

## National Asphyxia and Cooling Register in Switzerland

Barbara Brotschi<sup>1)</sup>, Bea Latal<sup>2)</sup>, Verena Rathke<sup>1)</sup>, Cornelia Hagmann<sup>3)</sup>

Therapeutic hypothermia (TH) improves the survival and neurodevelopmental outcome of infants with moderate to severe hypoxic ischaemic encephalopathy (HIE)<sup>1-3)</sup> and has become standard care in the developed world.

In Switzerland, TH has been offered since 2005 according to a TH protocol<sup>4)</sup>. A retrospective analysis of all cooled infants showed that passive cooling is the most common cooling method in Switzerland and that neuro-monitoring with cerebral MRI and amplitude EEG during cooling and thereafter is not applied uniformly and thus could be improved<sup>4)</sup>. Furthermore, passive cooling showed the highest variability in temperature compared to active cooling. So far, no prospective systematic data recording or follow-up assessment has been undertaken for cooled infants born in Switzerland. Therefore, to improve clinical management and provide standardized long-term follow-up assessments of children with HIE, a National Asphyxia and Cooling register was established in 2011. This register enables the evaluation of the efficacy of TH in Switzerland, ensures a safety control of applied cooling methods, allows comparing neurodevelopmental outcome depending on different cooling methods and in comparison with published outcome data.

TH is offered in nine neonatal intensive care units and in two paediatric intensive care units in Switzerland (Fig. 1). The aim of the register is to systematically record perinatal data, details on resuscitation, on cooling criteria, temperature management and neuro-monitoring in order to improve clinical management of these infants. Entry criteria for TH were set according to the randomized trial (Table 1)<sup>1)</sup>. A TH protocol on management of infants under TH has been agreed on by all

participating centers. Electronic case report forms (eCRF) are filled in for each infant who underwent cooling and this data is entered into the register database by a clinic representative. Since 2014, a minimal eCRF for all infants with HIE who were not cooled is also recorded. The eCRF is available online ([www.neonet.unibe.ch/php/manuel.php](http://www.neonet.unibe.ch/php/manuel.php)). The database is managed by a data manager. In addition, a register coordinator/nurse conducts regular data monitoring visits in each center to ensure correct data recording. The register is supervised by two neonatal consultants, regular register meetings are held with the clinic representatives and newsletters are posted four times a year. Follow-up is performed at the Neonatal Follow-up centers within the Neonatal Network (see article in this edition).

Since the introduction of the register, 257 infants have been registered of whom 193

were cooled and 64 not. From 2015 onwards, infants who are born with a mild encephalopathy at a secondary neonatal care unit not offering TH (e.g. Sion, Biel, Münsterlingen, Baden, Zurich (Zollikerberg, Triemli) and Schaffhausen) will also be registered.

Another important aim of the register is to organize and ensure short- and long-term follow-up assessments. Consistent data are lacking with respect to school outcomes in cooled children: the CoolCap study evaluated the efficacy of selective head cooling of 46% of the children at 7 to 8 years on the basis of parental questionnaires and demonstrated a moderate correlation with the 18 month assessments, although the study was underpowered to examine the effect on TH on cognitive function at an older age<sup>5)</sup>. In the NICHD study, there was a high follow-up rate among children at age 6 to 7 years, with children in the TH group having lower death rate than those in the control group, however, no significant differences in the rates of cognitive outcomes were detected<sup>6)</sup>. Long-term assessments of the children who participated in the TOBY trial<sup>1)</sup> showed that children in the hypothermia group, as compared with those in the control group had significant reductions in the risk of cerebral palsy and the risk of moderate

### NATIONAL ASPHYXIA AND COOLING REGISTER SWISS NEONATAL NETWORK & FOLLOW UP GROUP



Fig. 1: Cooling centers (blue circles): NICUs in Geneva, Lausanne, Basel, Lucerne, Zurich, Chur, St. Gallen, Winterthur, Aarau; PICUs at Children's University Hospital in Bern and Zurich.

- 1) Department of Paediatric and Neonatal Intensive Care, University Children's Hospital Zurich, Zurich, Switzerland.
- 2) Child Development Center, University Children's Hospital, Zurich, Switzerland.
- 3) Clinic of Neonatology, University Hospital Zurich, Zurich, Switzerland.

to severe disability; and they showed better motor function<sup>7</sup>.

These infants were all part of randomized controlled studies in which strict entry criteria for TH were set and the infants were treated according to a defined protocol. However, since TH has become standard of care, it is to the clinician's discretion which infants should be treated with TH and how this treatment is applied in reality. In order to know how cooled infants in Switzerland develop at older age a systematic and uniform follow-up has to take place. All cooled children after HIE (regardless of HIE severity) and those with a Sarnat II or III or a Thomson score of 7 or higher who were not cooled are being followed within the Swiss Neonatal Follow-up Network. The follow-up protocol is the same as for children born below 32 weeks of gestation and is presented in *table 2*.

A register is essential as modifying the treatment protocol for TH is being investigated both within and outside a formal randomised trial design, which includes changes in degree and duration of TH (Optimizing Cooling for neonatal HIE study, Clinical Trials Identifier NCT01192776), time window >6 h after birth Identifier NCT00614744) and cooling infants <36 weeks gestational age (GA) (Clinical Trials Identifier NCT01793 129). A recent study has shown that infants who do not fulfill standard TH entry criteria may benefit from TH. This study showed that short- and long-term outcome in cooled infants with neonatal encephalopathy following postnatal collapse, preterm birth or with an underlying surgical or cardiac condition and infants starting cooling > 6 postnatal hours were similar to those in cooled infants fulfilling the entry criteria (Smit, Liu et al. 2014). A register will provide us with detailed information on how Swiss clinicians adapt to such changes.

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### Term and near term infants less than six hours old who meet the following treatment criteria (A and B) may be considered for treatment with hypothermia:

- A. Infants  $\geq 36$  weeks gestation admitted to the neonatal unit, with at least two of the following:
  - a. Apgar score of  $\leq 5$  at (5)10 minutes after birth
  - b. Continued need for resuscitation, including endotracheal or mask ventilation, at 10 minutes after birth
  - c. Acidosis within 60 minutes of birth defined as any occurrence of umbilical cord, arterial or capillary pH  $\leq 7.00$
  - d. Base Deficit  $\geq 16$  mmol/L in umbilical cord or any blood sample (arterial, venous or capillary) within 60 minutes of birth
  - e. Lactate  $\geq 12$  mmol/l in umbilical cord or any blood sample (arterial, venous or capillary) within 60 minutes of birth
- B. Seizures or moderate to severe encephalopathy defined by Sarnat (Stage II or III) or Thompson Score  $\geq 7$

**Table 1:** Eligibility for hypothermia when resuscitation is completed and infant is stable

### Minimal follow-up protocol

- A) At 2 years of age Bayley III (cognition, language and motor composite scores)
  - a) Neurological examination: Cerebral palsy classification according to Surveillance of Cerebral Palsy in Europe (SCPE) and gross motor function classification system
  - b) Visual examination
  - c) Hearing examination
- B) At 5 years of age
  - a) Intellectual examination: Kaufmann Assessment Battery for Children (K-ABC)
  - b) Neurological examination: Cerebral palsy classification according to SCPE and gross motor function classification system
  - c) Motor examination: Zürcher Neuromotor Assessment
  - d) Behavior Strength and Difficulties Questionnaire (SDQ)
  - e) Visual examination

**Table 2:** Follow-up assessment of all registered children