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# Therapeutic hypothermia for neonatal encephalopathy with sepsis: a retrospective cohort study

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## ABSTRACT

**Objective** Neonatal encephalopathy remains a major cause of infant mortality and neurodevelopmental impairment. Infection may exacerbate brain injury and mitigate the effect of therapeutic hypothermia (TH). Additionally, infants with sepsis treated with TH may be at increased risk of adverse effects. This study aimed to review the clinical characteristics and outcomes for infants with sepsis treated with TH.

**Design and setting** Retrospective cohort study of infants treated with TH within Australia and New Zealand.

**Patients** 1522 infants treated with TH, including 38 with culture-positive sepsis from 2014 to 2018.

**Intervention** Anonymised retrospective review of data from Australian and New Zealand Neonatal Network. Infants with culture-positive sepsis within 48 hours were compared with those without sepsis.

**Main outcome measures** Key outcomes include in-hospital mortality, intensive care support requirements and length of stay.

**Results** Overall the rate of mortality was similar between the groups (13% vs 13%). Infants with sepsis received a higher rate of mechanical ventilation (89% vs 70%, p=0.01), high-frequency oscillatory ventilation (32% vs 13%, p=0.003) and inhaled nitric oxide for persistent pulmonary hypertension (38% vs 16%, p<0.001). Additionally, the sepsis group had a longer length of stay (20 vs 11 days, p<0.001).

**Conclusion** Infants with sepsis treated with TH required significantly more respiratory support and had a longer length of stay. Although this may suggest a more severe illness the rate of mortality was similar. Further research is warranted to review the neurodevelopmental outcomes for these infants.

### What is known about the subject?

- Therapeutic hypothermia (TH) for infants with intrapartum hypoxic brain injury improves neurodevelopmental outcomes in survivors.
- Infection prior to acute hypoxia may exacerbate brain injury and mitigate the therapeutic effects of hypothermia.
- There is a paucity of literature that describes the clinical characteristics and outcomes for infants with neonatal encephalopathy and sepsis treated with TH.

### What this study adds?

- In this cohort of infants treated with TH, the rate of mortality was similar for infants with culture-proven sepsis compared with those without sepsis.
- Infant with sepsis treated with TH may be more likely to require invasive respiratory support, including high-frequency oscillatory ventilation and inhaled nitric oxide .
- Further research is warranted to review the long-term therapeutic benefit of TH for infants with neonatal encephalopathy and sepsis.

## BACKGROUND

Neonatal encephalopathy (NE), related to intrapartum hypoxia ischaemia, remains a major global health burden. It is responsible for approximately one-quarter of neonatal deaths worldwide, with 62% of cases suffering moderate to severe encephalopathy and 20% surviving with severe neurodevelopmental impairment.[1] In New Zealand, NE occurs at a rate of approximately 1.30 per 1000 term births.[2] By definition, the term NE is descriptive and broad and does not specify the cause, but there are a small number of common aetiologies.[3] Some cases can be attributed to cumulative hypoxia-ischaemia or a sentinel hypoxic-ischaemic event.[4] In others, infection and inflammation,[5] and placental pathology[6] potentially contribute to neurological injury and adverse outcome.[4]

Hyperthermia during or following hypoxia-ischaemia may potentiate neurological injury.[7 8] Maternal hyperthermia in labour is associated with adverse neonatal outcomes including depression at birth,[9] encephalopathy[10] and mortality.[11] Hyperthermia may be secondary to infection or non-infectious causes such as epidural anaesthesia, prostaglandins, prolonged labour, dehydration or high-ambient temperature.[12] Perinatal infection itself is associated with long-term

neurological impairment in the neonate.[13 14] Importantly, perinatal infection in conjunction with acute hypoxia-ischaemia has been associated with a significantly increased risk for neurological injury compared with either in isolation.[15] This suggests the mechanism of injury may be multifactorial, though the underlying pathophysiology is not well understood.

Therapeutic hypothermia (TH) for neonates with moderate to severe encephalopathy secondary to acute hypoxic-ischaemic injury is the standard of care to improve neurodevelopmental outcomes in survivors.[16] However, 5%–12% of neonates treated with TH have early-onset sepsis (EOS),[16 17] and the clinical features may be indistinguishable. In adult populations, TH is not recommended in the context of sepsis as it is associated with increased morbidity[18] and mortality.[19] Currently, there are limited data on the outcomes for newborns with EOS treated with TH. In the current study, we aim to determine the clinical characteristics and short-term outcomes for infants with and without proven EOS who received TH.

## METHODS

### Study design

A retrospective cohort study of infants with and without proven EOS treated with TH for NE across Australia and New Zealand.

### Data source

The Australian and New Zealand Neonatal Network (ANZNN) retrospectively collects deidentified data annually from each individual neonatal intensive care unit (NICU) across Australia and New Zealand to monitor the care of high-risk neonates for quality assurance, benchmarking and research. This includes data for all infants who receive TH in a NICU in Australia or New Zealand. The data set includes maternal demographics, reason for presentation, antenatal complications and interventions, labour and birth details, condition at birth and resuscitation, duration of treatment with TH, details of intensive care support (ventilation mode and duration, nitric oxide, respiratory complications and cardiovascular support), discharge details, major morbidity and mortality.

### Study population

The cohort included infants born ≥36 weeks' gestation who received TH in tertiary NICUs in Australia and New Zealand including those who died during TH, or had hypothermia ceased prior to 72 hours of treatment for clinical reasons. Data collected between 2014 and 2018 were reviewed to obtain reasonable sample size of infants with culture-proven sepsis. Infants with major congenital malformations or a known genetic syndrome and those who required surgery within the first 72 hours after birth were excluded. Infants were separated into two groups for analysis: those with early culture-positive sepsis and those without. EOS was defined by positive blood culture or cerebrospinal fluid culture within the first 48 hours after birth, as per the ANZNN data dictionary definition.

### Study outcomes

The description of the infants' clinical characteristics and severity of illness was based on available data, including condition at birth (Apgar score, resuscitation detail, severity of acidosis (umbilical cord/infant blood gas and/or lactate testing) and temperature on admission), respiratory support during admission (invasive mechanical ventilation and non-invasive ventilation, high-frequency oscillatory ventilation (HFOV), duration and inhaled nitric oxide (iNO) and complications (respiratory failure, pneumothorax). Data for the use of haemodynamic support are limited, though we reviewed the prevalence of extracorporeal membrane oxygenation (ECMO) support. Key outcomes reviewed include mortality and length of hospital stay.

### Statistical analysis

Patient data were deidentified prior to review, including patient details, demographics and treating centre. Clinical data are presented as median (IQR) or n (%). Statistical analyses were performed using Prism V.9 software and statistical significance is taken as $p<0.05$. Continuous data were analysed using the Mann-Whitney U test and categorical variables were compared using $\chi^2$ test or Fisher's exact test. Where possible, 95% CIs were calculated to aid in interpretation of results. Logistic regression was used to analyse the association between mortality and other variables. Missing data were excluded from the analysis as it was not feasible to retrieve it given the retrospective nature of the ANZNN data set.

### Patient and public involvement

Although future work in this area may involve questions that arise from the family experience and preferences, this was not apposite for the current study using previously collected data. Thus, families and/or patients were not involved in the study design or recruitment.

## RESULTS

Antenatal characteristics for the NE group and the NE and sepsis group are shown in table 1. Gestational age and birth weight did not differ significantly between the groups. However, significantly more newborns in the NE and sepsis group were born following prolonged preterm rupture of membranes (p=0.02) and a significantly greater proportion of newborns in the NE group were delivered by instrumental vaginal delivery (p=0.01).

The neonatal characteristics of the two groups are shown in table 2. There was no significant difference in mortality rate between the two groups (p=0.9, OR 1.05, 95% CI 0.41 to 2.52). While there was a trend towards a greater need for any respiratory support in the NE and sepsis group, it did not reach significance (p=0.07). The

Table 1 Antenatal characteristics

| | Neonatal encephalopathy (n=1494) | Neonatal encephalopathy with sepsis (n=38) | P value |
|---|---|---|---|
| Maternal age, years (IQR) | 30 (26–47) | 29.5 (27–32) | 0.2 |
| Ethnicity (%) | | | |
| Aboriginal | 41 (3) | 1 (2) | 0.68 |
| Asian | 224 (15) | 9 (23) | 0.99 |
| Caucasian | 967 (64) | 20 (50) | 0.18 |
| Indigenous, other | 50 (3) | 1 (2) | 0.09 |
| Pacific | 49 (3) | 3 (8) | 0.99 |
| Māori | 91 (6) | 4 (10) | 0.15 |
| Not specified | 91 (6) | 2 (5) | 0.3 |
| Presenting problem (%) | | | |
| Preterm prologed rupture of membranes (PPROM) | 19 (2) | 3 (8) | 0.02 |
| Preterm labour | 19 (2) | 0 (0) | 0.13 |
| Hypertension | 88 (6) | 3 (8) | 0.51 |
| Antepartum haemorrhage (APH) | 91 (6) | 1 (3) | 0.73 |
| Intrauterine growth restriction (IUGR) | 28 (2) | 0 (0) | 0.1 |
| Fetal distress | 637 (42) | 18 (45) | 0.75 |
| Spontaneous labour, term | 438 (29) | 13 (33) | 0.6 |
| Fetal malformation | 5 (0.3) | 0 (0) | |
| Not specified | 203 (13) | 3 (8) | 0.35 |
| Previous perinatal death (%) | 25 (2) | 1 (2) | 0.5 |
| Plurality, twins (%) | 40 (3) | 1 (2) | 0.99 |
| Twins (%) | | | |
| First born | 12 (30) | 1 (100) | <0.001 |
| Second born | 28 (70) | 0 (0) | |
| Gestation (IQR) | 39 (38–40) | 39 (38–40) | 0.64 |
| Birth weight, g (IQR) | 3385 (3000–3730) | 3413 (3093–3903) | 0.25 |
| Male (%) | 848 (56) | 24 (60) | 0.25 |
| Delivery (%) | | | |
| Vaginal | 459 (31) | 14 (35) | 0.81 |
| Instrumental vaginal | 317 (21) | 2 (5) | 0.01 |
| Caesarean in labour | 493 (33) | 17 (43) | 0.23 |
| Caesarean without labour | 233 (15) | 7 (18) | 0.66 |
| Not specified | 11 (0.7) | 0 (0) | – |
| Breech (%) | 94 (6) | 3 (8) | 0.74 |

Data are presented as median (IQR) or n (%). The Mann-Whitney U test and the Pearson $\chi^2$ test or the Fisher's exact test were used for comparison between groups.

NE group and EOS group were significantly more likely to require mechanical ventilation (p=0.01, OR 3.6, 95% CI 1.36 to 9.54, d=0.5) and continuous positive airway pressure (CPAP) (p=0002, OR 0.31, 95% CI 0.16 to 0.58, d=0.5). These infants were also significantly more likely to require HFOV (p=0.003, OR 3.21, 95% CI 1.53 to 6.61, d=0.3) and iNO (p=0.01, OR 2.58, 95% CI 1.32 to 5.11, d=0.4). The requirement for ventilation was significantly more frequently attributed to pneumonia (p=0.002) or meconium aspiration (p=0.02) in infants with sepsis compared with those without. The underlying causes of infection are shown in table 3.

Logistic regression was used to assess the predictor of death in infants with NE. The model contained five independent variables (ventilated, sex, sepsis, 5 min Apgar and cord lactate). The model with all predictors

Table 2 Neonatal characteristics

| | Neonatal encephalopathy (n=1494) | Neonatal encephalopathy with sepsis (n=38) | P value |
|---|---|---|---|
| Apgar score (IQR) | | | |
| 1 min | 2 (1–3) | 2 (1–3) | 0.4 |
| 5 min | 4 (2–6) | 4 (2–6) | 0.4 |
| Intubation at resuscitation (%) | 833 (55) | 21 (53) | 0.7 |
| Temperature on admission (IQR) | 35.4 (34–36.3) | 35.8 (34.4–36.4) | 0.3 |
| Cord lactate (IQR) | 11 (7–14) | 8.7 (5.2–13.2) | 0.5 |
| Postnatal lactate (IQR) | 12 (8.5–16) | 13.6 (10.6–16.3) | 0.1 |
| Worst base excess (IQR) | 15 (20–10) | 16 (21–9) | 0.3 |
| Respiratory support (%) | 1373 (91) | 38 (100) | **0.07** |
| Indication (%) | | | |
| Neonatal encephalopathy | 905 (61) | 19 (48) | 0.08 |
| Respiratory distress | 141 (9) | 2 (5) | **0.02** |
| Hyaline membrane | 18 (1) | 0 (0) | 0.62 |
| Meconium aspiration | 137 (9) | 9 (23) | **0.02** |
| Pneumonia | 1 (0.06) | 2 (5) | **0.002** |
| PPHN | 73 (5) | 4 (10) | 0.13 |
| Apnoea | 14 (1) | 1 (2) | 0.32 |
| Not specified | 84 (6) | 3 (7) | 0.41 |
| Ventilated (%) | 1049 (70) | 34 (89) | **0.01** |
| Mechanical ventilation, hours (IQR) | 71 (27–110) | 104 (55–188) | **<0.001** |
| ECMO (%) | 9 (0.6) | 1 (3) | 0.22 |
| HFOV, ventilated (%) | 136 (13) | 11 (32) | **0.003** |
| HFOV, hours (IQR) | 57 (13–100) | 161 (22–202) | 0.09 |
| iNO (%) | 246 (16) | 15 (38) | **0.01** |
| CPAP, hours (IQR) | 22 (8–52) | 54 (23–95) | **<0.001** |
| Nasal high flow, hours (IQR) | 48 (24–98) | 49 (40–189) | 0.2 |
| Air leak (%) | 88 (6) | 4 (9) | 0.2 |
| Necrotising enterocolitis (NEC) (%) | 5 (0.3) | 0 (0) | 0.9 |
| Death (%) | 198 (13) | 5 (13) | 0.9 |
| Gastrostomy tube fed at discharge (%) | 75 (5) | 5 (13) | 0.052 |
| Length of stay, days (IQR) | 11 (8–17) | 20 (15–31) | **<0.001** |

Data are presented as median (IQR) or n (%). The Mann-Whitney U test and the Pearson $\chi^2$ test or the Fisher's exact test were used for comparison between groups.
Bold text indicates p< 0.05.
ECMO, extracorporeal membrane oxygenation; HFOV, high-frequency oscillatory ventilation; iNO, inhaled nitric oxide; PPHN, persistent pulmonary hypertension.

was significant, $X$ (5, n=3020)=5.5, p<0.001, and correctly classified 86.5% of cases. Need for mechanical ventilation was the only variable that made a significant contribution to the model.

## DISCUSSION

TH is fundamental to the management of NE in the newborn. However, in adults, TH is not recommended in the context of sepsis as it is associated with increased morbidity[18] and mortality.[19] Importantly, a significant proportion of neonates treated with TH also have EOS.[16 17] In the current analysis, approximately 2.5% of the infants receiving TH were culture positive. Importantly, mortality rates were not higher, but newborns with NE and sepsis did require more intensive care support with a significantly greater need for mechanical ventilation, HFOV and iNO for persistent pulmonary hypertension (PPHN). This suggested a greater illness severity during the period of TH and was associated with a significantly longer length of hospital stay in survivors. A greater proportion of the infants with sepsis were discharged home with gastrostomy tube feeding (5% vs

Table 3 Underlying aetiology of infection <48 hours of age

| | n=38 |
|---|---|
| Gram positive (%) | 15 (40) |
| Group B *Streptococcus* | 10 (26) |
| Group A *Streptococcus* | 1 (2) |
| Streptococci other | 2 (5) |
| Other Gram positive | 2 (5) |
| Gram negative (%) | 7 (18) |
| *Escherichia coli* | 1 (2) |
| *Haemophilus* sp | 4 (11) |
| Other | 2 (5) |
| Not specified (%) | 16 (42) |

13%), which may suggest more neurological impairment, though results did not quite meet significance.

The literature on the combined effect of NE and sepsis in newborns who received TH is conflicting. The current data are consistent with a European study of infants with perinatal asphyxia and probable or confirmed EOS, which did not identify an increased risk of mortality.[20] In contrast, a systematic review of infants with invasive group B *Streptococcus* infection treated with TH found an increased risk of mortality (risk ratio 2.07, 95% CI 1.47 to 2.91).[21] However, this review included infants from several countries including low-income settings where patients may have limited access to similar levels of neonatal intensive care.

The overall mortality rate in the current study was 13% and did not differ between the NE group and the NE and sepsis group. This is higher than reported mortality rates for term newborns with EOS alone, which are typically reported to be approximately 1.5%–3%[22–24] highlighting the significant burden of concurrent NE secondary to perinatal asphyxia. Overall, the rate of mortality for our cohort was comparable with the 10.9% reported in a review of infants who received TH in England and Wales.[25] Over the last decade, the mortality for infants treated with TH has improved from approximately 27% while the proportion of infants cooled with culture-proven sepsis has remained similar.[16] This may reflect changes in clinical practice with more infants with less severe NE receiving treatment with TH,[17] advances in intensive care and earlier recognition and treatment of NE.

In the current study, infants with NE and sepsis were more likely to require mechanical ventilation compared with those without sepsis. Further, the duration of mechanical ventilation was longer and they were more likely to receive support with HFOV and iNO. It is known that infants with sepsis are at risk of PPHN, a known complication of TH.[16] A recent case report of NE with sepsis treated with TH described severe PPHN with respiratory failure requiring ECMO.[26] Further, the clinical course was complicated by pulmonary haemorrhage thought to be secondary to left ventricular dysfunction with asphyxia, increased pulmonary blood flow with patent ductus arteriosus, capillary dysfunction and coagulopathy.[26] In our cohort, few infants were treated with ECMO with no significant difference between the groups, and pulmonary haemorrhage was not reported in either group. We do not have data on the frequency of hypotension requiring treatment as this was not collected in the ANZNN data set. However, data from animal models[27] and from case reports[26] suggest that the use of TH in infants with sepsis may be associated with profound hypotension refractory to medical treatment.

In considering the mechanism of neurological injury and resulting outcome, it is recognised that infection prior to acute hypoxia lowers the injury threshold exacerbating brain injury[28–30] and that the extent of injury may be pathogen dependent.[31] Further, animal data suggest a pre-existing infection may attenuate the therapeutic effects of cooling.[27 29 30] For instance, in piglets, TH is not protective in those with *Escherichia coli* sepsis, based on recovery of amplitude-integrated electroencephalogram, magnetic resonance spectroscopy lactate/N-acetylaspartate (NAA) peak area ratios in the thalamus and white matter, and histological cell death.[27] TH has also been reported to be ineffective at suppressing microglial activation, proinflammatory cytokine production and astrogliosis in preclinical models of infection and acute hypoxia.[27 32] In human infants, a report of term newborns with encephalopathy treated with TH reviewed for evidence of maternal chorioamnionitis and infant infection reported that newborns with NE and early bacteraemia had significant rates of moderate to severe basal ganglia or watershed injury on MRI, and a lower cognitive score on Bayley-III developmental assessment at 30 months of age.[33] A further study of placental pathology has also reported chorioamnionitis with fetal vasculitis and chorionic plate meconium to be associated with brain injury on MRI.[34] Finally, a recent paper reports an association between adverse short-term MRI outcome and both higher interleukin 6 (IL-6) before TH initiation and higher C-reactive protein (CRP) levels during and after TH.[35] These observations have driven research into adjuvant therapies with immunomodulatory potential for infants with acute hypoxic injury including erythropoietin, melatonin, magnesium, xenon, mesenchymal stem cells, steroids and anti-inflammatory cytokines, among others.[36] Although further validation is needed, work in this area is important.

Earlier, more accurate diagnosis is also a research goal as clinical signs of asphyxia may be indistinguishable from sepsis in a newborn infant.[37] A positive blood culture is the gold standard for diagnosis, but results are rarely available prior to 6 hours of age.[38] Currently used biomarkers include a complete blood count, though diagnostic performance is poor prior to 4 hours of age and acute hypoxia alters neutrophil dynamics.[39] Acute phase reactants such as CRP are non-specific with both infection and inflammation secondary to hypoxic injury

associated with increased levels, and additionally the rise may be delayed.[39] Procalcitonin is more sensitive for bacterial infection, though it requires further study for its use in neonatal EOS.[40] Multiplex bacterial PCR enables more rapid detection of bacterial pathogens, though it is not yet widely available.[41] Other biomarkers currently under investigation include IL-6, IL-8, serum amyloid A, neutrophil CD64 and cytokines such as tumour necrosis factor.[42]

A major strength of the current study is the reliability of the ANZNN data set with data checked for discrepancy by the local centre prior to submission and again on acceptance by ANZNN. The 5-year period studied and the availability of data from across ANZNN also ensured an adequate sample size based on a reasonable number of infants with culture-proven sepsis. The a priori decision to only include newborns in the NE and sepsis group who had blood culture-positive sepsis is both a strength and a limitation. While controlling for the uncertainty of 'suspected sepsis', we acknowledge that blood cultures may be falsely negative due to an inadequate sample volume or prior exposure to antibiotics. The current cohort included all infants treated with TH but the severity of NE was not defined, which may limit the interpretation of the results. An additional limitation is that ANZNN collects a predetermined limited data set without the ability to go back to source documents, which limits the reporting on hypotension and treatment, MRI and standardised severity of illness score for all infants. As a result, the impact of severity of NE in those newborns also diagnosed with blood culture-positive sepsis, if any, cannot be assessed. A further consideration is the impact of missing data from the ANZNN data set. This is particularly relevant for the logistic regression analysis of factors predicting death. While all the data were available for ventilation, sex and sepsis, 1% of data regarding 5 min Apgar were missing for the cooled no sepsis group and 38% and 60% of cord lactate data were missing for the cooled no sepsis group and cooled sepsis group, respectively. However, no significant differences between those infants with and without cord lactate data in either group were seen (data not shown), suggesting that the data were missing completely at random. As a result, a complete case analysis approach rather than multiple imputation was chosen. Finally, the focus of the current study was mortality and short-term outcomes in the immediate newborn period. The impact of TH on longer term neurodevelopmental outcomes in those newborns with NE and sepsis was beyond the scope of this study but is a significant knowledge gap that requires further investigation.

## SUMMARY

In this study, infants with culture-proven sepsis treated with TH for presumed birth asphyxia did not have a higher rate of mortality compared with those without sepsis. Infants with sepsis had a higher rate and duration of mechanical ventilation, HFOV and iNO, and length of stay suggesting a more severe illness. TH remains a standard care for infants with moderate to severe NE; however, further study is required to determine if TH provides a long-term therapeutic benefit for infants with birth asphyxia and bacterial sepsis.

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**Contributors** KS and MB conceived the study and applied for access to the data set. KS, TMC, MS and MB analysed the data. KS prepared the draft and all authors contributed to the writing, editing and final review of the manuscript. MB acts as guarantor.

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**Patient consent for publication** Not required.

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