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Administration of parenteral nutrition during therapeutic hypothermia: a population level observational study using routinely collected data held in the National Neonatal Research Database

Chris Gale ,[1] Dusha Jeyakumaran,[1] Nicholas Longford,[1] Cheryl Battersby,[1] Shalini Ojha ,[2,3] Kayleigh Oughham,[4] Jon Dorling[5]

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[1]Neonatal Medicine, School of Public Health, Imperial College London, London, UK
[2]School of Medicine, University of Nottingham, Derby, UK
[3]Neonatal Unit, University Hospitals of Derby and Burton NHS Foundation Trust, Derby, UK
[4]Neonatal Data Analysis Unit, Imperial College London Faculty of Medicine, London, UK
[5]Division of Neonatal—Perinatal Medicine, Dalhousie University—Faculty of Medicine, Halifax, Nova Scotia, Canada

Correspondence to
Dr Chris Gale, Neonatal Medicine, School of Public Health, Faculty of Medicine, Imperial College London, London SW7 2AZ, UK; christopher.gale@imperial.ac.uk

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ABSTRACT

Background Parenteral nutrition is commonly administered during therapeutic hypothermia. Randomised trials in critically ill children indicate that parenteral nutrition may be harmful.

Objective To examine the association between parenteral nutrition during therapeutic hypothermia and clinically important outcomes.

Design Retrospective, population-based cohort study using the National Neonatal Research Database; propensity scores were used to create matched groups for comparison.

Setting National Health Service neonatal units in England, Scotland and Wales.

Participants 6030 term and near-term babies, born 1/1/2010 and 31/12/2017, who received therapeutic hypothermia; 2480 babies in the matched analysis.

Exposure We compared babies that received any parenteral nutrition during therapeutic hypothermia with babies that did not.

Main outcome measures Primary outcome: blood culture confirmed late-onset infection; secondary outcomes: treatment for late onset infection, necrotising enterocolitis, survival, length of stay, measures of breast feeding, hypoglycaemia, central line days, time to full enteral feeds, discharge weight.

Results 1475/6030 babies (25%) received parenteral nutrition. In comparative matched analyses, the rate of culture positive late onset infection was higher in babies that received parenteral nutrition (0.3% vs 0.9%; difference 0.6; 95% CI 0.1, 1.2; p=0.03), but treatment for presumed infection was not (difference 0.8%, 95% CI −2.1 to 3.6, p=0.61). Survival was higher in babies that received parenteral nutrition (93.1% vs 90.0%; rate difference 3.1, 95% CI 1.5, 4.7; p<0.001).

Conclusions Receipt of parenteral nutrition during therapeutic hypothermia is associated with higher late-onset infection but lower mortality. This finding may be explained by residual confounding. Research should address the risks and benefits of parenteral nutrition in this population.

What is already known on this topic?

- There is little evidence to inform nutritional practice during and after therapeutic hypothermia for babies with hypoxic ischaemic encephalopathy.
- Parenteral nutrition is commonly administered to term and near-term babies during therapeutic hypothermia.
- A randomised trial in paediatric critical care found delayed provision of parenteral nutrition beyond 7 days superior to early parenteral nutrition in term babies.

What this study adds?

- Approximately one in four babies in the UK receive parenteral nutrition during therapeutic hypothermia and this proportion is increasing.
- Parenteral nutrition is associated with more late onset blood stream infection and also with higher survival.
- Randomised trials evaluating neurodevelopment and validated measures of infection are needed to determine the risks and benefits of parenteral nutrition in babies receiving therapeutic hypothermia.

BACKGROUND

Optimal nutrition for term and near-term babies receiving therapeutic hypothermia is uncertain. Although administration of parenteral nutrition to this population is not recommended by UK national guidance relating to therapeutic hypothermia[1] or parenteral nutrition,[2] national survey data suggest that this practice is common.[3]

Potential benefits of parenteral nutrition, rather than intravenous dextrose and electrolytes, include improved brain growth and repair with theoretical neurodevelopmental benefit. However, putative advantages must be balanced against accumulating evidence of harm, such as increased incidence of infection, from early parenteral nutrition from randomised trials of critically ill children.[4]

We aimed to identify an optimal approach to parenteral nutrition for infants receiving therapeutic hypothermia. Key outcomes such as blood-stream infection are rare in this population, consequently a randomised controlled would need to be very large. We therefore undertook an observational study using routinely recorded clinical data and applying

propensity score matching to form groups for comparison with near-identical distributions of background variables.

Our primary aim was to assess the association between parenteral nutrition administered during therapeutic hypothermia and the incidence of late-onset blood stream infection; predefined secondary outcomes were also examined.

METHODS

We undertook a retrospective cohort study using routinely recorded clinical data held in the National Neonatal Research Database (NNRD). The study was prospectively registered (ISRCTN47404296; NCT03278847) and the protocol published.[5] We applied propensity score methodology to form matched subgroups of infants with similar background characteristics that either received parenteral nutrition during therapeutic hypothermia or did not. We compared the rates of late-onset infection and other outcomes between these two matched groups.

The data source was the NNRD,[6] which holds data from infants admitted to National Health Service (NHS) neonatal units in England, Scotland and Wales (approximately 90 000 infants annually). In the UK, therapeutic hypothermia is not provided outside of NHS neonatal units. Data are extracted from neonatal electronic health records completed by health professionals during routine clinical care. A defined data extract, the Neonatal Dataset,[7] of approximately 450 data items, is transmitted quarterly, cleaned, and duplicates and queries about discrepant and implausible data are fed back to health professionals and rectified. Completeness and accuracy of NNRD data have been validated.[6] A patient-level dataset was extracted from the NNRD for the purposes of this analysis. Data linkage was not performed.

The a priori sample size was 1500 pairs of babies, estimated to detect (two-sided significance 5%, power 90%) a difference of 2% in late-onset infection assuming a 3% rate of infection in the parenteral nutrition group.

We extracted data from infants born 1/1/2008 to 31/12/2017 and admitted to neonatal units contributing to the NNRD in England, Scotland and Wales. All NHS neonatal units have contributed data to the NNRD since 2012 in England and Wales, and since 2015 in Scotland. Data were extracted for the duration of an infant's neonatal stay.

Infants were included if they had a recorded gestational age of $\geq 36^{+0}$ weeks$^{+\text{days}}$ at birth and were recorded as having received therapeutic hypothermia for 3 days or died during this 3-day period after receiving therapeutic hypothermia. Babies who had missing data for receipt of therapeutic hypothermia on the second day of hypothermia but who were recorded as receiving therapeutic hypothermia on both the preceding and following day and who did not die during cooling, had therapeutic hypothermia data for the second day imputed. No other data imputation was performed. Receipt of parenteral nutrition was defined as receiving parenteral nutrition of any type, by any route, for at least one day during therapeutic hypothermia. Codes used to define analysis groups are available in online supplemental table 1.

The primary outcome was late-onset blood stream infection using the National Neonatal Audit Programme case definition.[8] Secondary outcomes included suspected infection (five consecutive days of antibiotic treatment starting after day 3), severe necrotising enterocolitis (NEC) using the UK Neonatal Collaborative NEC study[9] definition, pragmatically defined NEC (a recorded diagnosis of NEC and five or more consecutive days of antibiotics while nil by mouth), survival to discharge, length of neonatal unit stay, hypoglycaemia (diagnosed during neonatal unit stay), breast feeding at discharge, onset of breast feeding, day of first maternal milk, central line days, duration of parenteral nutrition, and weight for age SD score (SDS) at neonatal discharge. Details are given in online supplemental table 3.

To address potential confounders (eg, infants with multisystem disease may be more likely to not receive parenteral nutrition and to have poorer outcomes), we used propensity matching to form two subgroups of infants with similar background characteristics, including clinical condition and treatment when therapeutic hypothermia was started. The variables in the propensity model included: infant sex; maternal factors (age, ethnicity, deprivation decile); pregnancy factors (smoking status, multiplicity, duration of rupture of membranes, fever, suspected chorioamnionitis, hypothyroidism, diabetes, parity); infant factors (mode of delivery, gestational age, birth weight SDS, 1 min and 5 min Apgar score, chest compressions during resuscitation, emergency resuscitation drugs, intubated at resuscitation, umbilical cord gas values, time to first spontaneous breath); condition on admission prior to therapeutic hypothermia (blood pressure, glucose, heart rate, oxygen saturation, temperature); culture positive early-onset infection; treatment on day one (inotropes, mechanical ventilation, inhaled nitric oxide) and organisational factors (postnatal transfer within 24 hours, neonatal network of birth); details are given in online supplemental table 2. Neonatal services in the UK are organised in managed neonatal networks that comprise a small number of tertiary units in each network and a larger number of non-tertiary units that generally transfer infants to tertiary centres for ongoing therapeutic hypothermia.

Analyses applied the potential outcomes framework and propensity score methodology.[10] We performed 1:1 matching of babies that received and did not receive parenteral nutrition during therapeutic hypothermia. For each infant, the propensity of the exposure (parenteral nutrition or no parenteral nutrition) was estimated by logistic regression that included all background variables as covariates, and a selection of their interactions. Matched pairs were formed within these groups. Pairs were first matched using birth year (four 2-year bands) and arterial umbilical cord pH (three bands: >7.0, 6.9–7.0, <6.9), 12 groups in total. Matched pairs were then formed within propensity score deciles defined separately for each background group; details are given in online supplemental material.

Outcomes in the resulting two matched subgroups were then compared and relative risks of outcomes derived. The SE of the estimate of the treatment effect was obtained by combining the within and between-replication SEs.[11] All p values are two-sided. Analyses were performed using SAS V.9.4 (SAS Institute, Cary, North Carolina, USA) and R.[12] To prevent potential identification of individuals where low numbers of events occurred, low counts are presented as <5.

Pre-planned sensitivity analyses:

1. Restricted to babies born 2012–2017 in England and Wales to determine whether less complete data prior to 2012 introduces bias.
2. Restricted to infants where all parenteral nutrition data were actively recorded, excluding infants missing nutrition data during the first 4 days.

A third, posthoc, sensitivity analysis was undertaken with the agreement of the Study Steering Committee to examine the impact of enteral nutritional practice on day one: enteral feeding on the first day of life was added as a background variable to the propensity model.

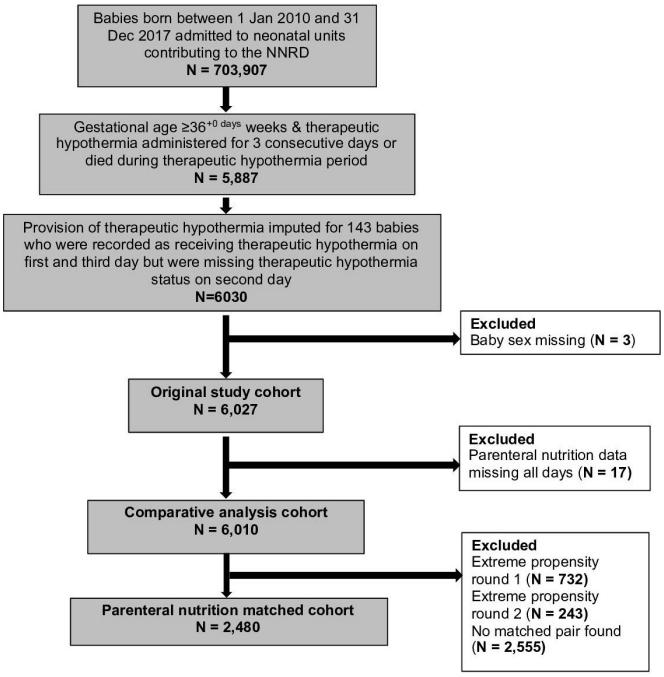

Figure 1 Participant flow through the study for the primary analysis. N, number; NNRD, National Neonatal Research Database.

Prior to comparative analyses, it became clear that the proportion of missing data was high in 2008 and 2009; analysis was therefore restricted to babies born between 2010 to 2017.

A multiprofessional investigator group which included a parent of a baby that received therapeutic hypothermia and a parent representative designed and oversaw the study. Study outcomes reflected those prioritised as important by parents, patients and professionals.[13] The study was overseen by an independent Study Steering Committee who approved all deviations from the original protocol.

RESULTS

Between 1/1/2010 and 31/12/2017, 703 907 babies were admitted to NHS neonatal units in England, Scotland or Wales; 6030 were ≥36 weeks gestational age and treated with therapeutic hypothermia for 3 days or died during treatment. Of these, 1475 babies (24.5%) received parenteral nutrition during therapeutic hypothermia, and this proportion increased slightly over time (linear slope=0.007, p=0.003).

Thirty babies (30/6030, 0.5%) had a pure growth of a recognised pathogen in a blood culture after day 3; 1559 babies (25.5%) had late onset infection when defined as five consecutive days of antibiotics. Survival to discharge was high (90.3%, 5444 babies) and median length of neonatal stay was 11 days (IQR 8–16). Almost all babies (5640, 93.6%) had a central line and the median duration was 5 days (IQR 3–6); 1208 babies (20.0%) had hypoglycaemia recorded at any point during their neonatal stay.

Propensity matching was used to form two subgroups of 1240 infants with similar background characteristics for comparative analyses (figure 1). Good balance was achieved for all recorded background variables (table 1). In matched analyses, the incidence of blood culture confirmed that late onset infection was very low in both groups but higher in babies that received parenteral nutrition compared with babies that did not (11 (0.9%) vs <5 (0.3%); rate difference 0.6% (0.1 to 1.2), p=0.03).

Table 1 Background variables by group: unmatched and matched cohorts

	Unmatched cohort		Matched cohort	
Variable	No parenteral nutrition	Parenteral nutrition	No parenteral nutrition	Parenteral nutrition
N	4535	1475	1240	1240
Male				
N (%)	2507 (55.3)	810 (54.9)	652 (52.6)	664 (53.5)
Gestational age at birth (weeks)				
Mean (SD)	39.4 (1.6)	39.4 (1.6)	39.4 (1.6)	39.4 (1.6)
Birth weight (g)				
Mean (SD)	3385 (621)	3321 (631)	3330 (609)	3328 (628)
Caesarean delivery				
N (%)	2066 (47.7)	667 (47.1)	545 (45.9)	549 (46.1)
Maternal age				
Median (IQR)	30 (26–35)	31 (26–34)	30 (26–34)	31 (26–34)
Maternal suspected chorioamnionitis				
N (%)	479 (12.8)	175 (14.5)	147 (14.5)	150 (14.6)
Smoking in pregnancy				
Yes N (%)	520 (13.3)	211 (16.9)	175 (16.6)	176 (16.8)
Missing N (%)	620 (15.8)	227 (18.2)	187 (17.8)	189 (18.0)
Ethnicity (maternal)				
White, %	65.7	61.4	80.8	79.9
Asian and Mixed, %	11.2	6.8	7.9	7.5
Black and Mixed, %	7.5	4.3	4.3	5.0
Other and missing, %	15.5	27.5	6.9	7.6
Maternal diabetes				
N (%)	191 (4.2)	65 (4.4)	49 (4.0)	53 (4.3)
Maternal deprivation score				
In deciles 1 or 2, %	27.9	22.3	23.9	21.7
Primiparous				
N (%)	2425 (53.5)	778 (52.7)	669 (54.0)	671 (54.1)
Umbilical cord arterial pH				
>7.0, N (%)	1439 (44.4)	451 (44.0)	396 (45.3)	396 (45.3)
6.9–7.0, N (%)	756 (23.3)	248 (24.2)	198 (22.7)	198 (22.7)
<6.9, N (%)	1049 (32.3)	326 (31.8)	280 (32.0)	280 (32.0)
Missing N (%)	1291 (28.5)	450 (30.5)	366 (29.5)	366 (29.5)
Apgar 5 min				
0–1 (%)	730 (16.1)	218 (14.8)	188 (15.1)	182 (14.7)
2–4 (%)	1704 (37.6)	563 (38.2)	450 (36.2)	470 (37.9)
5–7 (%)	1372 (30.3)	433 (29.4)	389 (31.3)	362 (29.2)
8–10 (%)	374 (8.2)	130 (8.8)	107 (8.6)	116 (9.4)
Missing (%)	355 (7.8)	131 (8.9)	107 (8.6)	109 (8.8)
Received chest compressions at resuscitation				
N (%)	1705 (37.6)	523 (35.5)	431 (34.8)	427 (34.4)
Received resuscitation drugs				
N (%)	719 (15.9)	206 (14.0)	176 (14.2)	172 (13.9)
Intubated at resuscitation				
N (%)	2925 (64.5)	935 (63.4)	784 (63.2)	783 (63.1)
Mechanical ventilation on day of admission				
N (%)	3508 (80.2)	1122 (79.5)	951 (79.6)	956 (80.2)
Treatment with inotropes on day of admission				
N (%)	1126 (26.0)	335 (23.9)	295 (25.0)	287 (24.2)

N, number.

Pragmatically defined late onset infection was similar in babies who did (323, 26.1%) and did not receive parenteral nutrition (313, 25.3%) (rate difference 0.8% (−2.1 to 3.6), p=0.61) (table 2).

Survival to discharge was higher in babies that received parenteral nutrition (1154, 93.1%) compared with those that did not (1116, 90.0%) (rate difference 3.1% (1.5 to 4.7), p<0.001). The incidence of pragmatically defined necrotising enterocolitis was

Table 2 Outcomes by feeding group: unmatched and matched cohorts

	Unmatched cohort		Matched cohort	
Variable	**No parenteral nutrition**	**Parenteral nutrition**	**No parenteral nutrition**	**Parenteral nutrition**
N	3975	1872	1240	1240
Blood culture positive late onset infection				
N (%)	16 (0.4)	14 (0.9)	<5 (<0.5)	11 (0.9)
Late onset infection (pragmatic definition)				
N (%)	1175 (25.9)	383 (26.0)	313 (25.3)	323 (26.1)
Severe NEC (confirmed at surgery, postmortem or recorded on death certificate)				
N	6 (0.1)	<5 (<0.5)	7 (0.6)	<5 (<0.5)
NEC (pragmatic definition)				
N (%)	52 (1.1)	16 (1.1)	17 (1.4)	13 (1.1)
Survival at discharge				
N (%)	4056 (89.5)	1374 (93.2)	1116 (90.0)	1154 (93.1)
Hypoglycaemia				
N (%)	946 (20.9)	258 (17.5)	235 (18.9)	212 (17.1)
Onset of breast feeding (days)				
Median (IQR)	7 (6–9)	7 (6–9)	7 (6–9)	7 (6–9)
Breast feeding at discharge				
N (%)	2110 (46.5)	670 (45.4)	582 (47.0)	575 (46.4)
Time to first mother's milk (days)				
Median (IQR)	5 (4–6)	5 (3–5)	5 (4–6)	5 (3–5)
Days with a central venous line in situ				
Median (IQR)	5 (3, 6)	5 (4, 7)	5 (3, 6)	5 (4, 7)
Weight Z-score at discharge				
Median (IQR)	−0.6 (−1.4 to 0.2)	−0.7 (−1.4 to 0.1)	−0.7 (−1.4 to 0.1)	−0.6 (−1.4 to 0.2)
Length of stay (days)				
Median (IQR)	11 (8–17)	10 (7–13)	11 (8–16)	11 (8–16)

N, number; NEC, necrotising enterocolitis.

low and similar in babies that received parenteral nutrition (13 cases, 1.1%) and those that did not (17 cases, 1.4%) (rate difference (95% CI) −0.3% (−1.0 to 0.4), p=0.39). The duration in time that a baby had a central line in situ was higher in babies that received parenteral nutrition (6.0 days) versus those that did not (5.1) (difference 0.9 days (0.5 to 1.2), p<0.001) (table 3). Placement of a central venous line was common in both groups (92.3% of babies that did not receive parenteral nutrition and 97.9 of those that did). Measures of breast feeding, incidence of recorded hypoglycaemia, weight for gestation SDS at neonatal unit discharge and length of neonatal unit stay were all similar between babies that received parenteral nutrition and those that did not (tables 2 and 3). These findings were robust to sensitivity analyses (online supplemental table 4).

DISCUSSION

One in four babies that receive therapeutic hypothermia in the UK receive concurrent parenteral nutrition. After extensive matching across a comprehensive number of background variables, we find that culture confirmed blood stream infection and survival were both higher in babies that received parenteral nutrition. Other short-term morbidities and measures of breast feeding were not materially different between babies that did and did not receive parenteral nutrition. The propensity score methodology used in this study can only address imbalances in observed confounders, so residual confounding by indication cannot be excluded. Optimal parenteral nutrition for babies receiving therapeutic hypothermia is not known and randomised evaluations comparing early versus delayed parenteral nutrition, able to assess short-term and long-term outcomes, are required.

Despite widespread use, there are few data describing parenteral nutrition in babies during therapeutic hypothermia. Case studies report electrolyte disturbances in such infants receiving parenteral nutrition[14 15] but we know of no published comparative data in this population. Randomised trials have compared early and delayed parenteral nutrition in critically ill adults[16] and children,[4] demonstrating beneficial outcomes with delayed commencement of parenteral nutrition. The latter, paediatric intensive care based, PEPaNIC trial reports data from 209 babies randomised to early (<24 hours) or late (>7 days) commencement of parenteral nutrition in a preplanned secondary analysis[17]: neonates with surgical or cardiac conditions that did not receive therapeutic hypothermia. This subgroup analysis found higher rates of infection in babies recruited below 1 week of age randomised to early parenteral nutrition, consistent with our results. However, and in contrast to our data, the PEPaNIC trial found no difference in mortality between early and delayed parenteral nutrition groups, although the sample size was low for such outcomes. The PEPaNIC trial also found a higher incidence of hypoglycaemia in neonates randomised to receive later parenteral nutrition which was not replicated in our study; this may be explained by diagnoses in the NNRD being linked with an 'episode' of care on a neonatal unit and not attributed to a specific day. Consequently, the temporal relationship between hypoglycaemia and parenteral nutrition cannot be directly examined. Evidence to support benefits of parenteral nutrition in this population is also limited. A putative benefit is improved brain growth, repair and consequent neurodevelopment; while this has not been directly evaluated, supplemental nutrition following brain injury shows promise.[18] Considering the limited

Table 3 Analysis of outcome variables for babies received vs did not receive parenteral nutrition

Variable	Intervention		Difference (95% CI)	OR estimate (95% CI)	P value
	No parenteral nutrition (95% CI)	Parenteral nutrition (95% CI)			
N	1240	1240			
Blood culture positive late onset infection, %	0.3 (0.1 to 0.5)	0.9 (0.4 to 1.4)	0.6 (0.1 to 1.2)	3.04 (0.95 to 9.76)	0.03*
Late onset infection (pragmatic definition), %	25.3 (23.6 to 27.1)	26.1 (23.8 to 28.3)	0.8 (–2.1 to 3.6)	1.04 (0.87 to 1.25)	0.61
NEC (pragmatic definition), %	1.4 (0.9 to 1.9)	1.1 (0.6 to 1.6)	–0.3 (–1.0 to 0.4)	0.77 (0.38 to 1.58)	0.39
Hypoglycaemia, %	19.0 (17.5 to 20.6)	17.0 (15.1 to 18.9)	–2.1 (–4.5 to 0.4)	0.87 (0.71 to 1.07)	0.10
Survival at discharge, %	90.0 (88.8 to 91.2)	93.1 (91.8 to 94.4)	3.1 (1.5 to 4.7)	1.50 (1.17 to 2.01)	<0.001
Breast feeding at discharge, %	47.0 (45.1 to 48.9)	46.4 (43.9 to 48.9)	–0.6 (–3.8 to 2.6)	0.98 (0.83 to 1.14)	0.71
Length of stay, days	14.1 (13.6 to 14.7)	15.0 (14.1 to 15.8)	0.8 (–0.2 to 1.8)		0.12
First suckling at breast, days	8.4 (8.0 to 8.7)	8.6 (8.0 to 9.1)	0.2 (–0.5 to 0.8)	–	0.56
First maternal milk, days	4.9 (4.8 to 4.9)	4.6 (4.5 to 4.8)	–0.2 (–0.4 to 0.1)	–	0.01
Duration of CV line, days	5.1 (5.0 5.3)	6.0 (5.7 to 6.3)	0.9 (0.5 to 1.2)	–	<0.001
Weight Z-score	–0.66 (–0.71 to 0.61)	–0.65 (–0.71 to –0.58)	0.02 (–0.07 to 0.10)	–	0.68

Results averaged over the 25 replications of the matching procedure.
CV, central venous; N, number; NEC, necrotising enterocolitis; NNAP, National Neonatal Audit Programme.

available neonatal data, the risks and benefits of parenteral nutrition in babies undergoing therapeutic hypothermia are clinically potentially important but highly uncertain.

This study was not a randomised evaluation of parenteral nutrition; however, we applied multiple approaches to limit bias: using multiple background data items, we formed matched groups for comparison. We followed a detailed, preregistered protocol that specified exposures, background factors and outcomes and the data items used to define them as well as the matching process.[5] To examine whether data completeness influenced results, we undertook sensitivity analyses which led to similar findings to the main analysis. In addition, the use of routinely recorded data captured during clinical care reduced the risk of ascertainment bias, as data collection occurred well in advance of study conception. Use of such data facilitated inclusion of a large number of infants—the study sample was several times larger than all previous randomised trials of therapeutic hypothermia combined.

In this non-randomised study, we used propensity scores to form matched groups for analysis; the main limitation of this approach is that it can account only for measured confounders. Although a wide range of background and day-one data items were used to undertake matching and acceptable balance was obtained, we cannot exclude residual confounding or confounding from differences in unmeasured factors. This is likely to overestimate the benefit of parenteral nutrition: the 'sickness' of a baby may be more evident to clinicians than can be discerned from data held in the NNRD, and sicker babies may be both less likely to be commenced on parenteral nutrition and to survive. As with any study that uses routinely recorded data, completeness and accuracy are variable; this is particularly relevant to culture positive blood stream infection which has been found to be under-reported previously.[8] However, data that form the NNRD are primarily entered as part of a baby's clinical care, are used for purposes including national audit, funding and staffing and have been validated against independent clinical trial data.[6] Results should be interpreted cautiously in light of these limitations.

These data and other published evidence suggest that parenteral nutrition may be associated with both harms and benefits in term and near-term babies who receive therapeutic hypothermia. Randomised controlled trials are required to elucidate whether the increasing use of parenteral nutrition in this group is beneficial. The low incidence of culture positive infection and low mortality confirm that a trial adequately powered to address such outcomes is unlikely to be feasible. Therefore, a future trial should focus on other validated measures of late-onset infection and neurodevelopmental outcomes with higher background rates that would make a randomised trial powered to detect a meaningful difference in such outcomes practicable.

CONCLUSION

The use of parenteral nutrition is relatively common in babies who are undergoing therapeutic hypothermia and appears to be increasing. Optimal parenteral nutritional support for babies receiving therapeutic hypothermia could not be established in this large observational study.

Twitter Chris Gale @DrCGale, Cheryl Battersby @DrCBattersby and Shalini Ojha @shaliniojha7

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Contributors CG conceived, designed and planned the study. He contributed to planning data extraction and analysis, interpretation of results, wrote first and final draft of the publication. DJ contributed to planning data extraction, analysis and interpretation the results, wrote first draft of the study publication, contributed to and approved the final publication. NL conceived, designed and planned the study. He led the analysis and undertook matching. He contributed to the interpretation of the results. He contributed to and approved the final report. He contributed to and approved the final publication. CB conceived, designed and planned the study. She contributed to planning data extraction and analysis, undertook data extraction, interpreted the results, contributed to and approved the final publication. KO contributed to the planning of the study and led data extraction. She contributed to and approved the final publication. SO conceived, designed and planned the study. She contributed to the analysis and interpretation of the results. She contributed to and approved the final publication. JD conceived, designed and planned the study. He contributed to the analysis and interpretation of the results. He contributed to and approved the final publication.

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Patient consent for publication Not required.

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ORCID iDs
Chris Gale http://orcid.org/0000-0003-0707-876X
Shalini Ojha http://orcid.org/0000-0001-5668-4227

REFERENCES

1 BAPM. *Therapeutic hypothermia for neonatal encephalopathy: a BAPM framework for practice*. In: BAPM, 2020.
2 NICE. *Neonatal parenteral nutrition (NG154)*. National Institute for Health and Care Excellence, 2020.
3 Hazeldine B, Thyagarajan B, Grant M, *et al*. Survey of nutritional practices during therapeutic hypothermia for hypoxic-ischaemic encephalopathy. *BMJ Paediatr Open* 2017;1:e000022.
4 Fivez T, Kerklaan D, Mesotten D, *et al*. Early versus late parenteral nutrition in critically ill children. *N Engl J Med* 2016;374:1111–22.
5 Battersby C, Longford N, Patel M, *et al*. Study protocol: optimising newborn nutrition during and after neonatal therapeutic hypothermia in the United Kingdom: observational study of routinely collected data using propensity matching. *BMJ Open* 2018;8:e026739.
6 Battersby C, Statnikov Y, Santhakumaran S, *et al*. The United Kingdom national neonatal research database: a validation study. *PLoS One* 2018;13:e0201815.
7 National Digital. National neonatal data set. Available: http://www.datadictionary.nhs.uk/web_site_content/navigation/national_neonatal_data_sets_menu.asp
8 RCPCH. *National neonatal audit programme (NNAP) 2018 annual report on 2017 data*. London: Royal College of Paediatrics and Child Health (RCPCH), 2018.
9 Battersby C, Longford N, Mandalia S, *et al*. Incidence and enteral feed antecedents of severe neonatal necrotising enterocolitis across neonatal networks in England, 2012–13: a whole-population surveillance study. *Lancet Gastroenterol Hepatol* 2017;2:43–51.
10 Imbens GW, Rubin DB. *Causal inference for statistics, social, and biomedical sciences. An introduction*. New York: Cambridge University Press, 2015.
11 Rubin DB. *Multiple imputation for nonresponse in surveys*. 2nd edn. New York: Wiley, 2002.
12 R Foundation for Statistical Computing. *R: a language and environment for statistical computing*, 2019.
13 Webbe J, Duffy J, Afonso E. *Core outcomes in neonatology: development of a neonatal core outcome set using an international Delphi consensus process*. Baltimore: Pediatric Academic Societies, 2019.
14 Tocco NM, Hodge AE, Jones AA, *et al*. Neonatal therapeutic hypothermia-associated hypomagnesemia during parenteral nutrition therapy. *Nutr Clin Pract* 2014;29:246–8.
15 Ting JY, Manhas D, Innis SM, *et al*. Elevated triglycerides levels in two infants with hypoxic-ischemic encephalopathy undergoing therapeutic hypothermia and receiving parenteral nutrition. *JPEN J Parenter Enteral Nutr* 2014;38:758–60.
16 Casaer MP, Mesotten D, Hermans G, *et al*. Early versus late parenteral nutrition in critically ill adults. *N Engl J Med* 2011;365:506–17.
17 van Puffelen E, Vanhorebeek I, Joosten KFM, *et al*. Early versus late parenteral nutrition in critically ill, term neonates: a preplanned secondary subgroup analysis of the PEPaNIC multicentre, randomised controlled trial. *Lancet Child Adolesc Health* 2018;2:505–15.
18 Andrew MJ, Parr JR, Montague-Johnson C, *et al*. Nutritional intervention and neurodevelopmental outcome in infants with suspected cerebral palsy: the dolphin infant double-blind randomized controlled trial. *Dev Med Child Neurol* 2018;60:906–13.

Supplementary material

Administration of parenteral nutrition during therapeutic hypothermia: a population level observational study using routinely collected data held in the National Neonatal Research Database

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Study Steering Committee members

David Odd (independent Chair), Senior Clinical Lecturer in Neonatal Medicine and Consultant Neonatologist, University of Bristol and North Bristol NHS Trust

Louise Linsell (independent), Senior Medical Statistician, Clinical Trials Unit, National Perinatal Epidemiology Unit (NPEU), University of Oxford

James Carpenter (independent), Professor of Medical Statistics, London School of Hygiene and Tropical Medicine

Carol Rhodes (independent), Mother of child who received therapeutic hypothermia as a baby

Chris Gale (non-independent), Reader in Neonatal Medicine and Consultant Neonatologist, Imperial College London and Chelsea and Westminster NHS Foundation Trust

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Supplemental table 1: Extraction procedures and definitions of enteral feeding exposure variable

Variable	Data items from NNRD	Definition
Parenteral Nutrition	PARENTERAL NUTRITION GROUP DEFINED AS Any of the following items entered in the *Daily Care Fluids and Feeding* during the first 3 days • Y entry for PARENTERAL NUTRITION RECEIVED INDICATOR OR The following drug code entered in the *Daily care medication* during the first 3 days • 1010238 *Total parenteral nutrition* NO PARENTERAL NUTRITION GROUP DEFINED AS All other babies not fulfilling above criteria For sensitivity analyses also extract • *Daily Care Fluids and Feeding* INTRAVENOUS INFUSION OF GLUCOSE AND ELECTROLYTE SOLUTION RECEIVED INDICATOR = Y/N	Dichotomous (No parenteral nutrition=0; provided parenteral nutrition=1)

Supplemental table 2: Extraction procedures, definitions and classifications of background variables

Variable	Data items from NNRD	Definition(s)	Classification
Cord blood gas pH in bands	*Labour and Delivery Details* UMBILICAL CORD BLOOD pH LEVEL (ARTERIAL) *Or, if not recorded, use Labour and Delivery Details* UMBILICAL CORD BLOOD pH LEVEL (ARTERIAL)	**CordpHArt:** Tricotomised into bands: >7·0, 6·9-7·0, <6·9	Principal
Birth year	*Baby Demographics* YEAR AND MONTH OF BIRTH (BABY)	**BirthYear:** Categorised into two-year bands: 2010-2011, 2012-2013, 2014-2015, 2016-2017	Principal
Gestational age week	*Baby Demographics* GESTATION LENGTH (AT DELIVERY): Gestational weeks and days	**GAweeks:** Integers	Highly important
Birthweight	*Baby Demographics* BIRTH WEIGHT	**Bweight:** Original entries trimmed from above at 3500g and entries smaller than 1000g with a non-zero digit are multiplied by 10. Square-root transformed.	Highly important
Sex	*Baby Demographics* PERSON PHENOTYPIC SEX	**Sex:** Dichotomous (Male=0; Female=1)	Highly important
Emergency resuscitation drugs administered	*Labour and Delivery Details* NEONATAL RESUSCITATION METHOD Dichotomous: Y= code 17 (Adrenaline) OR 88 (any other drug) N= any other codes OR no code	**ResusDrugs:** Dichotomous (No=0; Yes=1)	Highly important
Instrument of delivery	*Labour and Delivery Details* DELIVERY INSTRUMENT TYPE	**InstrDeliv:** Dichotomised (No instrument used=0; Forceps or ventouse=1)	Highly important
Mode of delivery	*Labour and Delivery Details* MODE OF DELIVERY	**Delivery:** Dichotomous (Vaginal=0, Caesarean=1)	Highly important

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Supplemental table 2: Extraction procedures, definitions and classifications of background variables

Variable	Data items from NNRD	Definition(s)	Classification
	Categorical: codes=1-4 AND *Labour and Delivery Details IN LABOUR BEFORE CAESARIAN SECTION INDICATOR*=Y/N		
Maternal smoking status	*Pregnancy Details* MOTHER CURRENT SMOKER AT BOOKING INDICATOR (categorical, codes 1-6)	**SmokePreg:** Dichotomised (Not smoking=0; Smoking during pregnancy=1) **SmokePregMs:** Binary missing indicator created (Not missing=0; Missing=1)	Highly important
Maternal suspected chorioamnionitis	*Labour and Delivery Details* INTRAPARTUM ANTIBIOTICS GIVEN INDICATORS	**IntrPartAntiB:** Dichotomous (No intrapartum antibiotics given=0, Intrapartum antibiotics=1)	Highly important
Apgar score at 1 minute	*Labour and Delivery Details* APGAR SCORE (1 MINUTE) Continuous: 0-10	**APGAR1min:** Categorical (0-10) **APGAR1minMs:** Binary missing indicator created (Not missing=0; Missing=1)	Highly important
Apgar score at 5 minutes	*Labour and Delivery Details* APGAR SCORE (5 MINUTE) Continuous: 0-10	**APGAR5min:** Categorical (0-10) **APGAR5minMs:** Binary missing indicator created (Not missing=0; Missing=1)	Highly important
Umbilical cord base excess	*Labour and Delivery Details* UMBILICAL CORD BLOOD BASE EXCESS CONCENTRATION (ARTERIAL) Continuous OR if not available use *Labour and Delivery Details* UMBILICAL CORD BLOOD BASE EXCESS CONCENTRATION (VENOUS)	**CordBaseExcess:** Continuous (to 1 decimal place) **CordBaseExcessMs:** Binary missing indicator created (Not missing=0; Missing=1)	Highly important
Admission mean blood pressure	*Admission Details* MEAN ARTERIAL BLOOD PRESSURE (ON ADMISSION TO NEONATAL CRITICAL CARE) Continuous	**AdmitBP:** Continuous, square-root transformed **AdmitBP.Ms:** Binary missing indicator created (Not missing=0; Missing=1)	Highly important
Admission blood glucose	*Admission Details* BLOOD GLUCOSE CONCENTRATION (ON ADMISSION TO NEONATAL CRITICAL CARE) Continuous	**AdmitBG:** Continuous, trimmed from above at 20 **AdmitBG.MS:** Binary missing indicator created (Not missing=0; Missing=1)	Highly important
Admission oxygen saturation	*Admission Details* OXYGEN SATURATION (ON	**AdmitOS:** Continuous, trimmed to be within the range (50, 100)	Highly important

Supplemental table 2: Extraction procedures, definitions and classifications of background variables

Variable	Data items from NNRD	Definition(s)	Classification
	ADMISSION TO NEONATAL CRITICAL CARE) Continuous	**AdmitOS.Ms:** Binary missing indicator created (Not missing=0; Missing=1)	
Maternal deprivation score (from lower super output area)	*Parents Demographics* POSTCODE OF USUAL ADDRESS (LSOA)	**LSOAdec:** Categorised into deciles (1, 2,…, 10) **LSOAdecMs:** Binary missing indicator created (Not missing=0; Missing=1)	Highly important
Multiplicity	*Labour and Delivery Details* BIRTH ORDER (MATERNITY SERVICES) *Labour and Delivery Details* NUMBER OF FETUSES (NOTED DURING PREGNANCY EPISODE)	**MultipleBrt:** Dichotomised (single birth=0; multiple births=1)	Moderately important
Maternal age	*Parents Demographics* YEAR OF BIRTH (MOTHER)	**MaternalAge:** Continuous (years) trimmed to be within range 17- 45	Moderately important
Maternal duration of rupture of membranes (time in hours)	*Labour and Delivery Details* RUPTURE OF MEMBRANES DATE TIME *or* RUPTURE OF MEMBRANES YEAR AND MONTH and *NUMBER OF MINUTES (BIRTH TO EVENT)* (continuous)		*Variable not used. (Too many missing values)*
Maternal disease during pregnancy	*Labour and Delivery Details* SIGNIFICANT MATERNAL PYREXIA IN LABOUR INDICATOR (Y/N) *Pregnancy Details* MATERNITY COMPLICATING MEDICAL DIAGNOSIS TYPE Dichotomous: Y=code 16 (endocrine disorder), N=any other or no code *Pregnancy Details* MATERNITY COMPLICATING MEDICAL DIAGNOSIS TYPE Dichotomous: Y=code 08 (diabetes) OR *Pregnancy Details* MATERNITY OBSTETRIC DIAGNOSIS TYPE Dichotomous: Y=code 06 (gestational diabetes mellitus) N=any other or no code	**MaternalDis:** Dichotomised (No diagnosis=0; At least one of pyrexia in labour, hypothyroid, diabetes=1)	Moderately important

Supplemental table 2: Extraction procedures, definitions and classifications of background variables

Variable	Data items from NNRD	Definition(s)	Classification
Maternal ethnicity	*Parents Demographics* ETHNIC CATEGORY (MOTHER) (categorical) Coded as: WHITE (A - British, B - Irish, C - Any other white background); MIXED (D - White and Black Caribbean. E - White and Black African, F - White and Asian, G - Any other mixed background); ASIAN OR ASIAN BRITISH (H - Indian, J - Pakistani, K - Bangladeshi, L - Any other Asian Background); BLACK OR BLACK BRITISH (M - Caribbean, N - African, P - Any other Black background); OTHER ETHNIC GROUPS (R - Chinese, S - Any other ethnic group); UNKNOWN (Z, DTA - Not stated, 99 - Not known) This data item is based on self-reported ethnicity as recorded in maternity notes	**Ethnicity:** Categorised into four groups (White=1; Asian & Mixed=2; Black & Mixed=3; Other and not given=4)	Moderately important
Parity of mother (primiparous Y/N)	*Pregnancy Details* PREGNANCY TOTAL PREVIOUS PREGNANCIES Dichotomous: code 00=Y; code 01-29=N	**Primiparous:** Dichotomous (Not first pregnancy=0; First pregnancy=1)	Moderately important
Chest compressions administered	*Labour and Delivery Details* NEONATAL RESUSCITATION METHOD Dichotomous: Code 16=Y; any other code=N	**ChestCompr:** Dichotomous (No chest compressions applied=0; Chest compressions applied=1)	Moderately important
Intubated at resuscitation	*Labour and Delivery Details* NEONATAL RESUSCITATION METHOD Dichotomous: Code 15=Y; any other code=N	**Intubation:** Dichotomous (Not intubated=0; Intubated=1)	Moderately important
Time to first spontaneous breath	*Labour and Delivery Details* TIME BETWEEN DELIVERY AND SPONTANEOUS RESPIRATION CODE Continuous	**SpontRespTime:** Dichotomised (≤5 mins=0; >5 mins=1) **SpontRespTimeMs:** Binary missing indicator created (Not missing=0; Missing=1)	Moderately important
Admission heart rate	*Admission Details* HEART RATE (ON ADMISSION TO NEONATAL CRITICAL CARE) Continuous	**AdmitHR:** Continuous, trimmed to be within the range 80-100	Moderately important

Supplemental table 2: Extraction procedures, definitions and classifications of background variables

Variable	Data items from NNRD	Definition(s)	Classification
		AdmitHR.Ms: Binary missing indicator created (Not missing=0; Missing=1)	
Admission temperature	*Admission Details* TEMPERATURE (ON ADMISSION TO NEONATAL CRITICAL CARE) Continuous	**AdmitTempCe:** Continuous, trimmed to be within 26-40 **AdmitTempMs:** Binary missing indicator created (Not missing=0; Missing=1)	Moderately important
Positive blood or cerebrospinal fluid culture with a recognised pathogen recorded in the first 3 days	Defined from *Infection Cultures (Episodic)* recorded up to and including day 3 • Pure growth of pathogen from blood OR • Pure growth of pathogen from CSF	**Infection:** Dichotomous (0=No infection; 1=infection)	Moderately important
Treatment for low blood pressure with an intravenous inotrope (e.g. dopamine, noradrenaline)	*Daily Care Medication* on day 1 only • 500098 Dopamine • 500096 Dobutamine • 500056 Adrenaline • 500210 Noradrenaline • 500116 Hydrocortisone • 1010173 Milrinone Dichotomous: any of above=Y, none of above=N OR *Daily Care Cardiovascular* INOTROPE INFUSION RECEIVED INDICATOR Y/N	**Inotropes:** Dichotomous (Inotropes not administered=0; Inotropes administered=1)	Moderately important
Mechanical ventilation method	*Daily Care Respiratory* on day 1 only; RESPIRATORY SUPPORT MODE Dichotomous: Codes 1, 2, 3=Y; any other or no code =N	**RespiSupprt:** Dichotomous (Respiratory support not provided=0; Respiratory support provided=1)	Moderately important
Received inhaled nitric oxide (Y/N)	*Daily Care Respiratory* on day 1 only; NITRIC OXIDE GIVEN INDICATOR Dichotomous: Y/N	**NitricOxide:** Dichotomous (Nitric oxide not given=0; Nitric oxide given=1)	Moderately important
Required acute postnatal transfer, within 24 hours (Y/N)	*Admission Details* SITE CODE (OF ADMITTING NEONATAL UNIT) or ORGANISATION CODE (OF ADMITTING NEONATAL UNIT) Different from *Baby Demographics* SITE CODE (OF ACTUAL PLACE OF DELIVERY) or ORGANISATION CODE (OF ACTUAL PLACE OF DELIVERY) And	**PostNTransfer:** Dichotomous (No transfer=0; Transfer=1)	Moderately important

Supplemental table 2: Extraction procedures, definitions and classifications of background variables

Variable	Data items from NNRD	Definition(s)	Classification
	Baby Demographics EPISODE NUMBER		
Maternal occupation	*Parents Demographics (withheld)* OCCUPATION MOTHER (SNOMED CT)	**MumJob:** Dichotomous (No occupation=0; Any occupation=1)	Moderately important
Onset of labour	*Labour and Delivery Details* LABOUR OR DELIVERY ONSET METHOD CODE	**OnsetLabour:** Categorised into four groups (Not in labour=0; Spontaneous=1; Induced=2; Missing=9)	Moderately important
Time to admission	*Admission Details* CRITICAL CARE START YEAR AND MONTH and NUMBER OF MINUTES (BIRTH TO EVENT)	**AdmitTime:** log-transformed with zero recoded to zero	Moderately important
Presentation at delivery	*Labour and Delivery Details* PRESENTATION AT DELIVERY 1 - Breech 2 - Cephalic 3 - Transverse 8 - Other 9 - Unknown	**FetusAtDelivC:** Dichotomised (Cephalic=1, Not cephalic=0)	Moderately important
Blood transfusion	*Daily care blood transfusion* BLOOD TRANSFUSION PRODUCT TYPE on day 1 only	**BloodTrans:** Dichotomised (No=0; Yes=1)	Moderately important
Maternal or obstetric medical problem	*Pregnancy Details* MATERNITY OBSTETRIC DIAGNOSIS TYPE (CURRENT PREGNANCY) *Pregnancy Details MATERNITY MEDICAL DIAGNOSIS TYPE (CURRENT PREGNANCY)*	**ProblMedic:** Dichotomised (No medical problems=0; Some medical problems=1)	Moderately important

Supplemental table 3: Extraction procedures and definitions of outcome variables

Variable	Data items from NNRD	Definition
Late onset blood stream infection NNAP definition	Defined from *Infection Cultures (Episodic)* recorded after day 3 • Pure growth of pathogen from blood OR • Pure growth of pathogen from CSF OR Either a pure growth of a skin commensal or a mixed growth with ≥3 clinical signs at the time of blood sampling	Dichotomous (No infection=0, Infection=1)
Late onset infection, non-NNAP	5 consecutive days of antibiotic treatment defined as 5 consecutive days of any of the following (including in combination and changing during the 5 days) after day 3 *Daily care medication* • 1010155 Benzyl Penicillin • 1010158 Augmentin • 1010179 Flucloxicillin • 500012 Flucloxacillin • 500016 Gentamicin • 500072 *Co-amoxiclav* • 500086 Co-amoxiclav • 500084 Ciprofloxacin • 500029 Netilmicin • 500002 Amikacin • 500211 Tazocin • 500023 Metronidazole • 500040 Vancomycin • 500007 Cefotaxime • 500004 Ampicillin • 500009 Cefuroxime • 500008 Ceftazidime • 500175 Ceftriaxone • 500032 Piperacillin • 500206 *Oflacillin* • 500005 Azlocillin • 1010171 Linezolid • 1010271 *Cefalexin* • 1010139 Amoxicillin • 500070 Amoxicillin • 500128 Meropenem • 500118 Imepenem • 500145 *Imipenem* • 500069 Ambisome (Liposomal Amphotericin) • 500003 Amphotericin • 1010195 Amphotericin Liposomal	Dichotomous (No infection=0, Infection=1)
Severe NEC	Gestational age specific NEC score based on Battersby et al., JAMA Pediatrics, 2017. Data items needed: ABDOMINAL X-RAYS (EPISODIC) • CONDITION SEEN IN ABDOMEN DURING X-RAY (NNRD field ID: XRayAppearances) • ABDOMINAL X-RAY PERFORMED REASON (NNRD field ID: ClinicalFindings) • TRANSFERRED FROM NEONATAL INTENSIVE CARE UNIT FOR NECROTISING ENTEROCOLITIS MANAGEMENT	Dichotomous (No severe NEC=0, Severe NEC=1)

Supplemental table 3: Extraction procedures and definitions of outcome variables

Variable	Data items from NNRD	Definition
	INDICATOR (NNRD field ID: TransferredForFurtheManagement) • LAPAROTOMY FOR NECROTISING ENTEROCOLITIS INDICATION CODE • NEC CONFIRMED BY VISUAL INSPECTION DURING LAPAROTOMY (INDICATOR)HISTOLOGY CONFIRMED NECROTISING ENTEROCOLITIS FOLLOWING LAPAROTOMY INDICATOR • POSTMORTEM CONFIRMED NEC • CAUSE OF DEATH Only available following introduction of ABDOMINAL X-RAY (EPISODIC) field • Cases identified using these data items were individually confirmed with clinicians.	
Necrotising enterocolitis (non-UKNC definition)	The following entered in the *Daily Care Gastrointestinal* on any one day during stay in a neonatal unit • Any entry (1 or 2) for TREATMENT TYPE FOR NECROTISING ENTEROCOLITIS OR the following diagnostic codes • 1010683 *Necrotising enterocolitis – suspected* • 10708 *Necrotising enterocolitis – Perforated* • 15809 *Necrotizing enterocolitis* AND 5 or more days nil by mouth defined by the *Daily Care Fluids and Feeding* for a continuous period of 5 days • No under ENTERAL FEED TYPE GIVEN • No entry under FORMULA MILK OR MILK FORTIFIER TYPE • No value OR 0 for TOTAL VOLUME OF MILK RECEIVED • No entry under ENTERAL FEEDING METHOD WHILE ALSO RECEIVING 5 or more days of antibiotics over the same 5 days as the baby was nil by mouth, defined as 5 consecutive days of any of the following *Daily care medication* • 1010155 Benzyl Penicillin • 1010158 Augmentin • 1010179 Flucloxicillin • 500012 Flucloxacillin • 500016 Gentamicin • 500072 *Co-amoxiclav* • 500086 Co-amoxiclav • 500084 Ciprofloxacin • 500029 Netilmicin • 500002 Amikacin • 500211 Tazocin • 500023 Metronidazole • 500040 Vancomycin • 500007 Cefotaxime • 500004 Ampicillin	Dichotomous (No NEC=0, NEC=1)

Supplemental table 3: Extraction procedures and definitions of outcome variables

Variable	Data items from NNRD	Definition
	• 500009 Cefuroxime • 500008 Ceftazidime • 500175 Ceftriaxone • 500032 Piperacillin • 500206 *Oflacillin* • 500005 Azlocillin • 1010171 Linezolid • 1010271 *Cefalexin* • 1010139 Amoxicillin • 500070 Amoxicillin • 500128 Meropenem • 500118 Imepenem • 500145 *Imipenem* • 500069 Ambisome (Liposomal Amphotericin) • 500003 Amphotericin • 1010195 Amphotericin Liposomal	
Survival to discharge	Defined from the *Discharge Details* from final neonatal unit stay • DISCHARGE DESTINATION FROM NEONATAL CRITICAL CARE = 1, 2, 4, 5, 6 (NOT code 3, *Died*)	Dichotomous (Died during neonatal stay=0, Survived until discharge =1)
Length of neonatal unit stay	Defined as the total number of days a baby received neonatal care (any level of care) from *Daily Care General Information* - LOCATIONS OF HIGHEST LEVEL OF CARE	Continuous, integers
Hypoglycaemia	Defined as any of the following *diagnostic codes* recorded at any time during an babies neonatal units stay: • 15771 Iatrogenic neonatal hypoglycaemia • 15773 Neonatal hypoglycaemia	Dichotomous (No hypoglycaemia=0, Hypoglycaemia =1)
Breastfeeding at discharge	Defined from final day of neonatal care entry in *Daily Care Fluids and Feeding* of • ENTERAL FEED TYPE GIVEN = code 1 (Breastfeeding) OR • ENTERAL FEEDING METHOD = code 1 (breast) Where final day is not entered, penultimate day will be used	Dichotomous (Not suckling at the breast at discharge=0, Suckling at the breast at discharge=1)
Onset of breastfeeding	Number of days until first entry in *Daily Care Fluids and Feeding* of • ENTERAL FEED TYPE GIVEN = code 1 (Breastfeeding) OR • ENTERAL FEEDING METHOD = code 1 (breast)	Continuous, integers
Time to first maternal breast milk feed	First day on which a baby is recorded to be receiving maternal breast milk by any route (including suckling at the breast, by bottle or nasogastric tube) defined as *Daily Care Fluids and Feeding* of • ENTERAL FEED TYPE GIVEN = code 1 (Breastfeeding); 2 (Mothers fresh expressed breast milk); 3 (Mothers frozen expressed breast milk); 4 (Donor expressed breast milk) OR	Continuous, integers

Supplemental table 3: Extraction procedures and definitions of outcome variables

Variable	Data items from NNRD	Definition
	• ENTERAL FEEDING METHOD = code 1 (breast)	
Number of days a baby has a central venous line in situ	Defined as the number of days that has a baby has: • *Daily Care Fluids and Feeding* VASCULAR LINE TYPE IN SITU = code 3 (Umbilical venous line); 4 (Percutaneous central venous line ('long line'); 5 (Surgically inserted central venous line)	Continuous, integers
Weight SDS at discharge	Defined as the following data item on the final day of neonatal care: • *Daily Care General Information* PERSON WEIGHT IN GRAMS If final day is not entered, the penultimate day is used	Continuous

Statistical methods: Propensity modelling

We fitted a propensity model in which the observed intervention group as the outcome is related to the background variables. The outcome variable in propensity analysis is binary, so logistic regression is applied. Since we had many background (confounding) variables, a model had to be selected from multiple candidate models. We followed the step-wise approach proposed by Imbens and Rubin[1]. The background variables classified as being *highly important* were included in the model *a priori*. Models were then fitted with each of the remaining background variables added individually. The model with the largest value of the chi-squared statistic (with one degree of freedom) was adopted, if the test statistic exceeded 1·0. This procedure constitutes one cycle. In the next and following cycles, all the remaining background variables were tested similarly and the one with the largest value of the chi-squared statistic was retained. The cycles were stopped when none of the chi-squared statistics for including a covariate exceeded 1·0 and the variables included in the model at this point are referred to as the main effects.

Next interactions were selected for the propensity model. The main effects were sorted in descending order of their absolute t-ratios ($|estimate/st.error|$). For each variable A we formed a list of variables B for which the interaction $A \times B$ was an appropriate candidate for inclusion. For example, no two categories of a discrete variable could appear in an interaction. A continuous variable could be interacted with itself (the result is the quadratic transformation of the variable), but a binary variable could not. Similarly, a variable could not be interacted with its missing value indicator.

Starting with the first covariate we fitted the models with one interaction of this covariate added and selected up to two of the interactions that have the largest values of the chi-squared statistic for inclusion, subject to the condition that they exceeded 2.71 (the 10th percentile of the chi-squared distribution with 1 degree of freedom). When an interaction $A \times B$ was adopted (added to the model), the interaction $B \times A$ was removed from the list of candidate interactions, to avoid singularity in the model search that followed. After the interactions of the first covariate, the interactions of the second and successive covariates were tested and the model was expanded by the interactions found most important, subject to the constraint of including at most two interactions in each cycle.

The concluding model yielded the fitted propensities – the estimated probabilities of being assigned to the groups receiving enteral feeds, given each baby's background profile. Thus, each baby was associated with a (fitted) propensity. The set of babies in the analysis was then reduced by excluding babies with extreme propensities; first, by reducing to the subjects in the overlap of intervention and control group. That is, let the propensities in the two groups be in the respective ranges (m_1, M_1) and (m_2, M_2). Then all subjects with propensities smaller than $m = \max(m_1, m_2)$ and greater than $M = \min(M_1, M_2)$ were excluded. Another criterion, described in Imbens and Rubin[1], was applied to reduce the sampling variance of the average treatment effect to be evaluated. It yields a positive constant $\gamma < 1$. Subjects with propensities outside the range $(\gamma, 1-\gamma)$ were discarded from the analysis. Such reduction of the dataset by discarding subjects with extreme propensities is referred to as trimming.

Next, the entire modelling exercise, with selection of the main effects (added to the covariates selected a priori) and selection of the interactions was repeated on the reduced (trimmed) dataset. This was followed by discarding subjects with extreme propensities (fitted by the revised model). Trimming was applied after each stage of model selection.

The variables in each final propensity model have no interpretation for inference. The sole purpose of the propensity model is to facilitate a good balance of all the background variables in matched groups.

Statistical methods: Matching on propensity scores

To form matched subgroups, we first formed background groups based on unique combinations of the two principal background variables. Four birth year groups (as birth year is grouped according to two-year bands) crossed with three cord blood pH groups generate 12 background groups. We then defined propensity groups within each background group by recoding the propensities to a set of (propensity) groups separated by cutpoints. An established method splits the propensities into K groups of approximately equal size. We use $K = 10$ to form propensity score deciles. Within each background group, a baby who received parenteral nutrition was paired to a randomly drawn baby that did not receive parenteral nutrition who fell within the same propensity group. After the matching process was complete, the matched pairs of babies were reconstituted as the intervention group (received parenteral nutrition) and control group (no parenteral nutrition) and termed the *matched cohort*. Since this matching procedure involves some randomness, it was replicated 25 times to

produce 25 matched cohorts. Every subsequent analysis is conducted separately for each matched cohort and the (replicate) results are averaged to reduce the impact of the uncertainty involved in matching.

Statistical methods: Assessment of the quality of the match

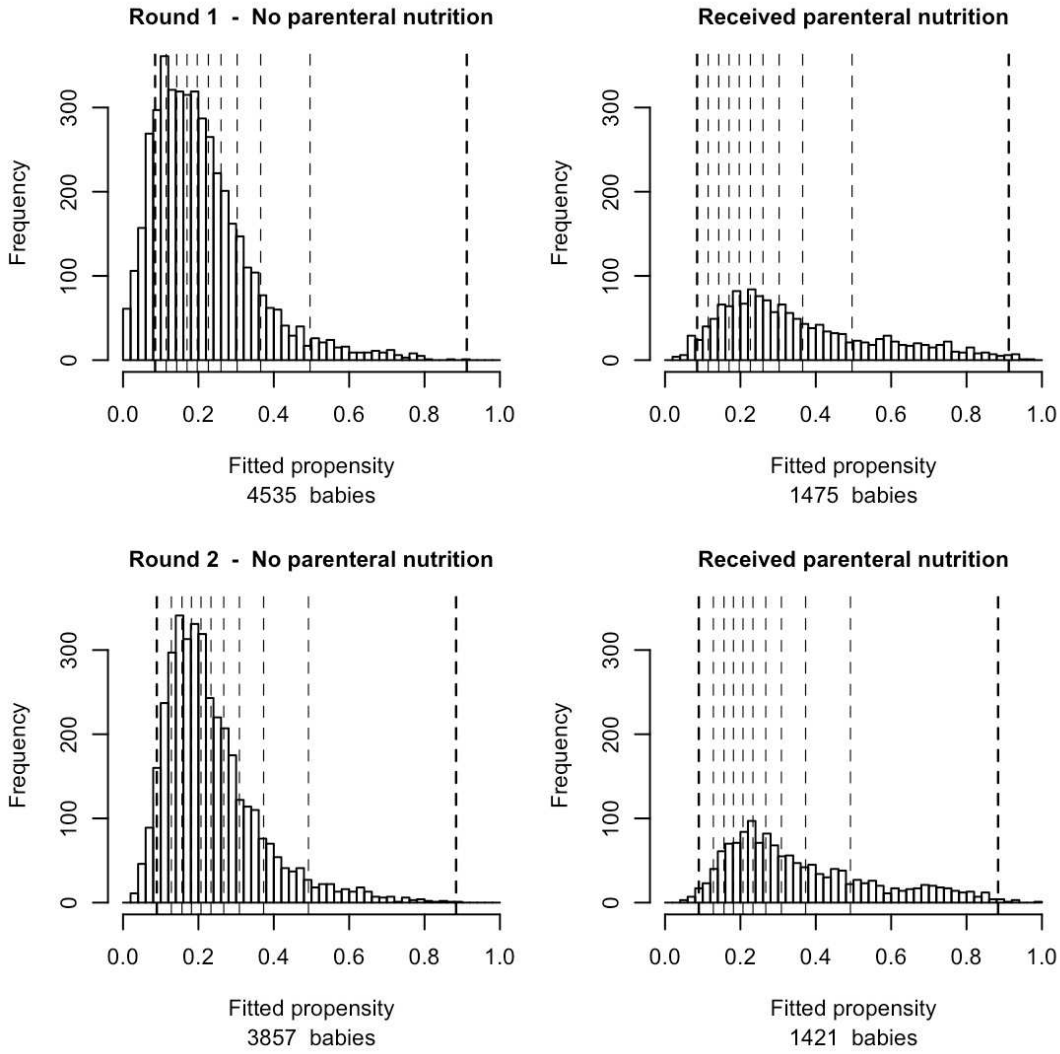
The selected (or any other) propensity model has no interpretation for inference; its sole purpose is to facilitate the formation of an exposure and control group (the matched cohorts) for analysis that is well balanced with regard to measured background variables. It was essential that no outcome variables, or more precisely, no variables that have differing potential outcomes, were involved in this stage. The motivation for this is that the background should be considered in earnest, and that this is done with no fore-knowledge of the outcomes. Accordingly, assessing the balance on all the background variables is the only relevant diagnostic for the fitted propensities.

The imbalance of an ordinal variable across two groups is defined as the difference of the within-group means divided by the standard deviation pooled across the two groups. The absolute imbalance is defined as the absolute value of the imbalance. The imbalance for a set of ordinal variables is defined as the mean of the absolute imbalances of the variables. We used this statistic as a summary or characteristic of the (overall) imbalance of two (sub-) groups. Smaller values indicate tighter balance. Imbens and Rubin[1] regard the balance of a variable as satisfactory if its absolute imbalance is smaller than 0·1. For a dataset, original or formed by matching, we report the total of the absolute imbalances and the largest and smallest imbalances. Variables that are not ordinal, that is, categorical variables, are avoided by defining indicator (dummy) variables; $H - 1$ indicators for a variable with H categories. The choice of the 'omitted' (reference) category is immaterial.

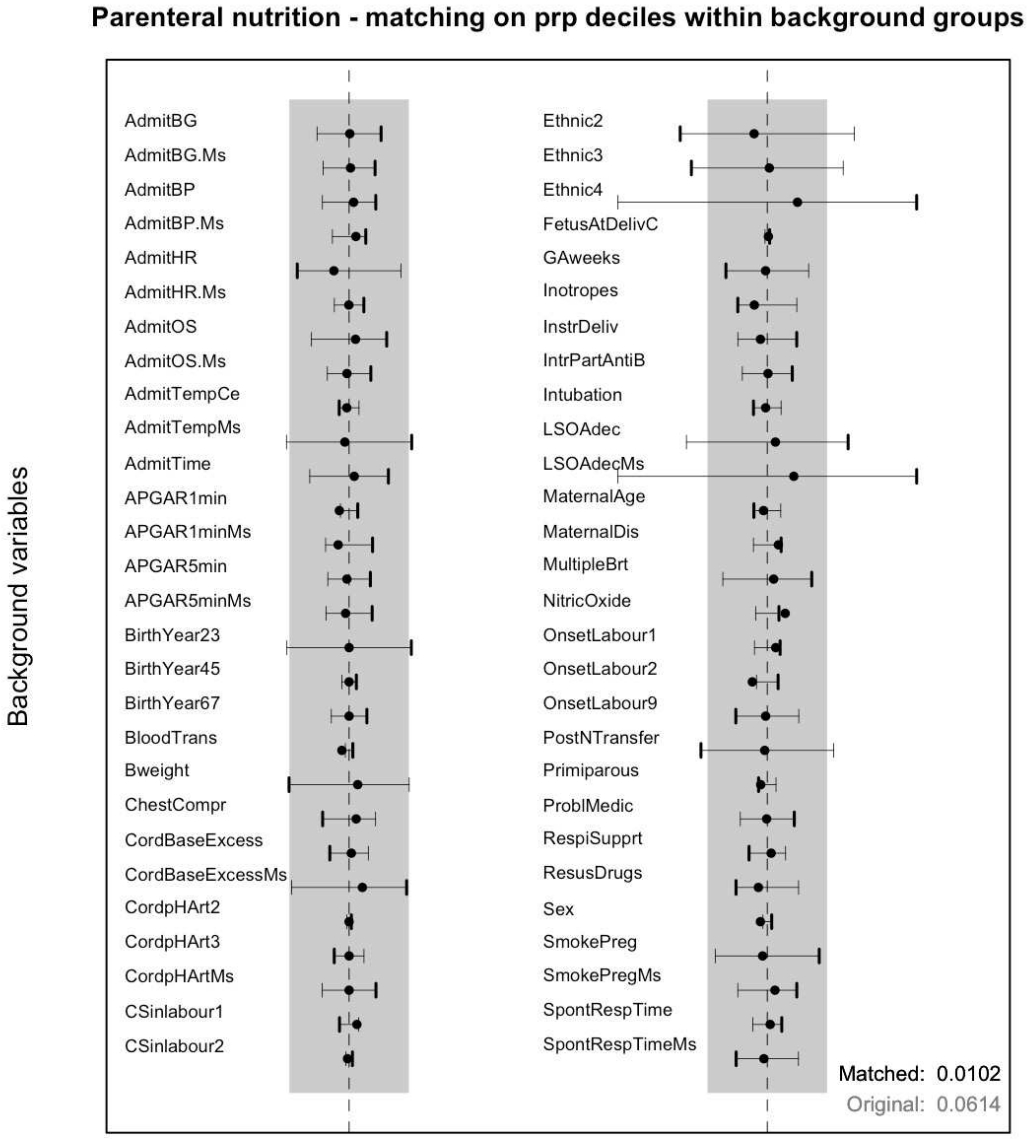
Supplemental figure 1 presents histograms of the estimated propensity scores from the final propensity model by intervention (received parenteral nutrition) and control (no parenteral nutrition) groups. There is good overlap of the propensity scores in the exposure and control groups, so many matched pairs can be formed. Data from 687 babies (11.4% of unmatched sample) were discarded due to extreme propensities.

Supplemental figure 2 presents the balance plot for the background variables included in the comparison propensity model. The dashed grey line indicates perfect balance between the groups for a specific background variable. The grey shaded area indicates the acceptable limits of imbalance for any variable, equivalent to an imbalance of $\leq 0 \cdot 1$ in absolute value. The imbalance for a specific background variable in the unmatched cohort is depicted by the bold dash and the light dash indicates the opposite of this imbalance (imbalance multiplied by -1), which represents the same extent of imbalance. The imbalance in the matched cohort is marked by the black disc. The balances for the background variables are summarised by the mean of their absolute values. Prior to matching the mean balance is 0.061, and the balances are in the range from -0.215 to 0.563. The mean balance for the matched dataset is 0.010, and the balances are between -0.025 and 0.051. The mean balances are displayed in Supplemental figure 2.

Supplemental figure 1: Histograms of estimated propensity scores. Thick vertical dashed lines indicate trimming thresholds for extreme propensities, thin vertical dashed lines indicate propensity deciles for babies retained for analysis



Supplemental figure 2: Balance plot (1:1 matching within propensity score deciles). The grey shaded area covers the region of acceptable balances, -0·1 to 0·1



Prp=propensity; AdmitBG=admission glucose; Ms= data for this item were missing; AdmitBP=admission blood pressure; AdmitHR=admission heart rate; AdmitOS=admission?; AdmitTempCe=admission temperature; AdmitTime=admission time; APGAR=Apgar score; min=minute; BloodTrans=blood transfusion on day 1; Bweight=birthweight; ChestCompr=chest compressions at resuscitation; CordBaseExcess=umbilical cord base excess; CordpHArt=Umbilican arterial pH; CSinLabour=In-labour Caesarean section; FetusAtDelivC=presentation of fetus at delivery; GAweeks=gestational age in weeks; InstrDeliv=Instrumental delivery; IntrPartAntiB=intrapartum antibiotics; LSOAdec=Lower Super Output Area decile; MaternalDis=maternal obstetric condition; MulipleBrt=multiple birth set; OnsetLabour=spontaneous/induced labour; PostNTransfer=postnal transfer; ProbMedic=maternal medical condition in pregnancy; RespiSupprt=Received respiratory support on day of admission; ResusDrugs=received drugs during resuscitation; SmokePreg=Maternal smoking in pregnancy; SpontRespTime=time to first breath

Supplemental table 4: Estimates of the effect of receiving parenteral nutrition for binary and continuous outcomes from sensitivity analyses. Results averaged over the 25 replications of the matching procedure

Variable	Sensitivity analysis		
	Years 12-17	**Intervention redefined**	**Inclusion of enteral nutrition on day 1 in propensity score**
N	2118	2506	2502
Binary outcomes: Estimate of rate difference [95% CI] (p-value)			
NEC (pragmatic definition)	0.6 [0.0, 1.2] (0.04)	0.6 [0.1, 1.1] (0.02)	0.6 [0.0, 1.1] (0.03)
Late onset BSI (NNAP definition)	2.2 [-0.8, 5.3] (0.15)	1.4 [-1.4, 4.2] (0.34)	1.7 [-1.0, 4.5] (0.22)
Late onset BSI (pragmatic definition)	-0.4 [-1.2, 0.4] (0.34)	-0.2 [-0.9, 0.5] (0.62)	-0.3 [-1.0, 0.4] (0.36)
Hypoglycaemia	-1.4 [-4.0, 1.3] (0.32)	-2.1 [-4.5, 0.3] (0.08)	-2.1 [-4.6, 0.3] (0.08)
Survival at discharge	2.8 [0.9, 4.8] (0.004)	3.0 [1.2, 4.7] (<0.001)	3.8 [2.0, 5.5] (<0.001)
Breastfeeding at discharge	-0.2 [-3.7, 3.3] (0.90)	-0.1 [-3.3, 3.1] (0.96)	0.4 [-2.8, 3.5] (0.82)
Continuous outcomes: mean difference [95% CI] (p-value)			
Length of stay	0.5 [-0.5, 1.4] (0.32)	0.6 [-0.3, 1.6] (0.16)	1.0 [0.1, 1.9] (0.02)
First day of suckling at breast	-0.2 [-0.7, 0.3] (0.51)	0.1 [-0.4, 0.7] (0.63)	0.0 [-0.5, 0.6] (0.88)
First day of maternal milk	-0.3 [-0.5, -0.1] (0.004)	-0.2 [-0.4, -0.1] (0.01)	-0.2 [-0.4, -0.1] (0.01)
Duration of PN	0.8 [0.4, 1.2] (<0.001)	0.9 [0.5, 1.2] (<0.001)	0.9 [0.6, 1.2] (<0.001)
Duration of CV line	0.01 [-0.08, 0.10] (0.88)	0.03 [0.0, 0.1] (0.42)	0.01 [-0.07, 0.09] (0.80)
Z score of at discharge	0.5 [-0.5, 1.4] (0.32)	0.6 [-0.3, 1.6] (0.16)	1.0 [0.1, 1.9] (0.02)

Abbreviations: BSI=blood stream infection; CI=confidence interval; CV=central venous; NEC=necrotising enterocolitis; NNAP=National Neonatal Audit Programme

References

1. Imbens GW, Rubin DB. *Causal Inference for Statistics, Social, and Biomedical Science. An Introduction.* New York: Cambridge University Press; 2015

United Kingdom Neonatal Collaborative leads at contributing neonatal units

Institution	Lead
Airedale General Hospital	Dr Matthew Babirecki
Arrowe Park Hospital	Dr Anand Kamalanathan
Barnet Hospital	Dr Tim Wickham
Barnsley District General Hospital	Dr Kavi Aucharaz
Basildon Hospital	Dr Aashish Gupta
Basingstoke & North Hampshire Hospital	Dr Nicola Paul
Bassetlaw District General Hospital	Dr L M Wong
Bedford Hospital	Dr Anita Mittal
Birmingham City Hospital	Dr Lindsay Halpern
Birmingham Heartlands Hospital	Dr Pinki Surana
Birmingham Women's Hospital	Dr Matt Nash
Bradford Royal Infirmary	Dr Sunita Seal
Broomfield Hospital, Chelmsford	Dr Ahmed Hassan
Calderdale Royal Hospital	Dr Karin Schwarz
Chelsea & Westminster Hospital	Dr Shu-Ling Chuang
Chesterfield & North Derbyshire Royal Hospital	Dr Aiwyne Foo
Colchester General Hospital	Dr Jo Anderson
Conquest Hospital	Dr Graham Whincup
Countess of Chester Hospital	Dr Stephen Brearey
Croydon University Hospital	Dr John Chang
Cumberland Infirmary	Dr Yee Aung
Darent Valley Hospital	Dr Abdul Hasib
Darlington Memorial Hospital	Dr Mehdi Garbash
Derriford Hospital	Dr Alex Allwood
Diana Princess of Wales Hospital	Dr Pauline Adiotomre
Doncaster Royal Infirmary	Dr Nigel Brooke
Dorset County Hospital	Dr Abby Deketelaere
East Surrey Hospital	Dr K Abdul Khader
Epsom General Hospital	Dr Ruth Shephard
Frimley Park Hospital	Dr Sanghavi Rekha
Furness General Hospital	Dr Anas Olabi
George Eliot Hospital	Dr Mukta Jain
Gloucester Royal Hospital	Dr Jennifer Holman
Good Hope Hospital	Dr Pinki Surana
Great Western Hospital	Dr Stanley Zengeya
Guy's & St Thomas' Hospital	Dr Geraint Lee
Harrogate District Hospital	Dr Sobia Balal
Hereford County Hospital	Dr Cath Seagrave
Hillingdon Hospital	Dr Tristan Bate
Hinchingbrooke Hospital	Dr Hilary Dixon
Homerton Hospital	Dr Narendra Aladangady
Hull Royal infirmary	Dr Hassan Gaili
Ipswich Hospital	Dr Matthew James
James Cook University Hospital	Dr M Lal
James Paget Hospital	Dr Ambadkar
Kettering General Hospital	Dr Poornima Pandey
Kings College Hospital	Dr Ravindra Bhat
King's Mill Hospital	Dr Simon Rhodes
Kingston Hospital	Dr Vinay Pai
Lancashire Women and Newborn Centre	Dr Savi Sivashankar
Leeds Neonatal Service	Dr Lawrence Miall
Leicester General Hospital	Dr Jonathan Cusack
Leicester Royal Infirmary	Dr Venkatesh Kairamkonda
Leighton Hospital	Dr Michael Grosdenier
Lincoln County Hospital	Dr Ajay Reddy
Lister Hospital	Dr J Kefas
Liverpool Women's Hospital	Dr Christopher Dewhurst
Luton & Dunstable Hospital	Dr Jennifer Birch
Macclesfield District General Hospital	Dr Gail Whitehead
Manor Hospital	Dr Krishnamurthy
Medway Maritime Hospital	Dr Ghada Ramadan
Milton Keynes General Hospital	Dr I Misra
Musgrove Park Hospital	Dr Chris Knight
New Cross Hospital	Dr Rob Negrine
Newham General Hospital	Dr Imdad Ali
Nobles Hospital	Dr Prakash Thiagarajan
Norfolk & Norwich University Hospital	Dr Mark Dyke
North Devon District Hospital	Dr Michael Selter
North Manchester General Hospital	Dr P Kamath
North Middlesex University Hospital	Dr Neeraj Jain
Northampton General Hospital	Dr Subodh Gupta

Northumbria Specialist Emergency Care Hospital	Laura Winder
Northwick Park Hospital	Dr Richard Nicholl
Nottingham City Hospital	Dr Steven Wardle
Nottingham University Hospital (QMC)	Dr Steven Wardle
Ormskirk District General Hospital	Dr Andreea Bontea
Oxford University Hospitals, John Radcliffe Hospital	Dr Eleri Adams
Peterborough City Hospital	Dr Katharine McDevitt
Pilgrim Hospital	Dr Ajay Reddy
Pinderfields General Hospital	Dr David Gibson
Poole General Hospital	Prof Minesh Khashu
Princess Alexandra Hospital	Dr Chinnappa Reddy
Princess Anne Hospital	Dr Mark Johnson
Princess Royal Hospital	Dr P Amess
Princess Royal Hospital	Dr Deshpande
Princess Royal University Hospital	Dr Elizabeth Sleight
Queen Alexandra Hospital	Dr Charlotte Groves
Queen Charlotte's Hospital	Dr Lidia Tyszcuzk
Queen Elizabeth Hospital, Gateshead	Dr Anne Dale
Queen Elizabeth Hospital, King's Lynn	Dr Glynis Rewitzky
Queen Elizabeth Hospital, Woolwich	Dr Olutoyin Banjoko
Queen Elizabeth the Queen Mother Hospital	Dr Bushra Abdul-Malik
Queen's Hospital, Burton on Trent	Dr Dominic Muogbo
Queen's Hospital, Romford	Dr Khalid Mannan
Rosie Maternity Hospital, Addenbrookes	Dr Angela D'Amore
Rotherham District General Hospital	Dr Shameel Mattara
Royal Albert Edward Infirmary	Dr Christos Zipitis
Royal Berkshire Hospital	Dr Peter De Halpert
Royal Bolton Hospital	Dr Paul Settle
Royal Cornwall Hospital	Dr Paul Munyard
Royal Derby Hospital	Dr John McIntyre
Royal Devon & Exeter Hospital	Dr Chrissie Oliver
Royal Hampshire County Hospital	Dr Lucinda Winckworth
Royal Lancaster Infirmary	Dr Joanne Fedee
Royal Oldham Hospital	Dr Natasha Maddock
Royal Preston Hospital	Dr Richa Gupta
Royal Stoke University Hospital	Dr Jyoti Kapur
Royal Surrey County Hospital	Dr Ben Obi
Royal Sussex County Hospital	Dr P Amess
Royal United Hospital	Dr Stephen Jones
Royal Victoria Infirmary	Dr Naveen Athiraman
Russells Hall Hospital	Dr Chandan Gupta
Salisbury District Hospital	Dr Jim Baird
Scarborough General Hospital	Dr Kirsten Mack
Scunthorpe General Hospital	Dr Pauline Adiotomre
Southend Hospital	Dr Vineet Gupta
Southmead Hospital	Dr Alison Pike
St George's Hospital	Dr Charlotte Huddy
St Helier Hospital	Dr Ralf Hartung
St Mary's Hospital, Isle of Wight	Dr Akinsola Ogundiya
St Mary's Hospital, London	Dr Lidia Tyszcuzk
St Mary's Hospital, Manchester	Dr Ngozi Edi-Osagie
St Michael's Hospital	Dr Pamela Cairns
St Peter's Hospital	Dr Peter Martin
St Richard's Hospital	Dr Nick Brennan
Stepping Hill Hospital	Dr Carrie Heal
Stoke Mandeville Hospital	Dr Sanjay Salgia
Sunderland Royal Hospital	Dr Majd Abu-Harb
Tameside General Hospital	Dr Jacqeline Birch
The Jessop Wing, Sheffield	Dr Porus Bastani
The Royal Free Hospital	Dr Marice Theron
The Royal London Hospital	Dr Vadivelam Murthy
Torbay Hospital	Dr Siba Paul
Tunbridge Wells Hospital	Dr Hamudi Kisat
University College Hospital	Dr Giles Kendall
University Hospital Coventry	Dr Puneet Nath
University Hospital Lewisham	Dr Ozioma Obi
University Hospital of North Durham	Dr Mehdi Garbash
University Hospital of North Tees	Dr Hari Kumar
Victoria Hospital, Blackpool	Dr Chris Rawlingson
Warrington Hospital	Dr Delyth Webb
Warwick Hospital	Dr Bird
Watford General Hospital	Dr Sankara Narayanan
West Cumberland Hospital	Dr Yee Mon Aung
West Middlesex University Hospital	Dr Eleanor Hulse
West Suffolk Hospital	Dr Ian Evans

Wexham Park Hospital	Dr Rekha Sanghavi
Whipps Cross University Hospital	Dr Caroline Sullivan
Whiston Hospital	Dr Ros Garr
Whittington Hospital	Dr Wynne Leith
William Harvey Hospital	Dr Vimal Vasu
Worcestershire Royal Hospital	Dr Liza Harry
Worthing Hospital	Dr Katia Vamvakiti
Wythenshawe Hospital	Dr Ngozi Edi-Osagie
Yeovil District Hospital	Dr Megan Eaton
York District Hospital	Dr Sundeep Sandhu
Aberdeen Maternity Hospital,	Dr Saulius Satas
Borders General Hospital, Melrose	Dr Clare Irving
Dumfries and Galloway Royal Infirmary	Dr Andrew Eccleston
Cross House Hospital, Kilmarnock	Dr S Kinmond
Dr Gray's Hospital, Elgin	Dr Shelagh Parkinson
Forth Valley Hospital, Larbert	Dr Dominic O'Reilly
Ninewells Hospital, Dundee	Dr Bhushan
Princess Royal Maternity Hospital, Glasgow	Dr Andrew Powls
Raigmore Hospital, Inverness	Dr P Van Der Heide
Royal Alexandra Hospital, Paisley	Dr Hilary Conetta
The Queen Elizabeth University Hospital Glasgow	Dr J Coutts and Dr AM Heuchan
Simpsons Centre for Reproductive Health, Royal Infirmary of Edinburgh	Professor Ben Stenson
St John's Hospital, Livingston	Helen Rhodes
Victoria Hospital, Kirkcaldy	Dr Sean Ainsworth
Wishaw General Hospital	Dr Caroline Delahunty
Aberdeen Maternity Hospital,	Dr Saulius Satas
Singleton Hospital	
Princess of Wales Hospital	Dr Arun Ramachandran
Royal Gwent Hospital	Dr Kate Creese
Nevill Hall Hospital	Dr Sunil Reddy
Glan Clwyd Hospital	Dr Sunil Reddy
Wrexham Maelor Hospital	Dr Ian Barnard
Ysbyty Gwynedd	Dr Brendan Harrington
University Hospital of Wales	Dr Mike Cronin
Prince Charles Hospital	Dr Nitin Goel
Glangwili General Hospital	Dr Iyad Al-Muzaffar
Withybush Hospital	Dr Prem Pitchaikani