A.11 PROBIOTICS

Recommendation and remarks

RECOMMENDATION A.11 (NEW)

Probiotics may be considered for human-milk-fed very preterm infants (< 32 weeks' gestation).
(Conditional recommendation, moderate-certainty evidence)

Remarks

- The recommendation is conditional on shared decision-making with parents; this includes informing parents about the benefits and risks and the need for further research.
- The GDG noted that there are many infant probiotic formulations available in the public domain that have variable quality control and formulation *(127,128)*.
- The GDG considered that only probiotics especially formulated for preterm or LBW infants that meet regulatory standards should be used, and clear instructions for safe use should be given to health workers.
- The GDG did not make a recommendation for infants born after 32 weeks' gestation because the data were insufficient.
- Only five trials (254 participants) included infants fed formula as the sole diet, so the GDG did not make a recommendation for these infants.
- The GDG was not able to make a recommendation on type (i.e. genera, species or strain), formulation (e.g. powder or drops), dose, timing or duration of probiotic administration as there was insufficient evidence. The GDG considered that type, formulation, dose, timing and duration should be based on clinical judgement.

Background and definitions

Probiotics are formulations given by the enteral route that contain bacteria (e.g. *Bifidobacterium* spp. or *Lactobacillus* spp.) or fungi (e.g. *Saccharomyces* spp.) *(129,130)*. A range of probiotic supplements are available commercially. Probiotics colonize the mucosal surface of the human gastrointestinal tract, modulate the intestinal microbiome and promote mucosal barrier functions *(129,130)*. Probiotics have been used to prevent and treat infectious or inflammatory gastrointestinal conditions primarily in adults, with only low-certainty evidence of any benefit for most conditions *(131-133)*. There have also been many trials of probiotics in preterm and LBW infants in the last 10 years showing varying effects, including reductions in sepsis and necrotizing enterocolitis *(134-137)*, but also increases in bacteraemia and fungaemia *(134,138,139)*.

Summary of the evidence

OVERVIEW	A.11 Probiotics
PICO	**Population** – Preterm or LBW infants **Intervention** – Any probiotics **Comparator** – No probiotics **Outcomes** – All-cause mortality, morbidity, growth, neurodevelopment at latest follow-up
Timing, setting, subgroups	**Timing of the intervention** – Birth to 6 months of age **Setting** – Health-care facility or home in any country or setting **Subgroups** • Gestational age at birth (< 32 weeks, ≥ 32 weeks) • Birth weight (< 1.5 kg, ≥ 1.5 kg) • Probiotic species (*Bifidobacterium* spp., *Lactobacillus* spp., other spp.) • Type of enteral feed (human milk, formula, mixed)

Effectiveness: Comparison – Any probiotics versus no probiotics

Sources and characteristics of the evidence

The effectiveness evidence was derived from a Cochrane systematic review of 56 trials totalling 10 812 very preterm (< 32 weeks' gestation) or VLBW infants (< 1.5 kg) *(127)*. An updated search conducted on 1 October 2021 located no new trials.

The average birth weight was 1.0–1.2 kg and average gestation at birth was 28–32 weeks. Four trials excluded infants who were born with birth weight below the 10th percentile for the reference population (i.e. small for gestational age, or SGA). Most trials were conducted during the past 20 years (4 trials were conducted pre-2000). The trials were from 21 countries (Australia, Bangladesh, Brazil, China, France, Germany, Greece, India, the Islamic Republic of Iran, Israel, Italy, Japan, Mexico, Pakistan, Poland, Slovenia, South Africa, Thailand, Türkiye, the United Kingdom and the USA). Fifty-five trials were individually randomized and one was cluster randomized. Twenty-one trials enrolled fewer than 100 participants, 20 enrolled 100–199, 12 enrolled 200–499 participants and 3 enrolled 500 participants or more. In most trials, participating infants were given human milk or formula feeding. Seven trials enrolled infants who received human milk only and five enrolled only formula-fed participants. The probiotic preparations varied, though were mostly lyophilized (freeze dried) or liquid commercially available products supplied by the manufacturer for use in the trial. Thirty-three trials used single-genus probiotics (most commonly, *Bifidobacterium* spp. or *Lactobacillus* spp.) and 23 used multi-genus combinations (most commonly, *Bifidobacterium* spp. plus *Lactobacillus* spp.). Most trials initiated supplementation during the first week after birth, typically with the first enteral feed. In most trials, the intervention period was at least six weeks, typically lasting until discharge from hospital. Eleven of the trials administered the intervention for a shorter period (7–30 days). One trial continued the intervention until the infant reached 2.0 kg body weight.

Critical outcomes

For probiotics compared with no probiotics, 51 trials reported all-cause mortality, 54 reported morbidity (54 reported necrotizing enterocolitis, 47 culture-confirmed infection) and 6 reported neurodevelopment (severe neurodevelopmental impairment). No trials reported growth. (Full details are provided in GRADE Table A.11, in the Web Supplement.)

- **Mortality**: Moderate-certainty evidence from 51 trials totalling 10 170 participants suggests a decrease in all-cause mortality by hospital discharge (RR 0.76, 95% CI 0.65 to 0.89).
- **Morbidity:** Low-certainty evidence from 54 trials totalling 10 604 participants suggests a decrease in necrotizing enterocolitis by hospital discharge (RR 0.54, 95% CI 0.45 to 0.65). Moderate-certainty evidence from 47 trials totalling 9762 participants suggests a decrease in invasive infection by hospital discharge (RR 0.89, 95% CI 0.82 to 0.97).
- **Neurodevelopment:** Low-certainty evidence from five trials totalling 1518 participants suggests little or no effect on neurodevelopment (severe neurodevelopmental impairment assessed using a validated test) between 18 months and 3 years (RR.1.03, 95% CI 0.84 to 1.26).

Other outcomes

There was a decrease in length of hospital stay (in days) (MD -1.93, 95% CI -3.78 to -0.08; 22 trials, 5458 infants).

Subgroup analyses

Subgroup differences for growth and neurodevelopment could not be assessed as there were insufficient studies. No difference was found for mortality, necrotizing enterocolitis or sepsis for any of the subgroups: gestational age and birth weight, probiotic species or type of enteral feed.

Other studies

Eight studies (3080 participants) recruited infants with gestational age 32–36 weeks (mean 33 weeks (SD 4 weeks) and showed decreases in all-cause mortality (RR 0.50, 95% CI 0.43 to 1.17; 4 trials, 2334 participants, low-certainty evidence), necrotizing enterocolitis (RR 0.32, 95% CI 0.16 to 0.66; 6 trials, 1493 participants, low-certainty evidence), sepsis (RR 0.50, 95% CI 0.29 to 0.85; 6 trials, 2708 participants, low-certainty evidence) and neurodevelopmental impairment (RR 0.48, 95% CI 0.29 to 0.80; 1 trial, 249 participants, very-low-certainty evidence).

Values and acceptability

The systematic review about what matters to families about the care of the preterm or LBW infant (see Table 1.1) reported that families want to be involved in delivering care to infants, and want to take an active role in deciding what interventions are given to infants, including what and how they are fed *(14)*. A study from the United Kingdom reported that families are willing to consider use of probiotics for their preterm or LBW infants if there is evidence of benefit and safety *(140)*. There was no other specific evidence available about whether families value probiotic supplements for their preterm or LBW baby or find them acceptable.

Resources required and implementation considerations

Organization of care

Probiotics can be provided in the health-care facility or at home. The family needs accurate information on the dose and how to administer the supplement. National or local guidance for health-care facilities should be used.

Infrastructure, equipment and supplies

Common probiotic preparations are either single-genus or multi-genus probiotic combinations (including *Bifidobacterium* spp. plus *Lactobacillus* spp). Dosing, amounts, frequency and duration vary. Probiotics can be provided as powder or liquids in bottles or mixed with infant milk or sterile water. National or local guidance for health-care facilities should be used.

Workforce, training, supervision and monitoring

Health workers at all levels can support mothers and families. Standardized packages are needed for training, supervision and monitoring. Dispensing needs to be documented in clinical records.

Feasibility and equity

There was no specific evidence available about the feasibility and equity of providing probiotics to preterm or LBW babies.

Summary of judgements

Comparison: Any probiotics vs no probiotics (A.11)	
Justification	In trials where most participants are very preterm (< 32 weeks' gestation) or VLBW (< 1.5 kg): • Evidence of moderate benefit: decreased mortality, necrotizing enterocolitis and invasive infection *(moderate-certainty evidence)* • No evidence of harms • Evidence of little or no effect on neurodevelopment *(low-certainty evidence)* • No evidence on other critical outcomes

Evidence-to-Decision summary	
Benefits	Moderate
Harms	Trivial or none
Certainty	Moderate
Balance	Probably favours probiotics
Values	No uncertainty or variability about outcomes
Acceptability	Varies
Resources	Low to moderate
Feasibility	Varies
Equity	Varies