A.3 DONOR HUMAN MILK

Recommendation and remarks

RECOMMENDATION A.3 (UPDATED)

When mother's own milk is not available, donor human milk may be considered for feeding of preterm or low-birth-weight (LBW) infants, including very preterm (< 32 weeks' gestation) or very LBW (< 1.5 kg) infants. *(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 potential harm of necrotizing enterocolitis from infant formula was considered by the GDG to be more clinically important than the benefit of increased growth from infant formula.
- Donor human milk was pasteurized in all but one trial, so the GDG was not able to make a recommendation on the use of unpasteurized milk.
- Safe and affordable milk-banking facilities are needed for the provision of donor human milk.
- Mothers should also be encouraged and supported before and after birth to provide their own breast-milk (including colostrum) for their infants.

Background and definitions

When mother's own milk is not available, preterm or LBW infants must be given other milks. Donor human milk is provided through human milk banks (i.e. places where human milk is collected, treated and/or distributed) *(56,66)*. Donor milk has differences in immune composition to mother's own milk. Human milk banks also usually pasteurize milk to remove infective organisms, which further alters milk components *(56,66)*. WHO LBW feeding guidelines in 2011 recommended feeding donor human milk rather than infant formula to preterm or LBW babies who cannot be fed mother's own milk *(19)*. However, new studies have been published since that time.

Summary of the evidence

OVERVIEW	A.3 Donor human milk
PICO	**Population** – Preterm or LBW infants **Intervention** – Infant formula **Comparator** – Donor human milk **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) • Amount of donor milk in the control arm (donor milk provided as the sole diet, mixed with infant formula)

Effectiveness: Comparison – Infant formula versus donor human milk

Sources and characteristics of the evidence

The effectiveness evidence was derived from a systematic review published in 2019 of 12 RCTs enrolling 1879 preterm or LBW infants from neonatal units in eight countries (Austria, Canada, Finland, Hungary, Italy, the Netherlands, the United Kingdom and the USA) *(67)*. An updated search conducted on 1 October 2021 located no new trials. Participants were clinically stable preterm or LBW infants. Most were below 32 weeks' gestational age or below 1.8 kg at birth. Many trials excluded infants who were small for gestational age at birth and infants with congenital anomalies or gastrointestinal or neurological problems. The

trials varied according to whether formula or donor milk was provided as the sole diet (5 trials) or as a supplement to mother's own milk (7 trials). A mix of term and preterm formula was used. The donor milk was a mix of preterm and term donor milk and a mix of fortified and unfortified milk. In all trials except one, the donor human milk was pasteurized. In general, feeds were allocated for several weeks, or until participating infants reached a specified body weight (generally > 2 kg). One trial used the allocated feed for less than 10 days after birth. Infants then received preterm formula if their mother's own milk was insufficient.

Critical outcomes

For infant formula compared with donor human milk, seven trials reported all-cause mortality, nine reported morbidity (9 reported necrotizing enterocolitis, 5 invasive infection), nine reported growth (9 reported weight gain, 8 length, 8 head growth) and two reported neurodevelopment (neurodevelopmental disability). (Full details are provided in GRADE Table A.3, in the Web Supplement.)

- **Mortality:** Moderate-certainty evidence from seven trials totalling 1527 participants suggests little or no effect on all-cause mortality by hospital discharge (RR 1.1, 95% CI 0.8 to 1.5).
- **Morbidity:** Moderate-certainty evidence from nine trials totalling 1675 participants suggests an increase in risk of necrotizing enterocolitis by hospital discharge (RR 1.87, 95% CI 1.23 to 2.85). Moderate-certainty evidence from five trials totalling 1025 participants suggests little or no effect on risk of invasive infection by hospital discharge (RR 0.94, 95% CI 0.79 to 1.12).
- **Growth:** Moderate-certainty evidence from nine trials totalling 1028 participants suggests an increase in weight gain (in grams per kilogram per day) by hospital discharge (MD 2.51, 95% CI 1.93 to 3.08). Moderate-certainty evidence from eight trials totalling 820 participants suggests an increase in linear growth (crown–heel length, measured in millimetres per week) by hospital discharge (MD 1.21, 95% CI 0.77 to 1.65). Moderate-certainty evidence from eight trials totalling 894 participants suggests an increase in head growth (in millimetres per week) by hospital discharge (MD 0.85, 95% CI 0.47 to 1.23).
- **Neurodevelopment**: Moderate-certainty evidence from two trials totalling 400 participants suggests little or no effect on neurodevelopmental disability by 18 months of age (RR 1.21, 95% CI 0.62 to 2.35).

Two studies in the review also reported on long-term growth outcomes. Neither individual study nor meta-analyses of data from both studies showed differences in weight, length or head circumference at follow-up at 9 months, 18 months or 7.5–8 years of age. For the latest follow-up at 7.5–8 years of age, there was no difference in growth parameters between infants fed formula milk or donor human milk (weight [kg], MD -0.56, 95% CI -1.42 to 0.29; length [cm], 0.05, 95% CI -1.12 to 1.23; and head circumference [cm], MD -0.19, 95% CI -0.54 to 0.16; 2 studies, 420 participants).

Other outcomes

There was higher risk of feeding intolerance in the formula-fed group compared with the donor milk group (moderate-certainty evidence) (RR 4.92, 95% CI 1.17 to 20.70; 2 trials, 148 participants).

Subgroup analyses

For the analyses by gestational age and birth weight and amount of donor milk in the control arm, differences for all critical outcomes could not be assessed as there were insufficient studies.

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, including supporting nutrition, and want to take an active role in deciding what interventions are given to infants, including what and how they are fed *(14)*. A number of studies report the facilitators and barriers to donating and receiving donor human milk *(68-71)*. These include preferences for receiving human rather than artificial milk, concerns about the effect of pasteurization and transportation, and concerns that the mother's own breast-milk supply will reduce *(68-71)*. A large cross-sectional survey among health workers in urban Zimbabwe reported that the concept of donor human milk banking was acceptable, and that the participants would accept donor human milk for their children, and many would encourage their clients to donate human milk *(68)*.

Resources required and implementation considerations

Organization of care

The provision of donor human milk requires access to a human milk bank where milk can be tested, pasteurized and transported safely.

Infrastructure, equipment and supplies

Infrastructure, equipment and supplies are needed for donor assessment (screening, informed consent, serological testing), milk expression, handling, storage, transport, pre-pasteurization testing, pasteurization, and post-pasteurization testing. Supplies are also needed for safe cup and gastric tube feeding.

Workforce, training, supervision and monitoring

Specialized staff are needed for the operation of donor human milk banks. Standardized packages are needed for training, supervision and monitoring. More detailed guidance on the operation of donor human milk banks is being developed and will be published separately. Health workers at all levels can provide feeding support.

Feasibility and equity

A census of milk banks from a systematic literature review reported 572 milk banks globally in 60 countries, with the majority in high-income countries *(68)*. It is well known that safe and affordable milk-banking facilities are needed for the provision of donor human milk. However, the base resources for donor milk feeding (i.e. donor recruitment, donor assessment [screening, informed consent, serological testing], milk expression, handling, storage, transport, pre-pasteurization testing, pasteurization, post-pasteurization testing) are much less available in low- and middle-income countries (LMICs), especially in smaller towns and villages *(66,72)*. The use of donor milk varies widely within and between countries and is influenced by cultural practices, access, costs, awareness, supportive policies and resources *(66,72)*.

Summary of judgements

Comparison: Infant formula vs donor human milk (A.3)	
Justification	In trials where most participants are very preterm (< 32 weeks' gestation) or VLBW (< 1.5 kg): • Evidence of small benefits from using infant formula instead of donor human milk: increased in-hospital weight gain, length and head circumference (*moderate-certainty evidence*) • Evidence of moderate harms from using infant formula instead of donor human milk: increased necrotizing enterocolitis and feed intolerance (*moderate-certainty evidence*) • Evidence of little or no effect of using infant formula on mortality and neurodevelopment (*moderate-certainty evidence*) • No evidence on other critical outcomes

Evidence-to-Decision summary	
Benefits	Benefits of infant formula are small
Harms	Harms of infant formula are moderate
Certainty	Moderate
Balance	Probably does not favour infant formula, probably favours donor human milk
Values	Probably no important uncertainty or variability about outcomes
Acceptability	Acceptability of infant formula and donor human milk varies
Resources	Resources for infant formula and donor human milk vary
Feasibility	Feasibility of infant formula and donor human milk varies
Equity	Equity of infant formula and donor human milk varies