Efficacy and Safety of Probiotic Supplementation for Neonatal Jaundice: a Systematic Review and Meta-Analysis

Probiotics and Antimicrobial Proteins

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Supplementary File 1. Literature search strategies

A. PubMed Search Strategy- Performed on January 16, 2025

((((((((((((((((((probiotics) OR (probiotic*)) OR (lactobacillaceae)) OR (lactobac*ill*)) OR ("Lactobacillaceae"[Mesh])) OR (lactobacillus)) OR (lactobacill*)) OR (Bifidobacterium)) OR ("Bifidobacterium"[Mesh])) OR (bifidobacter*)) OR (Saccharomyces)) OR (Saccharomyc*)) OR ("s boulardii")) OR ("S. boulardii")) OR (yeast)) OR (yogurt)) OR (Escherichia coli)) OR (Clostridium)) OR (Bacteroides)) OR (Streptococcus)) AND (((((jaundice) OR (neonatal jaundice)) OR (neonatal hyperbilirubinaemia)) OR (Hyperbilirubinemia)) OR ("Hyperbilirubinemia, Neonatal"[Mesh]))

B. Embase Search Strategy – Performed on January 16, 2025

(probiotics:ab,ti OR probiotic*:ab,ti OR lactobacillaceae:ab,ti OR lactobac*ill*:ab,ti OR 'lactobacillaceae'/exp OR lactobacillus:ab,ti OR lactobacill*:ab,ti OR bifidobacterium:ab,ti OR 'bifidobacterium'/exp OR bifidobacter*:ab,ti OR saccharomyces:ab,ti OR saccharomyc*:ab,ti OR 's boulardii':ab,ti OR 's. boulardii':ab,ti OR yeast:ab,ti OR yogurt:ab,ti OR 'escherichia coli':ab,ti OR clostridium:ab,ti OR bacteroides:ab,ti OR streptococcus:ab,ti) AND (jaundice:ab,ti OR 'neonatal jaundice':ab,ti OR 'neonatal hyperbilirubinaemia':ab,ti OR hyperbilirubinemia:ab,ti OR 'hyperbilirubinemia'/exp)

C. Cochrane Library– Performed on January 16, 2025

#1 (probiotics):ti,ab,kw OR (probiotic*):ti,ab,kw OR (lactobacillaceae):ti,ab,kw OR (lactobac*ill*):ti,ab,kw OR (lactobacillus):ti,ab,kw (Word variations have been searched)

#2 MeSH descriptor: [Lactobacillaceae] explode all trees

#3 (lactobacill*):ti,ab,kw OR (Bifidobacterium):ti,ab,kw OR (bifidobacter*):ti,ab,kw OR (Saccharomyces):ti,ab,kw OR (Saccharomyc*):ti,ab,kw (Word variations have been searched)

#4 MeSH descriptor: [Bifidobacterium] explode all trees

#5 ("s boulardii"):ti,ab,kw OR ("S. boulardii"):ti,ab,kw OR (yeast):ti,ab,kw OR (yogurt):ti,ab,kw OR (Escherichia coli):ti,ab,kw (Word variations have been searched)

#6 (Clostridium):ti,ab,kw OR (Bacteroides):ti,ab,kw OR (Streptococcus):ti,ab,kw (Word variations have been searched)

#7 (jaundice):ti,ab,kw OR (neonatal jaundice):ti,ab,kw OR (neonatal hyperbilirubinaemia):ti,ab,kw OR (hyperbilirubinemia):ti,ab,kw (Word variations have been searched)

#8 MeSH descriptor: [Hyperbilirubinemia] explode all trees

#9 #1 OR #2 OR #3 OR #4 OR #5 OR #6

#10 #7 OR #8

#11 #9 AND #10

D. China National Knowledge Infrastructure (CNKI) Search Strategy- Performed on January 16, 2025

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Supplementary Table S1. Characteristics of usual care

Study	Control regimen
Chen et al. 2022	PT for 10 days
Cui 2024	PT for 5 days
Dai 2020	PT for 9 days
Dong & Wu 2019	PT for 5 days
Gao et al. 2021	PT for 3 days
Hamed et al. 2019	PT
Hu et al. 2023	PT for 15 days
Jia 2021	PT for 5 days
Lai et al. 2022	PT for 2–3 days
Liang 2012	PT + phenobarbital 5 mg/kg/day + Nikethamide 75 mg/kg/day for 7–10 days
Liang et al. 2023	PT for 10 days
Lin & Lu 2021	PT for 7 days
Liu et al. 2015	PT + phenobarbital 5–8 mg/kg TID + 5% albumin 10–15 ml/kg QD for 3–5 days
Liu 2023	PT for 7 days
Lu & Ling 2017	PT for 8 days
Matin et al. 2022	500 mg placebo QD + PT for 28 days
Mutlu et al. 2020	Placebo QD + PT + IVIG 800 mg/kg for 4 days
Nasief et al. 2024	PT, continued until TSB fell below 2 mg/dL from the lowest limit for PT
Serce et al. 2015	Placebo 1 ml BID + PT, continued until TSB fell below 2 mg/dL from the lowest limit for PT
Tang et al. 2020	Placebo 1 ml QD + PT, continued until TSB <13 mg/dL
Tariq et al. 2021	PT, stopped when TSB <10 mg/dL (first week) or <11 mg/dL (after first week)
Torkaman et al. 2016	Placebo QD + PT, stopped when TSB <10 mg/dL (first week) or <11 mg/dL (after first week)

Study	Control regimen
Tsai et al. 2022	Placebo BID + PT, stopped when TSB decreased by 3 mg/dL from the baseline
Wang et al. 2014	PT+ Liver enzyme inducer for 6 days
Wu et al. 2019	PT for 9 days
Xue 2023	PT for 10 days
Zeng 2020	PT for 5 days
Zhang et al. 2008	PT + phenobarbital 5 mg/kg/day BID/TID + dexamethasone 0.3–0.5 /kg/day + albumin 1000 mg/kg or plasma for 5–7 days
Zhang 2019	PT for 4 days
Zhong 2018	PT for 8 days

QD: once a day, BID: twice a day, TID: three times a day, TSB: total serum bilirubin, PT: phototherapy, IVIG: intravenous immunoglobulin

Supplementary Table S2. Overall and subgroup analyses of total bilirubin levels (mg/dL) across different days

Subgroup	MD [95% CI]	*p*	Heterogeneity	
			I^2 (%)	*p*
1 day after treatment				
Overall	-0.35 [-0.63, -0.06]	0.02	14	0.32
Preterm	0.07 [-0.53, 0.66]	0.82	0	0.68
Full-term	-0.47 [-0.77, -0.17]	0.002	5	0.38
3 days after treatment				
Overall	-1.40 [-2.50, -0.29]	0.01	98	<0.00001
Preterm	-0.63 [-1.11, -0.16]	0.009	0	0.56
Full-term	-1.85 [-3.34, -0.35]	0.02	99	<0.00001
4 days after treatment				
Overall	-1.41 [-2.12, -0.69]	0.0001	91	<0.00001
Preterm	-0.76 [-1.21, -0.32]	0.0008	0	0.32
Full-term	-1.75 [-2.44, -1.05]	<0.00001	85	<0.0001
5 days after treatment				
Overall	-0.85 [-1.19, -0.52]	<0.00001	94	<0.00001
Preterm	-1.17 [-2.35, 0.02]	0.05	96	<0.00001
Full-term	-0.82 [-1.44, -0.19]	0.01	92	<0.00001
7 days after treatment				
Overall	-1.55 [-2.50, -0.60]	0.001	96	<0.00001
Preterm	-2.50 [-3.56, -1.44]	<0.00001	N/A	N/A
Full-term	-1.35 [-2.37, -0.34]	0.009	97	<0.00001

MD: mean difference; CI, confidence interval; N/A, not applicable.

Supplementary Table S3. GRADE summary table

Probiotics compared to standard care for newborn infants

Outcomes	Anticipated absolute effects* (95% CI)		No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Bilirubin	Risk with placebo			
Bilirubin on Day 1	MD 0.35 lower (0.63 lower to 0.06 lower)	The range of bilirubin at D1 was 9.67 to 18.25 mg/dL	769 (8 RCTs)	⊕⊕⊕◯ Moderate[a]	Probiotics probably results in a modest reduction in TSB on day 1.
Bilirubin on Day 10	MD 1.74 lower (2.54 lower to 0.95 lower)	The range of bilirubin at D10 was 2.35 to 11.57 mg/dL	270 (3 RCTs)	⊕◯◯◯ Very low[b,c]	Probiotics may reduce TSB on day 10 but the evidence is very uncertain.
Duration of phototherapy (hours)	MD 17.09 lower (24.43 lower to 9.76 lower)	The range of phototherapy duration was 26 to 156 hours.	782 (9 RCTs)	⊕⊕◯◯ Low[d]	Probiotics may moderately reduce phototherapy duration.
Duration of hospitalization (days)	MD 1.17 lower (1.6 lower to 0.74 lower)	The range of hospitalization was 2.03 to 27.6 days.	703 (9 RCTs)	⊕⊕◯◯ Low[e]	Probiotics may reduce the length of hospitalization.

* The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

a: For the target estimate of a modest reduction in serum bilirubin, the 95% CI ranges from a moderate to a very slight reduction. Certainty of the evidence was downgraded by one level.

b: There is a very large degree of heterogeneity as indicated by an I square value of 96%. Certainty of the evidence downgraded by two levels

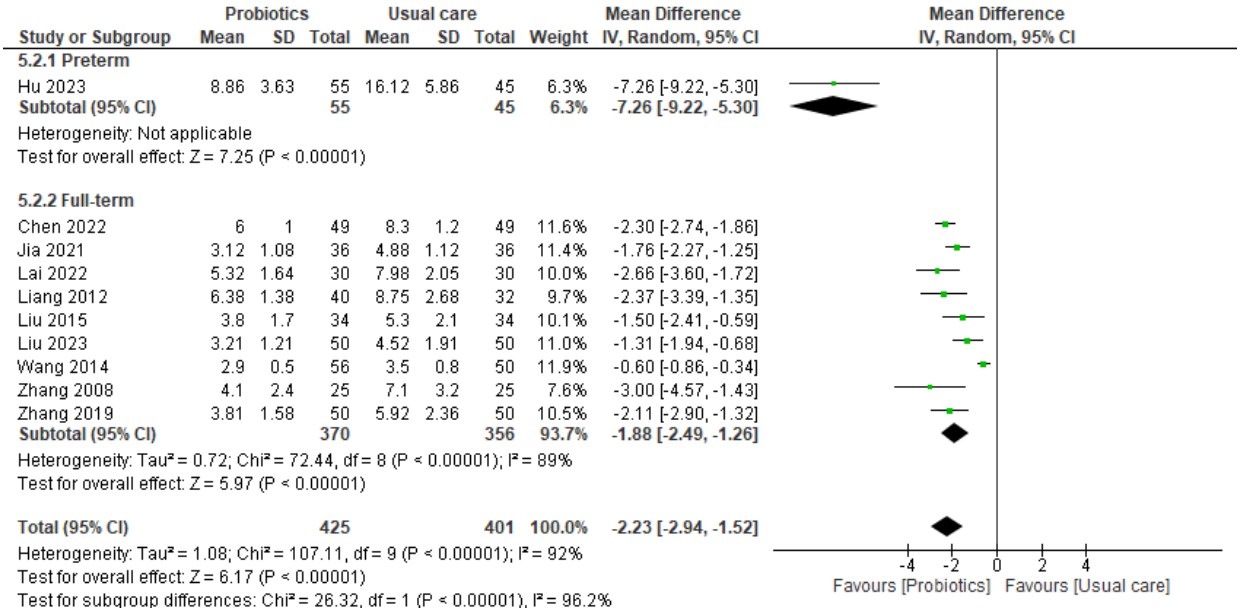
c: For the target estimate of a moderately large reduction in serum bilirubin, the 95% CI ranges from a large to a moderate reduction. Certainty of the evidence was downgraded by one level.

d: There is a large degree of heterogeneity, as indicated by an I square value of 81%.

e: There is a large degree of heterogeneity, as indicated by an I square value of 89%.

RCT: randomized controlled trial, MD: mean difference.

Supplementary Fig. S1 Forest plots of days to jaundice resolution in preterm and full-term infants



Supplementary Fig. S2 Forest plots of efficacy rates in preterm and full-term infants