from breastfeeding. Therefore, we hope to explore a safe and effective way to reduce weaning due to mastitis.

Relevant guidelines have proposed that the occurrence of mastitis during lactation is closely related to galactostasis and infectious pathogens.[12,19] In China, Jia et al[20] conducted bacterial culture and drug sensitivity tests on 236 milk specimens from patients with acute mastitis during lactation and isolated a total of 108 strains of pathogenic bacteria, including 86 strains of *Staphylococcus aureus* (*S. aureus*), accounting for 79.6%. Wang et al[21] identified strains in 107 specimens of breast abscess, with the bacterial detection rate reaching 44.6%, and 63% of the isolated strains were of *S. aureus*. Boccaccio et al[22,23] found that *S. aureus* was the main pathogen in postpartum breast abscess, accounting for 32% to 95% of the cultured bacteria from diagnosed patients, and its resistance to methicillin was >60%. However, Jiménez et al[24] have found that healthy breast milk also contains *S. aureus* In addition, Soto et al[25] found that the number of *Lactobacillus*- or *Bifidobacterium*-positive samples was significantly lower in women treated with antibiotics during pregnancy or lactation. Therefore, it is pondered deeply that lactational mastitis is related to not only bacterial invasion and infection but also the changes in breast microecology, which may destroy bacterial diversity.[26] This is different from the previous view that bacteria in breast milk only come from the mother's skin and oral cavity of infants.[27] As early as 1984, Benno et al[28] have found anaerobic bacteria that cannot survive under the aerobic environment in breast milk by testing the breast milk of healthy women, thus proving that the bacteria in breast milk are not completely come from the external environment. The hypothesis of the enteromammary pathway put forward in recent years suggests that bacteria may enter the breast milk from the gastrointestinal tract of breastfeeding women through an endogenous pathway.[29] Under normal conditions, bacteria in the milk form a dynamic and balanced microenvironment and breaking this balance may lead to mastitis.[30] Ma et al[31] have found in a cow model that transplanting the fecal microbiota of cows suffering from mastitis into mice may lead to mastitis in mice, while the symptoms of mastitis in mice taking probiotics are significantly relieved. Therefore, it is considered that the imbalance of intestinal flora is one of the important causes of mastitis, and probiotics are an important means to restore the function of intestinal flora. Moreover, another benefit of probiotic treatment for patients with mastitis lies in that it can avoid the potential impact of antibiotic residues in breast milk on infants.[32]

Martin et al[33] found that *L. fermentum* is a naturally occurring colonizing bacterium in breast milk and may be an important source of intestinal lactic acid bacteria in infants. In a randomized controlled double-blind trial, José et al[34] concluded that *L. fermentum* CECT5716 is safe for infants. In contrast, we selected this strain for the experiment not only because of its safety[35,36] but also because it may be an effective therapeutic alternative to antibiotics in patients with lactating mastitis.[37]

In the present study, no significant difference was found in the rate of stop breastfeeding between the experimental group (10%; 4/40) and the control group (25.6%; 11/43). Based on this, we excluded the patients with premature weaning for work and other personal reasons, and only counted the patients who stopped breastfeeding due to mastitis. Consequently, it was found that the probability of stopping breastfeeding due to mastitis might be reduced after oral *L. fermentum* CECT5716 for 4 weeks. Its potential cause lies in that the equilibrium of the microenvironment in the breast of the experimental group was good, the discomfort was mild, and had little effect on the enthusiasm of patients to continue breastfeeding. Although there was no significant difference in the probability of recurrent mastitis between both groups. However, the data volume in this study is small, so our results need more data support. In addition, no significant benefits were found in relieving breast pain and reducing recurrent mastitis between the experimental group and the control group, which may be because the causes of breast pain and

mastitis during lactation are very complex,[11] such as oral problems of infants, poor sucking posture, mixed feeding, breast squeezing, and missed feeding, and the use of *L. fermentum* CECT5716 cannot solve these problems.

The preliminary RCT lasted for 3 months, and there were differences in the enrollment time of subjects. This study conducted a cross-sectional investigation on all patients receiving follow-up, resulting in differences in the follow-up time, which may also have a certain impact on the results. Moreover, during this study, novel coronavirus pneumonia (coronavirus disease 2019) was raging around the world, fewer subjects were followed up, and we also considered interference of coronavirus disease 2019 with the choice of lactating women of weaning time, thereby affecting the trial results.

5. Conclusion

In lactating women with a history of breast abscess, oral *L. fermentum* CECT5716 may reduce the risk of weaning due to recurrence of mastitis.

Author contributions

GY is the corresponding author and conceived the study, designed the trial, and supervised the conduct of the trial and data collection. ZY undertook recruitment of participating centers and patients and managed the data, including the quality control. ZY chaired the data oversight committee, was responsible for design drawings and forms, and drafted the manuscript. HXP, DST, and GHF provided statistical advice on the study design and analyzed the data. All authors read and approved the final article.

References

[1] World Health Organization. Infant and young child feeding: model chapter for textbooks for medical students and allied health professionals. Available at: https://apps.who.int/iris/bitstream/handle/10665/44117/9789241597494_eng.pdf. [access date June 10, 2022].

[2] Horta BL, Victora CG. Long-term Effects of Breastfeeding: A Systematic Review. Geneva: World Health Organization; 2013.

[3] Black RE, Allen LH, Bhutta ZA, et al. Maternal and child undernutrition: global and regional exposures and health. Lancet. 2008;371: 243–60.

[4] Jones G, Steketee RW, Black RE, et al. Bellagio child survival study group. How many child deaths can we prevent this year? Lancet. 2003;9377:65–71.

[5] Li Q, Tian J, Xu F, Binns C. Breastfeeding in China: a review of changes in the past decade. Int J Environ Res Public Health. 2020;17:8234.

[6] Duan Y, Yang Z, Lai J, et al. Exclusive breastfeeding rate and complementary feeding indicators in China: a national representative survey in 2013. Nutrients. 2018;10:249.

[7] Foxman B, Arcy H, Gillespie B, et al. Lactation mastitis: occurrence and medical management among 946 breastfeeding women in the United States. Am J Epidemiol. 2002;155:103–14.

[8] Delgado S, Arroyo R, Martın R, et al. Pcr-dggePCR -DGGE assessment of the bacterial diversity of 540 breast milk in women with lactational infectious mastitis. BMC Infect Dis. 2008;8:51.

[9] Egbe TO, Ngonsai DT, Tchounzou R, et al. Prevalence and risk factors of lactation mastitis in three hospitals in Cameroon: a cross-sectional sectional study. Br J Med Med Res. 2016;13:1–10.

[10] Sun K, Chen M, Yin Y, et al. Why Chinese mothers stop breastfeeding: mothers' self-reported reasons for stopping during the first six months. J Child Health Care. 2017;21:353–63.

[11] Academy of Breastfeeding Medicine Protocol Committee. ABM clinical protocol #4: mastitis. Revision, May 2008. Breastfeed Med. 2008;3: 177–80.

[12] Amir LH, Forster D, McLachlan H, et al. Incidence of breast abscess in lactating women: report from an Australian cohort. BJOG. 2004;111:1378–81.

[13] WHO. Global Strategy for Infant and Young Child Feeding. Geneva: World Health Organization; 2003. Available at: http://www.who.int/nutrition/publications/infantfeeding/9241562218/en.

[14] World Health Organization. Mastitis: causes and management. Available at: https://apps.who.int/iris/bitstream/handle/10665/66230/WHO?sequence=1. [access date June 10, 2022].

[15] Arabi M, Frongillo EA, Avula R, et al. Infant and young child feeding in developing countries. Child Dev. 2012;83:32–45.

[16] Amir LH; Academy of Breastfeeding Medicine Protocol Committee. ABM clinical protocol #4: mastitis. Revised March 2014. Breastfeed Med. 2014;9:239–43.

[17] Scott JA, Robertson M, Fitzpatrick J, et al. Occurrence of lactational mastitis and medical management: a prospective cohort study in Glasgow. Int Breastfeed J. 2008;3:21.

[18] Vogel A, Hutchison BL, Mitchell EA. Factors associated with the duration of breastfeeding. Acta Paediatr. 1999;88:1320–6.

[19] Mastitis prevention and treatment and breastfeeding promotion group of the breast health care professional committee of the China maternal and child health association. Guidelines for the diagnosis and treatment of mastitis during lactation in China [in Chinese]. Chin J Breast Dis (electronic edition). 2020;14:10–14.

[20] Jia ZL, Xu LF, Yang Y. Distribution of pathogens and their antibiotic resistance in patients with acute mastitis [in Chinese]. Chin J Lab Med. 2008;18:478–9.

[21] Wang YY, Yang W, Lv LY, et al. Pathogens distribution and their drug resistance in 107 cases of mammary gland abscess [in Chinese]. Chin J Microecol. 2014;26:1437–40.

[22] Cenap D, Aydın IB. Abscesses in lactating women. World J Surg. 2003;27:130–3.

[23] Boccaccio C, Verdaguer Babic V, Botto L, et al. Methicillin-resistant Staphylococcus aureus (MRSA) isolation in breast abscesses in a public maternity. Medicina (B Aires). 2014;74:210–5.

[24] Jiménez E, de Andres J, Manrique M, et al. Metagenomic analysis of mlk of healthy and mastitis-suffering women. J Hum Lact. 2015;3:406–15.

[25] Soto A, Martín V, Jiménez E, et al. Lactobacilli and bifidobacteria in human breast milk: influence of antibiotherapy and other host and clinical actors. J Pediatr Gastroenterol Nutr. 2014;59:78–88.

[26] Patel SH, Vaidya YH, Patel RJ, et al. Culture independent assessment of human milk microbial community in lactational mastitis. Sci Rep. 2017;7:7804.

[27] West PA, Hewitt JH, Murphy OM. Influence of methods of collection and storage on the bacteriology of human milk. J Appl Bacteriol. 1979;46:269–77.

[28] Benno Y, Sawada K, Mitsuoka T. The intestinal microflora of infants: composition of fecal flora in breast-fed and bottle-fed infants. Microbiol Immunol. 1984;28:975–86.

[29] Jost T, Lacroix C, Braegger CP, et al. Vertical mother-neonate transfer of maternal gut bacteria via breastfeeding. Environ Microbiol. 2014;16:2891–904.

[30] Mediano P, Fernández L, Jiménez E, et al. Microbial diversity in milk of women with mastitis: potential role of coagulase-negative staphylococci, viridans group streptococci, and corynebacteria. J Hum Lact. 2017;33:309–18.

[31] Ma C, Sun Z, Zeng B, et al. Cow-to-mouse fecal transplantations suggest intestinal microbiome as one cause of mastitis. Microbiome. 2018;6:200.

[32] Barbosacesnik C, Schwartz K, Foxman B. Lactation mastitis. JAMA. 2003;289:1609–12.

[33] Martin R, Langa S, Reviriego C, et al. Human milk is a source of lactic acid bacteria for the infant gut. J Pediatr. 2003;143:754–8.

[34] José M, Francisco C, Luis S. Human milk probiotic Lactobacillus fermentum CECT5716 reduces the incidence of gastrointestinal and upper respiratory tract infections in infants. J Pediatr Gastroenterol Nutr. 2012;54:55–61.

[35] Lara-Villoslada F, Sierra S, Dı´az-Ropero MP, et al. Safety assessment of Lactobacillus fermentum CECT5716, a probiotic strain isolated from human milk. J Dairy Res. 2009;76:216–21.

[36] European Food Safety Authority(EFSA). Opinion of the scientific committee on a request from EFSA on the introduction of a qualified presumption of safety (QPS) approach for assessment of selected microorganisms referred to EFSA. EFSA J. 2007;587:1–16.

[37] Arroyo R, Martín V, Maldonado A, et al. Treatment of infectious mastitis during lactation: antibiotics versus oral administration of lactobacilli isolated from breast milk. Clin Infect Dis. 2010;50:1551–8.