Lactobacillus reuteri DSM 17938 Improves Feeding Intolerance in Preterm Infants

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ABSTRACT

Purpose: Feeding tolerance is extremely important in preterm infants. This study aimed to evaluate whether preterm infants receiving Lactobacillus reuteri DSM 17938 would develop fewer symptoms of feeding intolerance. Secondary outcomes were duration of parenteral nutrition, time to reach full feeding, length of hospital stay, sepsis, necrotizing enterocolitis (NEC), diarrhea, and mortality.

Methods: This double-blind randomized controlled trial of L. reuteri DSM 17938 versus placebo included 94 neonates with a gestational age of 28–34 weeks and birth weight of 1,000–1,800 g.

Results: Feeding intolerance (vomiting and/or distension) was less common in the probiotic group than in the placebo group (8.5% vs. 25.5%; relative risk, 0.33; 95% confidence interval, 0.12–0.96; p=0.03). No significant intergroup differences were found in proven sepsis, time to reach full feeding, length of hospital stay, or diarrhea. The prevalence of NEC (stages 2 and 3) was 6.4% in the placebo group vs. 0% in the probiotic group (relative risk, 1.07; 95% confidence interval, 0.99–1.15; p=0.24). Mortality rates were 2.1% in the probiotic group and 8.5% in the placebo group, p=0.36).

Conclusion: The administration of L. reuteri DSM 17938 to preterm infants was safe and significantly reduced feeding intolerance. No significant differences were found in any other secondary outcomes.

Keywords: Lactobacillus reuteri; Preterm; Feeding intolerance

INTRODUCTION

Probiotics are beneficial for commensal bacterial colonization and suppression of pathogenic bacterial colonization in the gastrointestinal tract. Probiotics increase the immunoglobulin A (IgA) response of the mucosal lining of the gastrointestinal tract, which reportedly improves the tolerance of enteral nutrition and regulates the immune responses [1-4]. The most commonly used probiotics are Lactobacilli and Bifidobacterium [5-9]. The administration
of *Lactobacillus reuteri* DSM 17938 has been suggested to decrease feeding intolerance and sepsis and shortening hospital length of stay [10-14]. It is unclear whether *L. reuteri* decreases the incidence and severity of necrotizing enterocolitis (NEC) [10,12,15-17]. *L. reuteri* DSM 17938 is often chosen due to its safe and easy administration through a suspension given orally or through an orogastric tube. Adverse events rarely occur with the administration of *L. reuteri* DSM 17938 [16-20]. However, the administration of *L. reuteri* DSM 17938 in preterm infants has not been sufficiently studied. Kaban [21] showed that counts of commensal bacteria in the gastrointestinal tract in preterm infants were very low compared to those of pathogenic bacteria.

The aim of the study was to evaluate the effect of *L. reuteri* DSM 17938 on feeding intolerance in preterm infants.

**MATERIALS AND METHODS**

This double-blind randomized controlled clinical trial compared the oral administration of *L. reuteri* DSM 17938 or placebo to neonates with a gestational age of 28–34 weeks and a birth weight of 1,000–1,800 g in a stable condition allowing the administration of oral and enteral nutrition and was conducted at the Neonatology Unit, Department of Pediatric Health of the Dr. Cipto Mangunkusumo Hospital from January to October 2017. The exclusion criteria were absolute contraindications for feeding such as lower gastrointestinal tract obstruction, massive gastrointestinal tract bleeding, NEC, sepsis and shock, and refusal of the infants’ parents to participate in the study. Dropout criteria were parents requesting discharge against medical advice and refusing participation after the intervention was started.

The study subjects were recruited through consecutive sampling by including every infant who fulfilled the inclusion criteria and met none of the exclusion criteria. The infants were then followed until discharge or the incidence of severe complications such as sepsis, NEC, or death. A total of 94 infants were needed (47 each in a probiotic group and a placebo group).

Subjects were allocated to the groups by a third party using a simple alternating randomization technique. The probiotic used in this study was *L. reuteri* DSM 17938 (Interlac) suspension. The dose administered was five drops per day, equivalent to $10^8$ colony-forming units/day, the recommended dose. The placebo contains a mixture of pharmaceutical-grade medium-chain triglycerides and sunflower oil together with pharmaceutical-grade silicon dioxide to give the product the correct rheological properties.

The probiotic or placebo was given as soon as the neonate reached a stable condition i.e. could be orally or enterally fed breast milk and/or formula at least 40–50 mL/kg body weight. Subjects with a suspected infection (signs including lethargy, respiratory distress in need of mechanic ventilation) but normal septic screening laboratory values (complete blood count, peripheral blood count, C-reactive protein, immature-to-total ratio, and blood culture) were included in the study. The probiotic or placebo was administered as soon as the infant had two sequential feedings of 40–50 mL/kg body weight. The intervention was given for the duration of at least 7 days or until the subject was discharged, experienced NEC, or died. Feeding was started at 10–20 mL/kg depending on the subject’s gestational age, and increased by 10–30 mL/kg each day according to the subject’s clinical condition and tolerance [22]. Feeding intolerance was defined as the difficulty in ingesting or digesting milk that disrupts the enteral feeding plan due to the manifestation of clinical symptoms [23].
feeding intolerance was present i.e. abdominal distension (increase in abdominal girth by 2 cm or more between feedings) and/or vomiting, the feeding was stopped or delayed until the tolerance improved. If a feeding contraindication was present, the probiotic or placebo administration was temporarily stopped. Feeding intolerance was the primary outcome. The secondary outcomes were differences between probiotics and placebo in duration of total parenteral nutrition (TPN), number of days needed to reach full enteral feeding, length of stay, sepsis, diarrhea, and NEC incidence and severity.

This study obtained ethical approval from the Ethics Committee of the Faculty of Medicine, Universitas Indonesia (Number 43.UN2.F1/ETIK/2017) as well as a study permit from Dr. Cipto Mangunkusumo Hospital.

The data analysis was conducted using the statistical program using IBM SPSS Statistics for Windows, Version 20.0 (IBM Co., Armonk, NY, USA). This study compared methods between categorical calculation scales as well as categoric-numerical unpaired groups. A bivariate analysis was conducted to analyze subject characteristics with NEC incidents. Two unpaired groups with normal distributions were analyzed with parametric methods (unpaired t-tests), while two unpaired groups without normal distributions were analyzed using a non-parametric method (Mann-Whitney U-test). p-values less than 0.05 were considered statistically significant. An intention-to-treat analysis was performed.

**RESULTS**

This study was performed between January and October 2017. A total of 105 infants were initially included; of them, 11 were excluded (3 refused to participate, 1 had a congenital anomaly, and 7 died before the probiotic or placebo could be administered). A total of 94 subjects fulfilled the inclusion criteria and were allocated in one of the study groups. No subjects dropped out.

There were no significant intergroup differences in subject characteristics at inclusion (Table 1). The majority of the subjects of both treatment groups were of moderately preterm gestational age (median gestational age, 33 weeks; range, 28–34 weeks). Ninety percent (85/94) received TPN; the TPN duration was less than or equal to 7 days in 36.5% (31/85) and more than 7 days in 63.5% (54/85). Nutritional intake consisted of predominantly breast milk in 9 (19.1%) subjects in the *L. reuteri* group and 10 (21.3%) in the placebo group. Feeding was predominantly formula in 38 (80.9%) subjects in the *L. reuteri* group and in 37 (78.7%) infants.

| Variable                  | *L. reuteri* (n=47) | Placebo (n=47) | p-value |
|---------------------------|---------------------|----------------|---------|
| Sex                       |                     |                | 0.02    |
| Male                      | 28 (59.6)           | 17 (36.2)      |         |
| Female                    | 19 (40.4)           | 30 (63.8)      |         |
| Gestational age           |                     |                | 0.66    |
| Moderately preterm        | 33 (70.2)           | 31 (66.0)      |         |
| Very preterm              | 14 (29.8)           | 16 (34.0)      |         |
| Birth weight              |                     |                | 0.84    |
| Very low birth weight     | 20 (42.6)           | 21 (44.7)      |         |
| Low birth weight          | 27 (57.4)           | 26 (55.3)      |         |

Values are presented as number (%). Median gestational age, 33 weeks; range, 28–34 weeks; values are presented as number (%). Moderate preterm: 32–33 weeks, 6 days of gestational age; very preterm: 28–31 weeks, 6 days of gestational age; very low birth weight: 1,000 to <1,500 g; low birth weight: 1,500–1,800 g.
in the placebo group ($p=0.80$). The clinical characteristics and maternal risk factors are listed in Tables 2 and 3.

The incidence of feeding intolerance differed significantly between the two study groups. Feeding intolerance in the form of vomiting and/or abdominal distension was reported in 4 (8.5%) subjects in the $L.\ reuteri$ group and 12 (25.5%) subjects in the placebo group (relative risk [RR], 0.33; 95% confidence interval [CI], 0.12–0.96; $p=0.03$) (Table 4). However, TPN duration and number of days needed to reach full enteral feeding did not differ between groups. Total and partial parenteral nutrition are often needed in patients with low birth weight or an unstable clinical condition. In this study, the median duration of parenteral nutrition was 8 days in the $L.\ reuteri$ group versus 9 days in the placebo group ($p=0.52$). The median length of stay was 27 days (range, 8–72 days) for the $L.\ reuteri$ group and 27 days (range, 11–73 days) in the placebo group ($p=0.28$). Subjects who were discharged in the second week of care were those of an older gestational age (>32 weeks) and had a higher birth weight (>1,500 g).

Data on secondary outcomes are presented in Table 5. One subject (2.1%) of the $L.\ reuteri$ group and 2 subjects (4.3%) of the placebo group developed diarrhea ($p=1.00$). There was a trend, but without a statistically significant difference, between the $L.\ reuteri$ and placebo group in NEC incidence and death. Three (6.4%) subjects of the placebo group and zero

| Table 2. Clinical characteristics of risk factors for NEC (n=94) |
|---------------------------------------------------------------|
| **Risk factors for NEC**                                       |
| **Lactobacillus reuteri**                                     |
| **(n=47)**                                                    |
| **Placebo group (n=47)**                                     |
| **p-value**                                                  |
| **Gestational age (wk)**                                     |
| 33 (28–34)                                                   |
| 33 (28–34)                                                   |
| 0.75                                                        |
| **Birth weight (g)**                                         |
| 1,520 (1,035–1,800)                                          |
| 1,605 (1,060–1,800)                                          |
| 0.73                                                        |
| **Cesarean section**                                         |
| 39 (83.0)                                                    |
| 40 (85.1)                                                    |
| 0.78                                                        |
| **Steroid administration**                                   |
| 35 (74.5)                                                    |
| 35 (74.5)                                                    |
| 1.00                                                        |
| **Length of steroid administration (d)**                     |
| 2 (0–4)                                                      |
| 2 (0–2)                                                      |
| 0.16                                                        |
| **Asphyxia**                                                 |
| 38 (80.9)                                                    |
| 42 (89.4)                                                    |
| 0.25                                                        |
| **Patent ductus arteriosus**                                 |
| 2 (4.3)                                                      |
| 3 (6.4)                                                      |
| 1.00                                                        |
| **APGAR score, 1 min**                                       |
| 7 (5–9)                                                      |
| 7 (3–9)                                                      |
| 0.72                                                        |
| **APGAR score, 5 min**                                       |
| 9 (6–10)                                                     |
| 9 (5–10)                                                     |
| 0.34                                                        |
| **Nutrition**                                                |
| **Age at first feeding (d)**                                 |
| 2 (0–12)                                                     |
| 1 (0–14)                                                     |
| 0.79                                                        |
| **Predominant breast milk**                                  |
| 9 (19.1)                                                     |
| 10 (21.3)                                                    |
| 0.80                                                        |
| **Predominant preterm formula milk**                         |
| 38 (80.9)                                                    |
| 37 (78.7)                                                    |
| -                                                            |
| **Duration of total parenteral nutrition (d)**                |
| 8 (0–35)                                                     |
| 9 (0–69)                                                     |
| 0.52                                                        |
| **Time to reach full feeding (d)**                           |
| 6 (0–25)                                                     |
| 7 (0–63)                                                     |
| 0.82                                                        |
| **Age at intervention (d)**                                 |
| 3 (0–18)                                                     |
| 4 (0–21)                                                     |
| 0.71                                                        |
| **Duration of intervention (d)**                             |
| 21 (8–53)                                                    |
| 21 (7–66)                                                    |
| 0.78                                                        |

Values are presented as mean (range) or number (%).

NEC: necrotizing colitis.

| Table 3. Clinical characteristics of maternal risk factors for NEC (n=94) |
|-------------------------------------------------------------------------|
| **Maternal risk factors**                                               |
| **Lactobacillus reuteri group (n=47)**                                   |
| **Placebo group (n=47)**                                                |
| **p-value**                                                             |
| **Premature rupture of membranes**                                      |
| 20 (42.6)                                                               |
| 19 (40.4)                                                               |
| 0.83                                                                    |
| **Oligohydramnios**                                                     |
| 2 (4.3)                                                                 |
| 4 (8.5)                                                                 |
| 0.68                                                                    |
| **Urinary tract infection**                                             |
| 3 (6.4)                                                                 |
| 3 (6.4)                                                                 |
| 1.00                                                                    |
| **Intrauterine infection**                                              |
| 2 (4.3)                                                                 |
| 3 (6.4)                                                                 |
| 1.00                                                                    |
| **Hypertension**                                                        |
| 1 (2.1)                                                                 |
| 4 (8.5)                                                                 |
| 0.36                                                                    |
| **Severe preeclampsia**                                                 |
| 12 (25.5)                                                                |
| 10 (21.3)                                                                |
| 0.63                                                                    |
| **Placenta previa**                                                     |
| 1 (2.1)                                                                 |
| 1 (2.1)                                                                 |
| 1.00                                                                    |
| **Cardiological anomaly**                                               |
| 2 (4.3)                                                                 |
| 2 (4.3)                                                                 |
| 1.00                                                                    |

Values are presented as number (%).

NEC: necrotizing colitis.
subjects of the *L. reuteri* group experienced NEC (RR, 1.07; 95% CI, 0.99–1.15; *p*=0.24). There were no significant differences in the incidence of proven sepsis (6.4% in the placebo group vs. 2.1% in the *L. reuteri* group; *p*=0.62). In the placebo group, the etiology based on blood culture findings included 3 gram-positive bacteria (*Staphylococcus epidermidis*, methicillin-resistant *S. epidermidis*, and *Staphylococcus aureus*) and one gram-negative bacteria (*Klebsiella pneumoniae*). In the probiotic group, the sepsis was caused by *S. aureus*. NEC was diagnosed according Modified Bell staging (stage 2 and 3) diagnostic criteria [24,25]. Three (6.4%) cases of NEC occurred in the placebo group versus none in the *L. reuteri* group (RR, 1.07; 95% CI, 0.99–1.15; *p=0.24). The mortality rate did not differ significantly between groups. One (2.1%) subject in the *L. reuteri* group and 4 (8.5%) subjects in the placebo group died (*p=0.36*). Two (4.2%) subjects from the placebo group had a cause of death related to NEC.

**DISCUSSION**

The incidence of feeding intolerance defined as vomiting or abdominal distension was higher in the placebo group (25.5%) than in the *L. reuteri* group (8.5%) (RR, 0.33; 95% CI, 0.12–0.96; *p=0.03*). Our findings confirm those of previous reports. Rojas et al. [12] reported a feeding intolerance incidence of 7% in a *L. reuteri* group versus 10.6% in a placebo group. According to recent data from Sweden, *L. reuteri* DSM 17938 did not reduce time to reach full enteral feeds in extremely low birth weight infants [26]. The results of this trial provides additional information about the effect of probiotics on feeding tolerance. The *L. reuteri*–supplemented infants, however, had a better cranial growth rate during the first month of life [26].

A prospective study with a large sample size reported that infants who were exclusively breastfed had a 6–10 times lower risk of developing NEC than those who received standard formula; the risk was 3 times lower than that of those who were given a mix of breast milk and standard formula [27]. Oncel et al. [15] reported that the incidence of NEC did not differ significantly between an *L. reuteri* group and a placebo group (RR, 1.26; 95% CI, 0.48–3.27). Shadkam et al. [10] reported that the incidence of NEC was lower in an *L. reuteri* group than in

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**Table 4.** Primary outcome comparison of feeding intolerance between subjects receiving *Lactobacillus reuteri* DSM 17938 or placebo (n=94)

| Feeding intolerance   | *Lactobacillus reuteri* DSM 17938 (n=47) | Placebo (n=47) | *p*-value | RR (95% CI) |
|-----------------------|------------------------------------------|----------------|-----------|-------------|
| Feeding intolerance   |                                          |                |           |             |
| Vomiting              | 4 (8.5)                                  | 12 (25.5)      | 0.03      | 0.33 (0.12–0.96) |
| Abdominal distension  | 1 (2.1)                                  | 6 (12.8)       | 0.11      | -           |

Values are presented as number (%). RR: relative risk, CI: confidence interval.

**Table 5.** Secondary outcomes (n=94)

| Variable             | *Lactobacillus reuteri* DSM 17938 | Placebo       | *p*-value | RR (95% CI) |
|----------------------|-----------------------------------|---------------|-----------|-------------|
| Total NEC (stage 2 and 3) | 0 (0)                             | 3 (6.4)       | 0.24      | 1.07 (0.99–1.15) |
| Age at onset (d)      | -                                 | 18 (10–46)    |           |             |
| Proven sepsis         | 1 (2.1)                           | 3 (6.4)       | 0.62      | -           |
| Length of stay (d)    | 27 (8–72)                         | 27 (11–73)    | 0.28      | -           |
| Diarrhea              | 1 (2.1)                           | 2 (4.3)       | 1.00      | -           |
| Death                 | 1 (2.1)                           | 4 (8.5)       | 0.36      | -           |
| Age at death (d)      | 31                                | 51 (21–62)    |           |             |

Values are presented as number (%) or mean (range). RR: relative risk, CI: confidence interval, NEC: necrotizing colitis.

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a placebo group (6.7% vs. 36.7%; \( p = 0.005 \)). A meta-analysis conducted by AlFaleh et al. [16] and van den Akker et al. [28] showed that probiotics may decrease the incidence of NEC (RR, 0.43; 95% CI, 0.33–0.56) and prevent mortality (RR, 0.56; 95% CI, 0.52–0.81). Wang et al. [29] conducted a meta-analysis of 20 randomized controlled trials (RCTs) and reported that probiotics significantly reduce the occurrence of NEC (RR, 0.22; 95% CI, 0.24–0.46; \( p = 0.00001 \)) and mortality rate (RR, 0.56; 95% CI, 0.43–0.73; \( p < 0.001 \)). Hunter et al. [17] reported that \( L. \) reuteri DSM 17938 significantly reduced NEC (2.5% vs. 15.1%; \( p = 0.047 \)) and delayed the onset of sepsis. However, a study by Escribano et al. [30] found an increased risk of NEC due to the routine administration of \( L. \) acidophilus and \( B. \) bifidum in extremely preterm infants.

In our study, the occurrence of proven sepsis was 6.4% in the placebo group vs. 2.1% in the \( L. \) reuteri group (\( p =0.62 \)). Sepsis was not caused by \( L. \) reuteri in any of the infants. Rojas et al. [12] reported that 9.1% of the infants in the \( L. \) reuteri group had a positive blood culture versus 10.6% in the placebo group (RR, 0.86; 95% CI, 0.56–1.33; \( p =0.51 \)). Romeo et al. [31] reported that the occurrence of delayed-onset sepsis was lower in a group receiving \( L. \) reuteri (1.2%) than in a placebo group (3.6%). Comparable findings were reported by Oncel et al. [15]. In the probiotic groups, no positive culture was related to \( L. \) reuteri intake.

The results of this study are in line with a previous study by Rojas et al. [12] reporting a nonsignificant difference in mortality rate between the probiotic and placebo groups (RR, 0.87; 95% CI, 0.63–1.19; \( p = 0.376 \)) and by Oncel et al. [15] showing a mortality rate of 10% in the probiotic group compared to 13.5% in the placebo group (RR, 1.4; 95% CI, 0.76–2.59; \( p = 0.27 \)). Shadkam et al. [10] reported a mortality rate in the probiotic group of 3.3% compared to 6.7% in the placebo group (\( p = 0.5 \)).

Hunter et al. [17] reported that no adverse effects of \( L. \) reuteri in 311 infants with birth weights less than 1,000 g. A systematic review by Shlomai et al. [32] analyzed results of 25 RCTs of 5,000 preterm infants and reported that adverse effects of probiotics rarely occurred. Several studies have reported infections occurring due to organisms present in probiotics, including fungemia in 33 cases reportedly due to Saccharomyces cerevisiae and/or Saccharomyces boulardii [19]. Cases were reported of sepsis due to Lactobacillus including \( L. \) acidophilus, \( L. \) casei, \( L. \) GG, \( S. \) boulardii, Bacillus subtilis, and Bifidobacterium breve [19,20].

A systematic review of eight studies (6 RCTs, 2 non-RCTs) reported several outcomes related to \( L. \) reuteri DSM 17938 supplementation in preterm infants including time to full feeds, duration of hospitalization, late-onset sepsis, and NEC risk. Based on the study by Athalye et al. [11], \( L. \) reuteri supplementation may reduce the risk of NEC and late-onset sepsis in preterm infants. Another study by Indrio et al. [33] reported the outcomes of \( L. \) reuteri DSM 17938 in preterm infants including feeding intolerance, weight gain, time to full enteral feeding, length of hospital stay, and days of antibiotic treatment. They concluded that \( L. \) reuteri DSM 17938 effectively prevents feeding intolerance in preterm infants.

About 20% of the infants included in our study were predominantly breastfed. Breastfeeding contains IgA, which influences the development of the intestinal immune system and the overall composition of the GI microbiota [34]. However, we did not collect data relevant to these aspects.

This is the first study conducted in Indonesia to support the use of probiotics in premature neonates. The study was conducted on the basis of data in a previous study which
found the number of commensal bacteria (*Lactobacillus* sp and *Bifidobacterium* sp) in the digestive tract of premature infants was very low compared to the number of pathogenic bacteria (*K. pneumoniae* and *Acinetobacter* sp) in the neonatology ward of Dr. Hospital Cipto Mangunkusumo, Jakarta [21].

In conclusion, the incidence of feeding intolerance in preterm infants of gestational age 28–34 weeks and birth weight of 1,000–1,800 g was found to be lower in the *L. reuteri* DSM 17938 group than in the placebo group (8.5% vs. 25.5%; *p*=0.33). The incidence of NEC in these infants was higher in the placebo group (6.4%) than in the *L. reuteri* group (0%; NS). Proven sepsis, length of time to reach full feeding, length of hospital stay, diarrhea, and mortality did not differ significantly between the groups.

**REFERENCES**

1. de Vrese M, Schrezenmeir J. Probiotics, prebiotics, and symbiotics. Adv Biochem Eng Biotechnol 2008;111:1-66. [PUBMED] [CROSSREF]
2. Sinkiewicz G, Ljunggren L. Occurrence of *Lactobacillus reuteri* in human breast milk. Microb Ecol Health Dis 2008;20:112-6. [CROSSREF]
3. 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;126:1217-31. [PUBMED] [CROSSREF]
4. Pietzak M. Bacterial colonization of the neonatal gut. J Pediatr Gastroenterol Nutr 2004;38:389-91. [PUBMED] [CROSSREF]
5. Reuter G. The *Lactobacillus* and *Bifidobacterium* microflora of the human intestine: composition and succession. Curr Issues Intest Microbiol 2001;2:43-53. [PUBMED]
6. Huda S, Chaudhery S, Ibrahim H, Pramanik A. Neonatal necrotizing enterocolitis: clinical challenges, pathophysiology and management. Pathophysiology 2014;21:3-12. [PUBMED] [CROSSREF]
7. Lin HC, Hsu CH, Chen HL, Chung MV, Hsu JF, Lien RJ, et al. Oral probiotics prevent necrotizing enterocolitis in very low birth weight preterm infants: a multicenter, randomized, controlled trial. Pediatrics 2008;122:e693-700. [PUBMED] [CROSSREF]
8. Wu SF, Caplan M, Lin HC. Necrotizing enterocolitis: old problem with new hope. Pediatr Neonatol 2012;53:158-63. [PUBMED] [CROSSREF]
9. Chu A, Hageman JR, Caplan MS. Necrotizing enterocolitis predictive markers and preventive strategies. *Neoreviews* 2013;14:e113-20. [CROSSREF]
10. Shadkam MN, Jalalizadeh F, Nasiriani K. Effects of probiotic *Lactobacillus reuteri* (DSM 17938) on the incidence of necrotizing enterocolitis in very low birth weight premature infants. Iran J Neonatol 2015;6:15-20. [CROSSREF]
11. Athalye-Jape G, Rao S, Patole S. *Lactobacillus reuteri* DSM 17938 as a probiotic for preterm neonates: a strain-specific systematic review. JPEN J Parenter Enteral Nutr 2016;40:783-94. [PUBMED] [CROSSREF]
12. Rojas MA, Lozano JM, Rojas MX, Rodriguez VA, Rondon MA, Bastidas JA, et al. Prophylactic probiotics to prevent death and nosocomial infection in preterm infants. Pediatrics 2012;i30:e1113-20. [PUBMED] [CROSSREF]
13. Indrio F, Riezio G, Raimondi F, Bisceglia M, Cavallo L, Francavilla R. The effects of probiotics on feeding tolerance, bowel habits, and gastrointestinal motility in preterm newborns. J Pediatr 2008;152:801-6. [PUBMED] [CROSSREF]
14. Rao SC, Athalye-Jape GK, Deshpande GC, Simmer KN, Patole SK. Probiotic supplementation and lateonset sepsis in preterm infants: a meta-analysis. Pediatrics 2016;137:e20153684.

15. Oncel MY, Sari FN, Arayici S, Guzoglu N, Erdeve O, Uras N, et al. Lactobacillus reuteri for the prevention of necrotising enterocolitis in very low birthweight infants: a randomised controlled trial. Arch Dis Child Fetal Neonatal Ed 2014;99:F110-5.

16. AlFaleh K, Anabrees J. Probiotics for prevention of necrotizing enterocolitis in preterm infants. Cochrane Database Syst Rev 2014;(4):CD005496.

17. Hunter C, Dimagula MA, Gal P, Wimmer JE Jr, Ransom JL, Carlos RQ, et al. Effect of routine probiotic, Lactobacillus reuteri DSM 17938, use on rates of necrotizing enterocolitis in neonates with birthweight <1000 grams: a sequential analysis. BMC Pediatr 2012;12:142.

18. Lee JH. An update on necrotizing enterocolitis: pathogenesis and preventive strategies. Korean J Pediatr 2011;54:368-72.

19. Doron S, Snyderman DR. Risk and safety of probiotics. Clin Infect Dis 2015;60 Suppl 2:S129-34.

20. Vahabnezhad E, Mochon AB, Wozniak LJ, Ziring DA. Lactobacillus bacteremia associated with probiotic use in a pediatric patient with ulcerative colitis. J Clin Gastroenterol 2013;47:437-9.

21. Kaban RK. Analisis dampak perbedaan pajanan konsentrasi oksigen awal pada resusitasi bayi prematur terhadap displasia bronkopulmonal, integritas mukosa, dan mikrobiota usus, disertasi. Jakarta: Universitas Indonesia, 2016.

22. Sjarif DR, Rohssiswatmo R, Rundjan L, Yuliarti K. Panduan berbasis bukti: asuhan nutrisi untuk bayi prelumin. Jakarta: Departemen Ilmu Kesehatan Anak FKUI-RSCM, 2016.

23. Khashana A, Moussa R. Incidence of feeding intolerance in preterm neonates in neonatal intensive care units, Port Said, Egypt. J Clin Neonatol 2016;5:230-2.

24. Dominguez KM, Moss RL. Necrotizing enterocolitis. Clin Perinatol 2012;39:387-401.

25. Christensen RD, Lambert DK, Baer VL, Gordon PV. Necrotizing enterocolitis in term infants. Clin Perinatol 2013;40:69-78.

26. Wejryd E, Marchini G, Frimmel V, Jonsson B, Abrahamsson T. Probiotics promoted head growth in extremely low birthweight infants in a double-blind placebo-controlled trial. Acta Paediatr 2019;108:62-9.

27. Schanler RJ. Human milk is the feeding strategy to prevent necrotizing enterocolitis. Curr Pediatr Rep 2014;2:264-8.

28. van den Akker CHP, van Goudoever JB, Szajewska H, Embleton ND, Hojsak I, Reid D; ESPGHAN Working Group for Probiotics, Prebiotics & Committee on Nutrition Probiotics for preterm infants: a strainspecific systematic review and network meta-analysis. J Pediatr Gastroenterol Nutr 2018;67:103-22.

29. Wang Q, Dong J, Zhu Y. Probiotic supplement reduces risk of necrotizing enterocolitis and mortality in preterm very low-birth-weight infants: an updated meta-analysis of 20 randomized, controlled trials. J Pediatr Surg 2012;47:241-8.

30. Escribano E, Zozaya C, Madero R, Sánchez L, van Goudoever I, Rodríguez JM, et al. Increased incidence of necrotizing enterocolitis associated with routine administration of Inflloran™ in extremely preterm infants. Benef Microbes 2018;9:683-90.

31. Romeo MG, Romeo DM, Trovato L, Oliveri S, Palermo F, Cota F, et al. Role of probiotics in the prevention of the enteric colonization by Candida in preterm newborns: incidence of late-onset sepsis and neurological outcome. J Perinatol 2011;31:63-9.

32. Ofek Shlomi N, Deshpande G, Rao S, Patole S. Probiotics for preterm neonates: what will it take to change clinical practice? Neonatology 2014;105:64-70.
33. Indrio F, Riezzo G, Tafuri S, Ficarella M, Carlucci B, Bisceglia M, et al. Probiotic supplementation in preterm: feeding intolerance and hospital cost. Nutrients 2017;9:E965.

34. Pabst O, Cerovic V, Hornef M. Secretory IgA in the coordination of establishment and maintenance of the microbiota. Trends Immunol 2016;37:287-96.