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Hemolytic disease of the fetus and newborn: awareness precedes change

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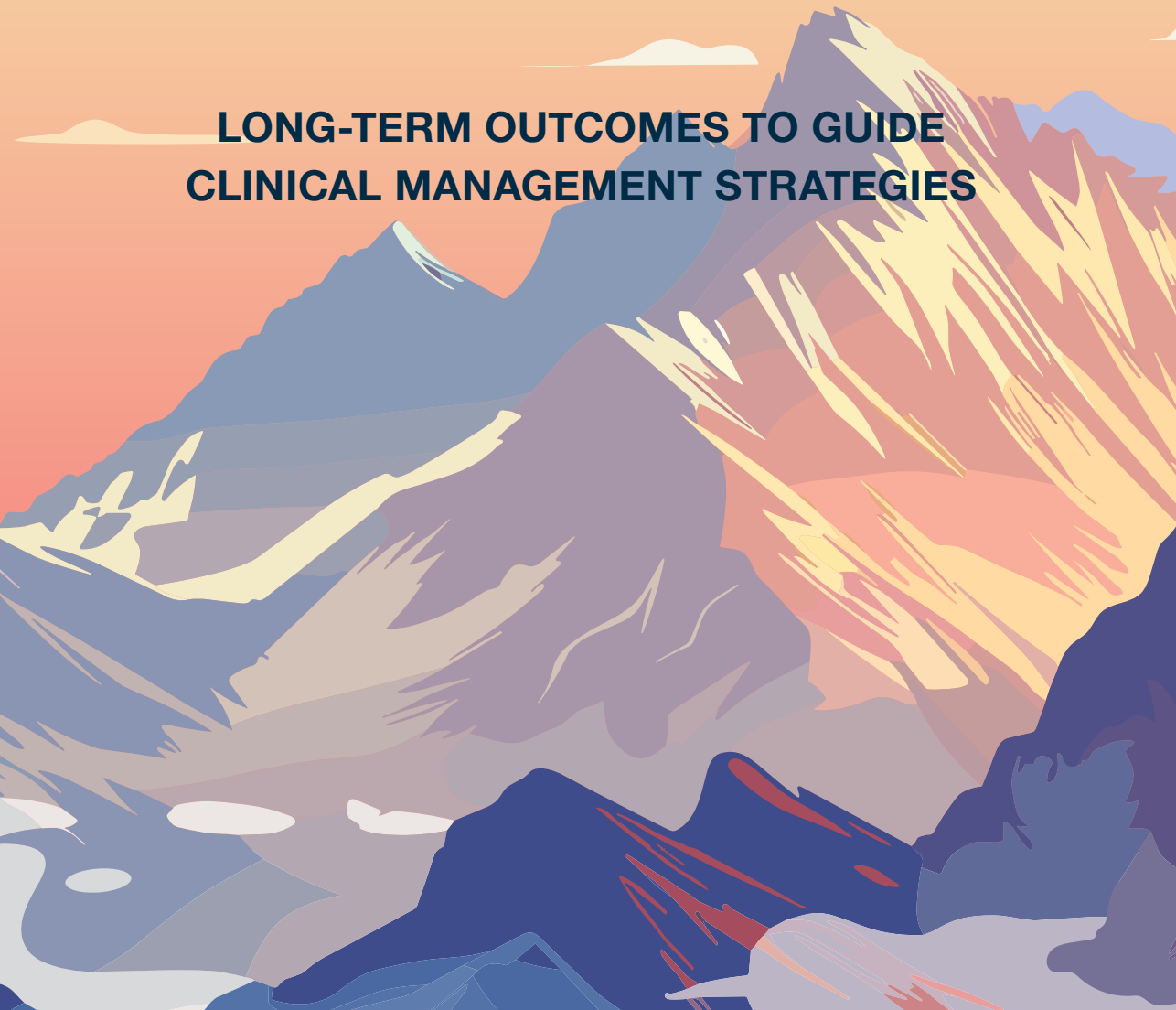
Citation
Winter, D. P. de. (2026, March 31). *Hemolytic disease of the fetus and newborn: awareness precedes change*. Retrieved from https://hdl.handle.net/1887/4299998

Version:	Publisher's Version
License:	Licence agreement concerning inclusion of doctoral thesis in the Institutional Repository of the University of Leiden
Downloaded from:	https://hdl.handle.net/1887/4299998

Note: To cite this publication please use the final published version (if applicable).

PART VI

LONG-TERM OUTCOMES TO GUIDE CLINICAL MANAGEMENT STRATEGIES




Chapter
12

Long-Term Neurodevelopmental Outcomes In Infants With Haemolytic Disease Of The Newborn Treated With Darbepoetin

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Published in The Lancet Haematology, March 2025, E169-E170

Newborns treated with intrauterine transfusions (IUT) for severe haemolytic disease of the fetus and newborn (HDFN) have a high transfusion dependency after birth. Antenatal transfusions with consequently an inhibition of erythropoiesis, combined with continued haemolysis postnatally, can cause anaemia after birth.[1] Up to approximately 90% of affected newborns require at least one erythrocyte transfusion and a median of two erythrocyte transfusions during the first 3 months of life.[2] Transfusion dependency in preterm neonates has been shown to affect neurodevelopment, showing increasingly worse long-term outcome with increasing number of transfusions.[3]

In *The Lancet Haematology*, Ree and colleagues evaluated the effect of darbepoetin alfa, a long-acting erythropoiesis-stimulating agent (ESA), on the number of erythrocyte transfusions in newborns with HDFN who were treated with IUT. This open-label, single-centre, phase 2, randomised controlled trial showed a significant reduction in the number of erythrocyte transfusions in newborns with weekly subcutaneous administrations of 10 µg/kg darbepoetin alfa (median of 1·0 transfusions [IQR 1·0–2·0]) compared with standard care (median of 2·0 transfusions [1·3–3·0]). Importantly, no short-term complications were observed.[4] The long-term neurodevelopmental outcomes that could aid clinicians in determining whether ESAs could be used in this population were not yet reported upon.

We therefore invited all 43 children who participated in the trial for standardised neurodevelopmental assessment at 2 years of age. Follow-up consisted of a neurological examination and assessment with the Bayley Scales of Infant and Toddler Development—Third Edition (Bayley-III) to assess cognitive and motor development. A composite outcome of neurodevelopmental impairment (NDI) was used, subdivided into mild-to-moderate NDI (defined as the presence of cerebral palsy [Gross Motor Function Classification System grade 1], Bayley- III cognitive score <85, Bayley-III motor score <85, or mild visual or hearing impairment) and severe NDI (defined as the presence of severe cerebral palsy [Gross Motor Function Classification System grade ≥2], Bayley- III cognitive score <70, or Bayley-III motor score <70, or severe visual or hearing impairment).[3,5,6] The Bayley-III cognitive and motor composite scores are calculated from the child's raw scores. The child's performance on each item in a subtest is scored as 1 or 0. These individual item scores are summed to obtain a raw score for each domain (cognition, fine motor, and gross motor). This raw score is converted into a scaled score using age-specific norms (mean 10 [SD 3]). The scaled scores from individual subtests within a domain are combined and converted into a composite score using normative tables. The composite scores have a mean of 100 and an SD of 15.

Of the 43 children included in the randomised controlled trial, 38 (88%) were seen for follow-up at a median corrected age of 2 years and 3 months. A total of five children (11%) were lost to follow-up, of which two were withdrawn from the study at the parents' request, two parents were not reached despite multiple efforts, and one family emigrated. The baseline characteristics of the children seen at follow-up did not differ from the original population,[4] and, except for the distribution of K-mediated alloimmunisation, did not differ between the treatment group and control group in the current analyses (table).

Among 19 children treated with darbepoetin, cognitive and motor development was assessed in 17 children using the Bayley-III (although motor development was not assessed in two of these children due to uncooperative behaviour). In the remaining two children, parents completed the Parent Report of Children's Abilities—Revised (PARCA-R) and neurological and motor functioning was queried via telephone consultation, due to the COVID-19 pandemic. The PARCA-R is a parent-completed questionnaire that can be used to assess children's cognitive development. Among 19 children in the control group, cognitive and motor development was assessed in 18 children using the Bayley-III. In the remaining child in the control group, cognitive and motor assessment was not performed using the Bayley-III at the parents' request, but follow-up did include a neurological assessment. Both composite cognitive scores (median 96 [IQR 90–102] *vs* 101 [91–105]) and composite motor scores (98 [88–108] *vs* 100 [91–109]) did not differ between the control group and the children treated with darbepoetin alfa, respectively.

The rate of NDI was similar between groups. We found that mild-to-moderate NDI was present in three (16%) of 19 children treated with darbepoetin and in three (16%) of 19 children with standard treatment. Severe NDI was found in one child in the standard care group based on a motor composite score below 70, with no other signs of NDI. None of the children showed any signs of cerebral palsy or hearing or vision deficits at 2 years of age.

Thus, the neurodevelopment outcomes in children at 2 years of age who participated in the trial published by Ree and colleagues were similar between those who received darbepoetin alfa and those who received standard care for HDFN. We hypothesised that a decrease in the number of transfusion episodes would lead to better neurodevelopmental outcomes. However, this effect could not be demonstrated as this post-hoc analysis is limited by a small sample size that was not powered to detect such differences. Also, it is noteworthy that the neuroprotective effect of ESAs, which was previously suggested in animal and human studies,[7] might be more elaborate

in (extremely) preterm infants compared with infants with HDFN, who are generally born at near-term gestation. Lastly, the neuroprotective effects of ESAs have more commonly been shown in studies with higher doses that allow passage through the blood–brain barrier.[8]

Taken together, weekly subcutaneous administrations of 10 µg/kg darbepoetin alfa can be considered in the postnatal treatment of newborns affected by severe HDFN to reduce the number of erythrocyte transfusion episodes. Considering the limitations of this study, further trials powered to detect differences in neurodevelopmental outcomes are needed.

Table: Baseline characteristics and neurodevelopmental outcomes by treatment group

	Treatment group (n=19)	**Control group (n=19)**
Sex of the infant		
Female	11 (57·9%)	13 (68.4%)
Male	8 (42·1%)	6 (31.6%)
Type of alloimmunisation		
D-mediated alloimmunisation	12 (63·2%)	17 (89%)
c-mediated alloimmunisation	1 (5·3%)	1 (5%)
K-mediated alloimmunisation	6 (31·6%)	1 (5%)
Gestational age at first IUT, weeks	28·9 (23·9–32·9)	30·7 (26·6–33·5)
Number of IUTs	3 (1–4)	2 (2–4)
Gestational age at delivery, weeks	36·7 (36·4–37·1)	36·6 (36·3–37·0)
Birthweight, grams	2845 (2725–3083)	2795 (2650–3072)
Total number of transfusion episodes	1·0 (1·0–2·0)	2.0 (1.0–2.5)
Age at follow-up, months	27 (27–30)	27 (26–31)
Corrected age at follow-up, months	27 (25–29)	26 (24–30)
Mild-to-moderate NDI	3/19 (16%)	3/19 (16%)
Severe NDI	0/19 (0%)	1/19 (5%)
Composite cognitive score	96 (90–102) (17/19)	101 (91–105) (18/19)
Composite motor score	98 (88–108) (15/19)	100 (91–109) (17/19)

Data are n (%) or median (IQR). NDI = neurodevelopmental impairment. IUT = intrauterine transfusion.

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