

Taylor & Francis
Taylor & Francis Group

Paediatrics and International Child Health

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/ypch20

Effectiveness of phototherapy with and without probiotics for the treatment of indirect hyperbilirubinaemia in preterm neonates: a randomised controlled trial

Hisham Nasief, Meshari A. Alaifan, Shadi Tamur, Khalid Khadawardi, Ammar A. Bahauddin, Aijaz Ahmed, Sarfraz Ahmad, Rajinder Singh, Bakr H. Alhussaini & Amber Hassan

To cite this article: Hisham Nasief, Meshari A. Alaifan, Shadi Tamur, Khalid Khadawardi, Ammar A. Bahauddin, Aijaz Ahmed, Sarfraz Ahmad, Rajinder Singh, Bakr H. Alhussaini & Amber Hassan (2024) Effectiveness of phototherapy with and without probiotics for the treatment of indirect hyperbilirubinaemia in preterm neonates: a randomised controlled trial, Paediatrics and International Child Health, 44:1, 24-29, DOI: 10.1080/20469047.2024.2328416

To link to this article: https://doi.org/10.1080/20469047.2024.2328416

Published online: 14 Mar 2024.

Submit your article to this journal

Article views: 99

View related articles

View Crossmark data

Full Terms & Conditions of access and use can be found at
https://www.tandfonline.com/action/journalInformation?journalCode=ypch20

PAEDIATRICS AND INTERNATIONAL CHILD HEALTH
2024, VOL. 44, NO. 1, 24–29
https://doi.org/10.1080/20469047.2024.2328416

Taylor & Francis
Taylor & Francis Group

Check for updates

Effectiveness of phototherapy with and without probiotics for the treatment of indirect hyperbilirubinaemia in preterm neonates: a randomised controlled trial

Hisham Nasief[a], Meshari A. Alaifan[g], Shadi Tamur[b], Khalid Khadawardi[c], Ammar A. Bahauddin[d], Aijaz Ahmed[e], Sarfraz Ahmad[f], Rajinder Singh[f], Bakr H. Alhussaini[g] and Amber Hassan[h,i]

[a]Departments of Obstetrics and Gynecology and Pediatrics, Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia; [b]Department of Pediatrics, College of Medicine, Taif University, Saudi Arabia; [c]Department of Obstetrics and Gynecology, Faculty of Medicine, Umm Al-Qura University, Makkah, Saudi Arabia; [d]Department of Pharmacology and Toxicology, College of Pharmacy, Taibah University, Madinah, Saudi Arabia; [e]National Institute of Child Health, Karachi, Pakistan; [f]Departments of Paediatrics and Neonatology, Dr Sulaiman al Habib Hospital, Dubai, United Arab Emirates; [g]Department of Pediatrics, Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia; [h]Faculty of Allied Health Sciences, University of Lahore, Lahore, Pakistan; [i]System Medicine, Translational Neuroscience Laboratory, CEINGE Biotecnologie Avanzate, Naples, Italy

ABSTRACT

Introduction: Raised serum bilirubin levels can cause kernicterus, and premature infants are at increased risk owing to metabolic immaturity. The standard treatment for neonatal jaundice is phototherapy, but probiotics alone can reduce the duration of phototherapy and hospitalisation.
Objectives: To determine the effectiveness of phototherapy with and without probiotics for the treatment of indirect hyperbilirubinaemia in preterm neonates.
Patients and methods: The open-labelled randomised controlled trial was conducted from January 2022 to January 2023 in the neonatal unit of the University of Lahore Teaching Hospital, Pakistan. A total of 76 preterm neonates who fulfilled the selection criteria were included and divided into two groups. Both groups received standard phototherapy. In Group B, a probiotic (*Saccharomyces boulardii*) 125 mg, twice daily, orally (in 5 cc of whichever milk the infant was receiving) was given until discharge from hospital. The primary outcome measurements were the duration of phototherapy and the length of hospitalisation.
Results: The mean (SD) duration of phototherapy was 36.55 (14.25) hours in Group A and 24.61 (9.25) hours in Group B (p <0.05). The mean (SD) duration of hospital stay was 47.36 (16.51) hours in Group A and 33.13 (8.93) hours in Group B (p <0.05).
Conclusion: Oral probiotics (*Saccharomyces boulardii*) have a significant effect on the duration of phototherapy for neonatal hyperbilirubinaemia, and they decrease the chances of nosocomial infection. Exploration of clinical outcomes by investigating faecal flora and undertaking large randomised controlled trials of various probiotics are needed.

Abbreviations: ABE: acute bilirubin encephalopathy; CNS: central nervous system;GA: gestational age; IVIG: intravenous immunoglobulin; KSD: kernicterus;NNU: neonatal unit; RCT: randomised controlled trial; S. boulardii: Saccharomyces boulardii.

ARTICLE HISTORY
Received 9 October 2023
Accepted 5 March 2024

KEYWORDS
Hyperbilirubinaemia; preterm neonates; probiotics; phototherapy

Introduction

Neonatal indirect hyperbilirubinaemia, also known as neonatal jaundice, is typically harmless, and minor hyperbilirubinaemia in term newborns does not require therapy [1]. Bilirubin accumulation in the brain leads to neurotoxicity, causing kernicterus (KSD), a condition with acute, potentially fatal symptoms and long-term effects [2]. Hyperbilirubinaemia can be conjugated or unconjugated [3,4]. Unconjugated hyperbilirubinaemia, characterised by plasma bilirubin levels <5 mg/dL, causes noticeable jaundice in newborns, starting at the head and spreading to other parts [5]. The 2020 Global Burden of Disease Study reported that neonatal jaundice was the seventh leading cause of neonatal mortality in the early neonatal period, resulting in 1008 fatalities per 100,000 live births [6]. Sub-Saharan Africa and South Asia have the highest incidence of infant deaths from jaundice and the greatest burden of the disease [7]. The incidence of newborn hyperbilirubinaemia is greater in Asians than in Caucasians, with the highest burden in low- and middle-income countries [8]. Case–control research indicates that neonates with UGT1A1 gene variations and those who are breastfed are more likely to develop hyperbilirubinaemia [9]. Maternal variables, birth location, blood-type incompatibilities, and infants under 36 weeks gestational age with infections or high bilirubin levels within the first 24 hours require additional surveillance [10].

The treatment of neonatal jaundice includes phototherapy, hydration, exchange transfusion and medication such as phenobarbitone, albumin intravenous immuno-

CONTACT Amber Hassan amberhassan7@gmail.com
© 2024 Informa UK Limited, trading as Taylor & Francis Group

globulin (IVIG), metal porphyrins and probiotics [11]. Pakistan's health sector has significantly improved the quality of care, but challenges remain to improve disease control and prevention [12]. Identifying requirements and improving healthcare management can significantly reduce acute bilirubin encephalopathy (ABE) and improve the health of thousands of infants worldwide [13,14]. Probiotics have been shown to lower bilirubin levels faster than phototherapy alone, but little progress has been made in this area [15].

The duration of phototherapy was shorter when probiotics were used in conjunction with phototherapy than with phototherapy alone [16]. The probiotics were beneficial in shortening the duration of phototherapy in extremely low birthweight and preterm neonates with indirect hyperbilirubinaemia [17]. Another study found that it had no meaningful influence on the duration of phototherapy or levels of blood bilirubin [18,19].

The study assessed the effect of orally administered *Saccharomyces boulardii*, a probiotic yeast, on the progression of indirect hyperbilirubinaemia and aimed to reduce the duration of hospitalisation to prevent the risk of nosocomial infection by reducing the duration of phototherapy in preterm neonates with indirect hyperbilirubinaemia.

Subjects and methods

Selection criteria

The study was undertaken between January 2022 and January 2023 and included all neonates with indirect hyperbilirubinaemia born at <37 weeks gestation. The following were excluded: those with sepsis, a bilirubin level in the exchange transfusion range (Table 1), direct hyperbilirubinaemia, respiratory distress syndrome, severe birth asphyxia and those who were intubated or critically sick. Infants with hypoxia, significant congenital defects, ABO/Rh incompatibility, gastrointestinal obstruction, cephalhaematoma or infection were excluded.

Data collection

A total of 76 preterm neonates fulfilled the selection criteria and were enrolled into the study from the neonatal unit (NNU) of the University Teaching Hospital, Lahore, Pakistan. Patients were randomly assigned to Group A without probiotics or Group B with probiotics using random allocation software 1.0, resulting in a trial sequence hidden in sealed envelopes. A sample size of 72 (36 in each group) was calculated using a mean (SD) difference of 1.5 for the duration of jaundice in the phototherapy with probiotic group [3.8 (1.7) days] and the phototherapy without a probiotic group [5.3 (2.1) days] using a 95% confidence level, 80% power of the test, and after adding a 20% drop-out rate. Age, gender, gestational age at birth and birthweight, length, head circumference and mode of delivery were recorded from the admission file.

Ethics

The study was approved by the Institutional Review Board and Ethics Committee of the University of Lahore (IRB-UOL-FAHS/1224-I/2022), and parents granted informed consent.

Clinical investigation

Neonatal demographics, clinical features and adverse events were documented, with gestational age calculated by ultrasonography before 20 weeks (73%), or from the last menstrual cycle. The principal investigator clinically examined each infant on admission for bruises and cephalhaematoma. Baseline serum total bilirubin levels, haematocrit, peripheral smear, reticulocyte count, direct Coomb's test and infant and maternal ABO blood groups were investigated. As per the NNU protocol, all neonates were not on oral feeds and were on 20% maintenance intravenous fluids (10% dextrose water and n/5 saline) for phototherapy.

Table 1. Demographic data of the study participants.

	Group A Phototherapy alone	Group B Phototherapy + probiotics	*p*-value
Age, days, mean (SD)	4.86 (1.86)	4.91 (2.53)	0.92[a]
Male, mean (SD)	14 (38.9)	20 (55.6)	
Female, mean (SD)	22 (61.1)	16 (44.4)	0.16[b]
Type of feed			
Breastfed, f (%)	16 (44.4)	19 (52.8)	
Formula milk, f (%)	16 (44.4)	12 (33.3)	
Both, f (%)	4 (11.1)	5 (13.9)	0.625[b]
Gestational age,wks, mean (SD)	33.62 (1.95)	33.5 (1.71)	0.92[a]
Birthweight, g, mean (SD)	2257.88 (420.79)	2476.1 (410.8)	0.03[a]
Bilirubin, mg/dL, mean (SD)	16.92 (1.63)	16.68 (1.69)	0.54[a]
Mode of delivery			
SVD, f (%)	22 (61.1)	28 (77.8)	
Caesarean section, f (%)	14 (38.9)	8 (22.2)	0.125[b]

[a]Independent sample *t*-test; [b]χ^2 test; SVD: spontaneous vaginal delivery; f: frequency.

Treatment plan

The Neoblue® LED phototherapy system was used for treatment that was stopped when serum bilirubin levels fell below 2 mg/dl. Group A received LED phototherapy (430–470 nm) only and Group B received LED phototherapy (430–470 nm) with probiotics (125 mg *S. boulardii*, twice a day orally, mixed in 5 cc of whichever milk the neonate was receiving). The dosage of *S. boulardii* was empirically determined on the basis of previous research in neonates [19].

In both groups, continuous phototherapy with a 20-cm distance between the neonate and the phototherapy unit was administered, except during feeding and nursing care. Preterm neonates were followed up clinically 8-hourly in the NNU and monitored for any side-effects of phototherapy (dehydration, rash, diarrhoea and thermal instability). Daily blood samples were obtained in a 3-cc disposable syringe and sent to the hospital laboratory for serum bilirubin testing. Serum bilirubin concentrations in venous blood samples were tested using Virto's 750 Ortho-Clinical Diagnostics at various times during and after phototherapy. The Neoblue LED phototherapy system was deployed, and irradiance was recorded weekly. The criteria for commencing phototherapy were based on the American Academy of Pediatrics' recommendations [20].

Phototherapy was discontinued when blood bilirubin levels decreased to <2 mg/dL, the lowest limit for phototherapy. Reports were assessed and, if bilirubin levels were out of the phototherapy range, it was discontinued and the duration of phototherapy and of hospital stay in hours were noted. Data were recorded on a standardised form designed for the study. Infants were discharged from the hospital when serum bilirubin levels were in the normal range.

Data analysis

Data were entered and analysed using SPSS version 26. Quantitative variables such as age, gestational age at birth, baseline bilirubin level and duration of phototherapy and hospital stay are presented as mean (SD). Qualitative variables such as gender and mode of delivery are presented as frequency and percentage. The mean duration of phototherapy and of hospital stay were compared in both groups using an independent sample *t*-test, and $p \leq 0.05$ was considered statistically significant.

Results

In Group A, the mean (SD) age was 4.9 (1.9) days and in Group B it was 4.9 (2.5) days. There were 14 male and 22 female infants in Group A and in Group B there were 22 male and 16 female infants. In Group A, 16 infants were breastfed, 16 were receiving formula milk and 4 were on both; in Group B, 19 were breastfed, 12 were on formula milk and 5 received both (Table 2). In Group A, gestational age (GA) at birth was 33.6 (1.9) weeks and in Group B it was 33.5 (1.7) weeks. In Group A, mean birthweight was 2258 (420.8) g and in Group B it was 2476 (411) g ($p = 0.029$). In Group A, mean (SD) bilirubin levels were 16.9 (1.6) mg/dL and in Group B 16.7 (1.7) mg/dL. In Group A, there were 22 spontaneous vaginal deliveries (SVD) and 14 caesarean sections while in Group B there were 28 SVDs and 8 caesarean sections (Table 1). Breastfeeding and formula milk did not affect outcome (Table 2). Mean (SD) duration of phototherapy was 36.5 (14.25) hours in Group A and in Group B it was 24.6 (9.25) hours. The difference between the two groups was statistically significant ($p = 0.0001$). The mean (SD) duration of hospital stay was 47.4 (16.5) hours in Group A and in Group B it was 33.1 (8.9) hours, which was statistically significant ($p = 0.0001$) (Figure 1). Side-effects of phototherapy included skin rash in 8.3% in Group A and in 2.8% in Group B, diarrhoea in 2.8% in Groups A and B and thermal instability in only 8.3% of Group A and in 2.8% of Group B (Figure 2). In both groups, there was a significant difference in the duration of phototherapy and hospital stay. However, both of these were shorter in Group B, suggesting a better outcome when probiotics are given along with phototherapy.

Table 2. Demographic data of study participants.

		Mean (SD)	*p*-value
Duration of phototherapy	Breastfed	29.31 (14.05)	0.74
	Formula milk	31.85 (12.85)	
	Both	31.55 (13.14)	
	Total	30.58 (13.35)	
Duration of hospitalisation	Breastfed	40.20 (14.19)	0.37
	Formula milk	41.78 (15.14)	
	Both	48.11 (17.17)	
	Total	41.80 (14.94)	

Discussion

The purpose of hyperbilirubinaemia therapy is to keep indirect bilirubin levels from rising to the point at which neurotoxicity, deafness and kernicterus are likely to develop. The neonates in Groups A and B had similar mean ages but demonstrated significant differences in treatment outcome. Group A neonates had fewer side-effects and required phototherapy for longer [38.3 (16.4) h] and a longer hospital stay [47.8 (15.8) h] than Group B [phototherapy 29.3 (11.2) h, hospital stay 36.45 (11.3) h] ($p = 0.002$).

The current study's findings align with those of other research into probiotics which has demonstrated that they can significantly reduce the duration of phototherapy and hospitalisation in infants with elevated bilirubin levels. This not only shortens treatment

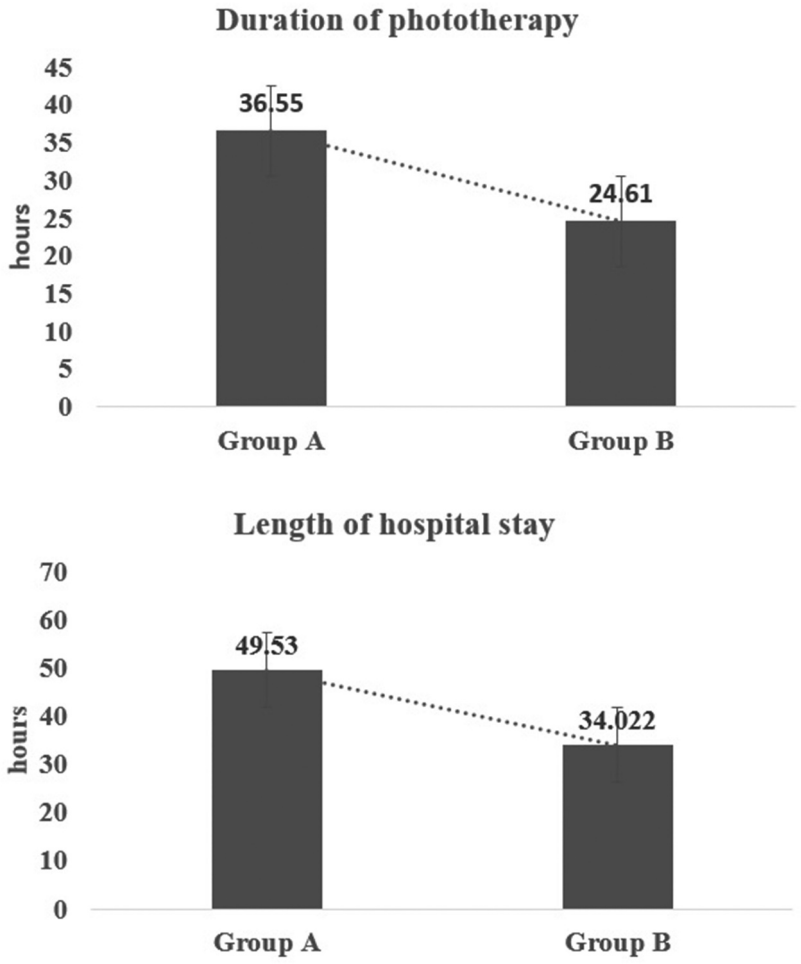


Figure 1. Comparison between duration of phototherapy and length of hospital stay.

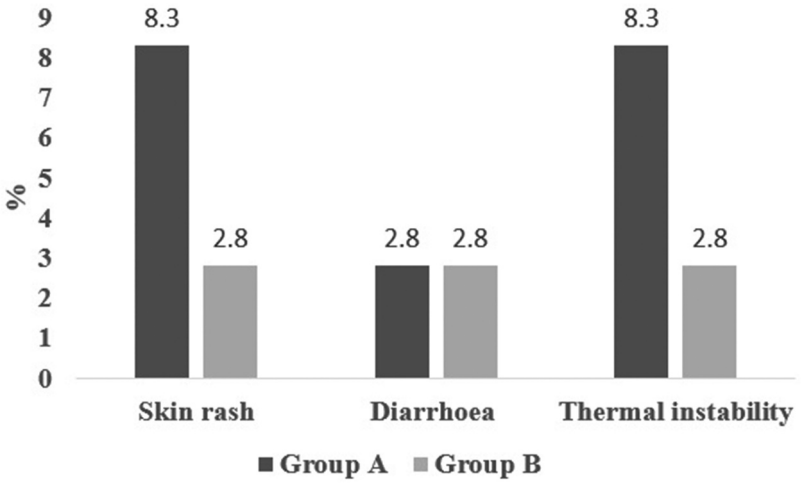


Figure 2. Adverse outcome in both groups.

and hospital stay but also has the potential to decrease healthcare costs. A meta-analysis of 13 clinical studies involving 1067 newborns reported that probiotic supplementation is safe and efficient in the treatment of pathological neonatal jaundice [21]. Another study reported that administering probiotics to newborns with jaundice could potentially reduce the duration of phototherapy [22].

Another study assessed the impact of probiotics on serum bilirubin levels in neonates with jaundice and reported that they did not significantly influence serum bilirubin levels or the duration of phototherapy [23]. These findings differ from those of the current study.

In this investigation, the probiotics administered were oligosaccharides. There was an increase in

bowel motions and a drop in bilirubin levels in Group B. A possible reason for the discrepancy between our findings and those of the previous study is that different probiotics were given [24]. Breast-milk jaundice can be reduced by a probiotic supplement, and probiotics have also been shown to help reduce neonatal jaundice [25]. Various other studies have found that probiotics can noticeably lower serum bilirubin levels in jaundiced neonates, hastening reduction of bilirubin levels and lessening the need for prolonged phototherapy [26,27].

The study found that probiotics can significantly reduce the duration of phototherapy for neonatal hyperbilirubinaemia, thereby reducing the risk of nosocomial infection. Further research should explore the benefits and drawbacks of probiotics, as well as their convenience in regular use. Investigation of faecal flora and large, randomised controlled trials are needed to further understand the clinical outcome of using probiotics.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

The author(s) reported that there is no funding associated with the work featured in this article.

ORCID

Meshari A. Alaifan http://orcid.org/0000-0002-0540-8430
Bakr H. Alhussaini http://orcid.org/0000-0002-3912-9843
Amber Hassan http://orcid.org/0000-0001-9362-0935

References

[1] Anderson NB, Calkins KL. Neonatal indirect hyperbilirubinemia. NeoReviews. 2020;21:e749–e760. doi: 10.1542/neo.21-11-e749
[2] Jayanti S, Ghersi-Egea JF, Strazielle N, et al. Severe neonatal hyperbilirubinemia and the brain: the old but still evolving story. Pediatr Med. 2021;4:e1–e20. doi: 10.21037/pm-21-5
[3] Muniyappa P, Kelley D. Hyperbilirubinemia in paediatrics: evaluation and care. Curr Probl Pediatr Adolesc Health Care. 2020;50:100842. doi: 10.1016/j.cppeds.2020.100842
[4] Brumbaugh D, Mack C. Conjugated hyperbilirubinemia in children. Pediatr Rev. 2012;33:291–302. doi: 10.1542/pir.33.7.291
[5] Harsha L, Priya J, Shah KK, et al. Systemic approach to management of neonatal jaundice and prevention of kernicterus. Res J Pharm Technol. 2015;8:1087–1092. doi: 10.5958/0974-360X.2015.00189.4
[6] Svenson IR. Impact of corporate interests on infant feeding practices and maternal child health. Am J Maternal/Child Nursing. 2024;49:54. doi: 10.1097/NMC.0000000000000966
[7] Olusanya BO, Teeple S, Kassebaum NJ. The contribution of neonatal jaundice to global child mortality: findings from the GBD 2016 study. Pediatrics. 2018;141:e20171471. doi: 10.1542/peds.2017-1471
[8] Malik S, Kapu M, Jain MK, et al. Effects of timing of cord clamping on neonatal hemoglobin and bilirubin levels in preterm and term infants – a prospective observational cohort study. PLoS One. 2024;19:e0295929. doi: 10.1371/journal.pone.0295929
[9] Hansen TW, Wong RJ, Stevenson DK. Molecular physiology and pathophysiology of bilirubin handling by the blood, liver, intestine, and brain in the newborn. Physiol Rev. 2020;100:1291–1346. doi: 10.1152/physrev.00004.2019
[10] Chee W, Chung H, Wong RM, et al. Jaundice in infants and children: causes, diagnosis and management. Hong Kong Med J. 2018;24:285–292. doi: 10.12809/hkmj187245
[11] Zhang M, He Y, Tang J, et al. Intensive phototherapy vs. exchange transfusion for the treatment of neonatal hyperbilirubinemia: a multicenter retrospective cohort study. Chinese Med J. 2022;135:598–605. doi: 10.1097/CM9.0000000000001962
[12] Ashraf MW, Munir I, Munir N, et al. Incidence and patterns of neonatal jaundice in tertiary medical facility. J Popul Therapeut Clin Pharmacol. 2024;31:1825–1831.
[13] Amin SB, Saluja S, Kler N. Unbound bilirubin and acute bilirubin encephalopathy in infants born late preterm and term with significant hyperbilirubinemia. J Pediatr. 2024;266:113880. doi: 10.1016/j.jpeds.2023.113880
[14] Vakili O, Mafi A, Pourfarzam M. Liver disorders caused by inborn errors of metabolism. Endocr Metab Immune Disord Drug Targets. 2024;24:194–207. doi: 10.2174/1871530323666230623120935
[15] Liu Q, Tang Z, Li H, et al. The development and validation of a predictive model for neonatal phototherapy outcome using admission indicators. Front Pediatr. 2022;10:745423. doi: 10.3389/fped.2022.745423
[16] Wang D, Kuzma ML, Tan X, et al. Phototherapy and optical waveguides for the treatment of infection. Adv Drug Delivery Rev. 2021;179:114036. doi: 10.1016/j.addr.2021.114036
[17] Nouri SA, Mohammadi MH, Moghaddam YN, et al. Therapeutic effects of synbiotic on neonates with gestational age over 34 weeks admitted for jaundice. J Neonat Perinat Med. 2022;15:327–333. doi: 10.3233/NPM-210847
[18] Mreihil K, Madsen P, Nakstad B, et al. Early formation of bilirubin isomers during phototherapy for neonatal jaundice: effects of single vs. double fluorescent lamps vs. photodiodes. Pediatr Res. 2015;78:56–62. doi: 10.1038/pr.2015.61
[19] Matin M, Homayouni-Rad A, Mostafa-Gharehbaghi M, et al. Maternal and infant probiotic administration for morbidity of very low birth weight infants: a three-arm randomized placebo-controlled trial. Eur J Nutr. 2022;61:3637–3648. doi: 10.1007/s00394-022-02905-z
[20] American Academy of Pediatrics Subcommittee on Hyperbilirubinemia. Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. Pediatrics. 2004;114:297–316. doi: 10.1542/peds.114.1.297
[21] Donneborg ML, Hansen BM, Vandborg PK, et al. Extreme neonatal hyperbilirubinemia and kernicterus spectrum disorder in Denmark during the years 2000–2015. J Perinatol. 2020;40:194–202. doi: 10.1038/s41372-019-0566-8

[22] Chen Z, Zhang L, Zeng L, et al. Probiotics supplementation therapy for pathological neonatal jaundice: a systematic review and meta-analysis. Front Pharmacol. 2017;8:432. doi: 10.3389/fphar.2017.00432
[23] Ahmed AE, Nazeer MV, Bakri AH. Evaluation of using agar combined with phototherapy in management of neonatal unconjugated hyperbilirubinemia. SUV - Int J Med Sci. 2022;5:325–330.
[24] Zahed Pasha Y, Ahmadpour-Kacho M, Ahmadi Jazi A, et al. Effect of probiotics on serum bilirubin level in term neonates with jaundice; a randomized clinical trial. Int J Pediatr. 2017;5:5953–5958.
[25] Zhou S, Wang Z, He F, et al. Association of serum bilirubin in newborns affected by jaundice with gut microbiota dysbiosis. J Nutr Biochem. 2019;63:54–61. doi: 10.1016/j.jnutbio.2018.09.016
[26] Hamed AM, Abdelmeguid MM, Omar SA. The effect of probiotics on reducing duration of hospitalization in infants with indirect hyperbilirubinemia. Egyp J Hospital Med. 2019;77:5900–5905. doi: 10.21608/ejhm.2019.64968
[27] Goodarzi R, Saadat SH, Arshadzadeh M, et al. Efficacy and safety of probiotics in neonatal hyperbilirubinemia: randomized controlled trial. J Neonat Nursing. 2022;28:286–290. doi: 10.1016/j.jnn.2021.10.003