

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Beardsall K, Vanhaesebrouck S, Ogilvy-Stuart AL, et al. Early insulin therapy in very-low-birth-weight infants. *N Engl J Med* 2008;359:1873-84.

Neonatal Insulin Replacement Therapy Study



Definitions

Primary End Point

Reduction in mortality before expected date of delivery

Secondary End Points

i. Episodes of sepsis in the first 2 weeks of life:

- a) culture positive systemic infection will be defined as microbiologically positive cultures of blood, cerebrospinal fluid or suprapubic aspirate of urine plus clinical signs of sepsis.
- b) culture negative infection will be defined as clinical signs suggestive of sepsis and considered to warrant >48 hours of antibiotics but with negative cultures.

ii. Growth: all babies will have measurements of weight, length and head circumference at birth and every seven completed days after recruitment until 28 days of age. Growth will be assessed as change in weight, length and head circumference standard deviation score (SDS) from birth to 28 days of age using conditional charts.

iii. Incidence of necrotizing enterocolitis: radiological evidence of necrotizing enterocolitis assessed by consultant radiologist blinded to the treatment. Classified as having radiological evidence or not.

iv. Retinopathy of Prematurity: all these babies will be routinely screened for retinopathy of prematurity (by an ophthalmologist blinded to the treatment received). They will be graded using the internationally recognised grading system ^{1,2}:

Stage 1	Demarcation line
Stage 2	Ridge
Stage 3	Extraretinal fibrovascular proliferation
Plus disease	Dilation and tortuosity of posterior retinal vessels
Stage 4	Retinal detachment

Infants will be scored by the most severe degree of retinopathy and classified into two groups as either having a score <3 or ≥3.

v. Incidence of intracranial haemorrhage: defined as cranial ultrasound evidence as assessed by Consultant Neonatologist (blinded to the treatment received) from standard views. Patients will be classified as having H0 vs H1-4.

H0	No haemorrhage
H1	Localised Haemorrhage (subependymal or choroidal)
H2	Intraventricular Haemorrhage with no ventricular dilatation
H3	Intraventricular Haemorrhage with ventricular dilatation
H4	Parenchymal/Periventricular Lesions

vi. Chronic Lung disease: defined as respiratory support or oxygen dependency at 36 weeks corrected gestational age ³.

vii. Death in the first 28 days after delivery (where day 1 is considered to be the first day of life)

viii. Days of Neonatal Intensive Care: As defined by BAPM 2002 ⁴:

Level 1 (Intensive Care)

1. Receiving respiratory support via a tracheal tube and in the first 24 hours after its withdrawal
2. Receiving NCPAP for any part of the day and less than 5 days old
3. <1000g current weight and receiving NCPAP for any part of the day and for 24 hours after withdrawal
4. <29 weeks gestation and <48 hours of age
5. Requiring major emergency surgery, for the pre-operative period and post-operatively for 48 hours
6. Any other very unstable baby considered by the nurse in charge to need 1:1 nursing
7. Day of Death

Level 2 (High Dependency Care)

1. Receiving NCPAP for any part of the day and not fulfilling any of the criteria for intensive care
2. <1000g current weight and not fulfilling any of the criteria for intensive care
3. Receiving parenteral nutrition
4. Having convulsions
5. Receiving oxygen therapy and <1500g current weight
6. Requiring treatment for neonatal abstinence syndrome
7. Requiring specified procedures that do not fulfil any criteria for intensive care: care of an intra-arterial catheter or chest drain, partial exchange transfusion, tracheostomy care until supervised by a parent
8. Requiring frequent stimulation for severe apnoea

Level 3 (Special Care)

Special care encompasses all babies who could not reasonably be expected to be looked after at home by their mother

Level 4 (Ordinary Care)

All babies who themselves have no medical indication to be in hospital.

References

1. An international classification of retinopathy of prematurity. The Committee for the Classification of Retinopathy of Prematurity. Arch Ophthalmol 1984;102(8):1130-4.
2. An international classification of retinopathy of prematurity. II. The classification of retinal detachment. The International Committee for the Classification of the Late Stages of Retinopathy of Prematurity. Arch Ophthalmol 1987;105(7):906-12.
3. Shennan AT, Dunn MS, Ohlsson A, Lennox K, Hoskins EM. Abnormal pulmonary outcomes in premature infants: prediction from oxygen requirement in the neonatal period. Pediatrics 1988;82(4):527-32.
4. BAPM. BAPM standards for hospitals providing neonatal intensive and high dependency care and categories of babies requiring neonatal care. 2001.