MANAGEMENT OF EARLY ONSET SEPSIS IN NEONATES

NeoTRIPS

3rd June – 2nd August 2019

Study Protocol

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1. Title: Management of suspected early onset sepsis in neonates

2. Background

Neonatal infection is a significant cause of mortality and morbidity in newborn babies and can lead to life-threatening sepsis which is responsible for 10% of all neonatal deaths. Sepsis can be early-onset (within 72 hours of birth) or late-onset (more than 72 hours after birth). Whilst the identification and treatment of symptomatic babies is without controversy, defining the management of asymptomatic infants with risk factors is a challenge, particularly in the absence of timely reliable tests that can be confidently used to exclude sepsis. It is known that neonatal blood cultures have poor yield, and inflammatory markers such as C-Reactive Protein (CRP) are non-specific and should be interpreted with caution in the clinical context (1).

The NICE (National Institute for Clinical Excellence) guideline was published in August 2012 to provide recommendations for the management of infants with risk factors for early onset sepsis (EOS). The aims were to prioritise the treatment of sick babies; to minimise antibiotic exposure in infants who do not have EOS; promote antibiotic stewardship to avoid the development of resistant organisms. However, there is evidence that the guidance has had the opposite effect to intended, with further investigations, increased lumbar punctures (LP) and longer duration of treatment and stay for 'at risk' infants with raised inflammatory markers (2).

The NICE guidance outlined a strategy for determining which infants had septic screens based on maternal risk factors; either one 'red flag' or two or more 'non-red' flags. In addition, it includes guidance on the interpretation and use of biochemical and clinical parameters to guide management; specifically a second CRP within 18-24 hour of the first CRP; to consider doing a LP in an asymptomatic infant with a CRP > 10mg/L; to stop antibiotics at 36 hours if confirmation of negative blood culture is provided.

Although the 'red flags' are clearly indicated, there are marked differences in practice between units that may lead to differing thresholds of asymptomatic infants being screened. For example, there may be differences in screening policies for Group B streptococcus (GBS) leading to variation in the proportion of colonised women identified, definitions of clinical chorioamnionitis and thresholds for treatment of mothers with antibiotics. NICE has recognised this and new evidence has prompted a review of the current guideline with a draft scope published in Dec 2018, and expected guidance publication in March 2021 (3).

Uptake of the NICE guidance has been variable. The lack of provision of automated blood culture reporting systems means that only half of neonatal units have been able to stop antibiotics in asymptomatic infants within 36 hours of a negative blood cultures (4, 5). One specific controversial guidance is the recommendation of considering a LP in a well infant with a CRP above 10 mg/dL. CRP is a very non-specific marker and can be raised in non-infectious conditions. The evidence for investigation with CRP levels is based on symptomatic infants and should not be extrapolated without further studies, to asymptomatic infants. The guidance has led to more LPs and several units increasing the threshold of CRP locally to avoid unnecessary invasive investigation in well babies (1).

The Kaiser neonatal sepsis calculator offers a multivariate risk factor assessment of the newborn infant as opposed to the categorical risk factor assessment used currently (6) . This calculator was developed by Kaiser Permanente Northern California, USA, and has been implemented in some parts of the UK too. It is a web-based tool that uses an objective dataset of risk factors present at birth and the evolving newborn clinical condition to obtain an estimate of sepsis risk for the individual newborn. There is evidence suggesting that use of the calculator reduces the number of babies started on

antibiotics using standard guidelines without an increase in 'missed' cases of sepsis (7). Whilst early identification and treatment of infants with sepsis is important, avoiding unnecessary investigations and treatment in asymptomatic infants without sepsis is also a priority. This avoids unnecessary painful invasive investigations, antibiotic exposure which disrupts the gut microbiota, separation of mother and baby, prolonged inpatient stay, costs of antibiotics and workload. In addition, administration of antibiotics and investigations may increase the separation of mother and baby depending on where this takes place. This interruption disrupts the normal bonding and can have major impact on breastfeeding, and long term maternal and infant morbidity (8). Promoting practices to help minimise mother and baby separation is therefore of utmost importance, as is the parent perception of having their baby on antibiotics soon after birth and what this means for them.

3. Aims

1) To study the variation in management of suspected early onset neonatal sepsis for babies born ≥34 weeks cared for on postnatal/transitional care wards within London hospitals:
    a. Criteria for initiating antibiotics
    b. Investigations including CRP (timing and frequency), full blood count (FBC; whether performed), blood cultures (turnover time) and criteria for LP
    c. Criteria to inform duration of antibiotics
2) To compare proportion of babies screened as per the local unit guidelines, adherence/variance from the NICE guidelines and the potential impact of Kaiser Permanente neonatal sepsis calculator as a screening tool.
3) To determine the incidence of sepsis and meningitis for babies treated with antibiotics on the postnatal/transitional care wards
4) To understand parental experience of their baby receiving antibiotics after birth

4. Methods

Setting: We invited all 28 London Neonatal units to take part in this regional study. 18 Neonatal units volunteered to participate.

Participating units

Level 1 hospitals (Special care)	West Middlesex, Royal Free, North Middlesex
Level 2 hospitals (Local units)	Northwick Park, Hillingdon, St. Mary's, Barnet, Croydon, St Helier's, Queen Elizabeth, Kingston
Level 3 hospitals (Intensive care units)	Queen Charlotte's, Chelsea and Westminster, University College, Homerton, Royal London (TBC), St Thomas', Kings

This included 7 level 3 units, 8 level 2 units and 3 level 1 units. Each site is represented by at least one lead Consultant and trainee.

Time period: 2-month period starting 3rd of June 2019 till 2nd of August 2019.

Study Population:

Inclusion criteria: Babies born ≥34 weeks gestation started on antibiotics soon after birth and deemed suitable to be cared for on the postnatal ward or transitional care. Data capture should be completed for babies who are thereafter admitted to the neonatal unit.

Exclusion criteria: 1) Gestation <34 weeks, 2) Any baby admitted to the neonatal unit immediately after birth

Roles and responsibilities

Trainee role at each unit: To disseminate study and proforma information to clinical teams and facilitate data collection. The trainee will then collate the proformas and enter these data onto electronic centralised data sheets.

Supervising Consultant at each unit: Responsible for overseeing the data collection, troubleshooting locally and ensuring data is uploaded on the electronic platform regularly.

Data collection:

Data required include:

Unit level information (required only once per unit)

- Total number of live births during the 2-month time period
- Total number of babies admitted to the to the neonatal unit during the 2-month time period
- Are blood cultures in your unit reported from the time taken or the time booked into lab?
- Are blood cultures reported on the computer system at 36/48/72 hrs or 5 days
- Does the lab have to be called for 36-hour blood culture results or is it automatically reported?
- Does your hospital have 'Point of Care' CRP testing and is this used in decision making?
- What antibiotics does your unit use as first line for early onset neonatal sepsis?
- Do these come as prefilled syringes from pharmacy?
- Who is administering the antibiotics? Midwives/Nurses/Junior doctors
- Where are the antibiotics being administered? Postnatal ward/Neonatal unit/Transitional care
- Are babies on antibiotics recorded as activity on Badgernet?
- If your hospital has a transitional care unit, is this a virtual space or a dedicated area whereby babies are admitted to Badgernet?

Baby level data (required for each baby) proforma (Appendix 1) competed at 2 time points:

- Part 1 - Completed at the time the decision is made to commence antibiotics (completed by doctor initiating antibiotics)

This will include: NICE maternal risk factors for EON sepsis, maternal GBS status, highest maternal temperature during or within an hour after labour, intrapartum antibiotic choice for mother (if given at all), clinical signs in baby.

- Part 2 - Completed at time of discharge (completed by doctor discharging baby)

This will include: where baby was cared for, whether baby was admitted to the neonatal unit at any point, whether an initial CRP, FBC and blood culture was done, was a 2nd CRP done and if yes when was this and its value, how many CRPs in total did the baby have, was a LP done and the rational for doing this, and the duration of antibiotics the baby received.

Parent questionnaire (Appendix 2)

Questions related to information provision and mother and baby separation. To be given to the parents to complete. There are only 4 questions, and this should take no longer than 1 minute.

5. Data analysis

We will report the following for each hospital, operational delivery network and for London as a whole.

Variation in practice

- Proportion of babies cared for on the postnatal/transitional care ward started on antibiotics for suspected sepsis after delivery.
- Proportion of babies started on antibiotics for maternal risk factors only; combination of maternal risk factors and clinical signs in baby; clinical signs in baby only.
- Proportion of babies who had an initial CRP performed
- Proportion of babies who had a blood culture done
- Proportion of babies who had a FBC done
- Proportion of babies who had a 2nd CRP level performed within 18-24 hours
- Median frequency of CRP levels
- Proportion of babies in which LP performed because of high CRP; and the mean and median (IQR) of this CRP level
- Median (IQR) days for the antibiotic duration for babies with negative blood cultures

Comparison with NICE and Kaiser calculator

- Proportion of babies that would have been started on antibiotics based on NICE guidelines
- Proportion of babies that would have been started on antibiotics based on the Kaiser sepsis risk calculator recommendation (0.6/1000 will be used as the baseline EOS rate for London)

Incidence of sepsis and meningitis

- Proportion of babies who had a positive blood culture.
- Proportion of LP samples obtained that were considered to be indicative of meningitis

Parent perception

- Proportion of parents who felt that they were given adequate information about why their baby was on antibiotics.
- Proportion of parents that were given written information about their baby being started on antibiotics and what this meant for them.
- Mean duration (in hours/day) that mothers and babies are being separated for due to the administration of antibiotics?

We will use Chi-square testing and Mann-Whitney testing for categorical data and continuous data, respectively.

6. Approvals

Research Ethics approval is not required as this is a service evaluation project and involves collecting anonymised patient data.

7. Governance

The NeoTRIPs team will have access to the data from all sites and will be responsible for collating the data and analysis. Each individual unit will only be able to access their own data. All data will be anonymised.

8. Publications/Presentations

All individuals involved in the NeoTRIPS project will be acknowledged in any publications/presentations directly related to this project.

9. References

1. Brown JVE, Meader N, Cleminson J, McGuire W. C-reactive protein for diagnosing late-onset infection in newborn infants. Cochrane Database Syst Rev. 2019;1:Cd012126.

2. Watson G, Caldwell C, Kennea N. Neonatal early onset sepsis: a reflection on the NICE guidance Infant 2016;12(3):133-5.

3. National Institute for Health and Care Excellence. Guideline Scope: Neonatal infection (early onset): antibiotic for prevention and treatment (update) 2018 [Available from: https://www.nice.org.uk/guidance/GID-NG10111/documents/draft-scope

4. Mukherjee A, Davidson L, Anguvaa L, Duffy DA, Kennea N. NICE neonatal early onset sepsis guidance: greater consistency, but more investigations, and greater length of stay. Arch Dis Child Fetal Neonatal Ed. 2015;100(3):F248-9.

5. Paul SP, Caplan EM, Morgan HA, Turner PC. Barriers to implementing the NICE guidelines for early-onset neonatal infection: cross-sectional survey of neonatal blood culture reporting by laboratories in the UK. J Hosp Infect. 2018;98(4):425-8.

6. Kaiser Permanente Sepsis Risk Calculator https://neonatalsepsiscalculator.kaiserpermanente.org/InfectionProbabilityCalculator.aspx

7 Kuzniewicz MW et al. A quantitative, risk-based approach to the management of neonatal early-onset sepsis. JAMA Pediatr. 2017 Apr 1;171(4):365-371

8. Crenshaw JT. Healthy Birth Practice #6: Keep Mother and Baby Together— It's Best for Mother, Baby, and Breastfeeding. J Perinat Educ 2014 Fall; 23(4): 211–217.

Appendix 1: NeoTRIPS. Management of Early Onset Sepsis- Data Proforma

Part 1 – to be filled by doctor after decision made to start antibiotics

Demographics

Patient no.		DOB. (DD/MM/YY)		Gestation weeks + days (only include ≥34/40)	
Sex (M/F)		Time of birth (24 hr clock)		Birth weight (g)	

Indication for antibiotics according to NICE/unit guidelines (Delete/Circle as appropriate)

Risk factor	
Invasive group B streptococcal (GBS) infection in a previous baby	Yes/No
Maternal GBS colonisation, bacteriuria or infection in the current pregnancy	Yes/No/unknown
Prelabour rupture of membranes	Yes/No
Preterm birth following spontaneous labour (before 37 weeks' gestation)	Yes/No
Suspected or confirmed rupture of membranes for more than 18 hours in a preterm birth	Yes/No
Maternal fever higher than 38°C during delivery or within an hour of delivery, or confirmed or suspected chorioamnionitis	Yes/No
Parenteral antibiotic treatment given to the woman for confirmed or suspected invasive bacterial infection (such as septicaemia) at any time during labour, or in the 24-hour periods before and after the birth [This does not refer to intrapartum antibiotic prophylaxis]	Yes/No
Suspected or confirmed infection in another baby in the case of a multiple pregnancy	Yes/No
Abnormal clinical signs	Yes/No
Respiratory distress	Yes/No
Temperature instability	Yes/No
Jaundice <24 hours	Yes/No
Other: please comment	

Additional data to be collected necessary for Kaiser sepsis calculator (Circle as appropriate)

Highest maternal antepartum temperature (include temperature recorded within 1 hour of delivery)	
Rupture of membranes (in hrs):	
Intrapartum antibiotics: o Broad spectrum >4 hrs pre delivery (e.g. Amoxicillin, Co-amoxiclav, Cefotaxime, Ceftriaxone, Meropenem, Metronidazole, Tazocin) o Broad spectrum 2 to 4 pre delivery (e.g. Amoxicillin, Co-amoxiclav, Cefotaxime, Ceftriaxone, Meropenem, Metronidazole, Tazocin) o GBS specific antibiotics >2 hrs prior to birth (e.g. Benzylpenicillin, Clindamycin, Vancomycin) o No antibiotics or antibiotics <2hrs prior to birth	Yes/No Yes/No Yes/No Yes/No

NeoTRIPS. Management of Early Onset Sepsis

Part 2 – to be filled by discharging doctor

Where was this baby cared for?	Transitional care unit/postnatal ward/both
Were any of these clinical findings present within the **first 12 hours of life?** **One** of the below: Persistent physiologic abnormality **lasting ≥ 4 hrs** 1. Tachycardia (HR ≥ 160) 2. Tachypnoea (RR ≥ 60) 3. Temperature instability (≥ 38˚C or < 36.4˚C) 4. Respiratory distress (grunting, flaring, or retracting) not requiring supplemental O_2 **Two or more** physiologic abnormalities **lasting for ≥ 2 hrs** 1. Tachycardia (HR ≥ 160) 2. Tachypnoea (RR ≥ 60) 3. Temperature instability (≥ 38˚C or < 36.3˚C) 4. Respiratory distress (grunting, flaring, or retracting) not requiring supplemental O_2	Yes/No Yes/No
Was a CRP taken prior to starting antibiotics?	Yes/No
If yes, what was the value (mg/L)?	
Was a 2nd CRP done?	Yes/No
If yes, what was the value of the 2nd CRP (mg/L)?	
What was the baby's age if a 2nd CRP was done (hours)?	
How many times in total was a CRP performed?	1/2/3/4/5/>5
Was a FBC done? Yes/No/clotted	Yes/No/Clotted
If clotted – was it repeated?	Yes/No
Was a blood culture done?	Yes/No
What was the blood culture result?	Positive/Negative
If positive, what was the organism?	
Was a LP done?	Yes/No
Why was the LP done?	High CRP Positive maternal blood culture Positive baby blood culture Clinical suspicion of meningitis Other
If the LP was done because of a high CRP, what was the value? (mg/L)	
What was the LP result?	Positive culture/Cell count indicative of meningitis Negative for meningitis Failed tap
Total duration of antibiotics (36 hrs or no. of total days)	
Criteria used to determine duration of antibiotics	Clinical progress Highest CRP Falling CRP level A specific CRP level prior to stopping Blood culture result LP result
Was this baby ever admitted to the neonatal unit?	Yes/No
If yes, what was the principal diagnosis?	
Please write the exact time and data in a 24 hour clock format (eg 29/05/2019 20:17) on your paper form **when you submit a completed online form.** This will become your unique baby identifier.	

Abbreviations

FBC Full blood count	CRP C Reactive Protein	NNU Neonatal Unit
LW Labour Ward	PNW Postnatal Ward	LP Lumbar Puncture

Appendix 2: Early onset sepsis - Parent questionnaire

Congratulations on the birth of your baby!

We are conducting a pan-London survey looking at babies receiving antibiotics on the postnatal ward. As part of this, we would like to capture some details about the parental experience. All data collected will be anonymous and will not affect the care of you or your baby. The information for your local unit will be used to the highlight areas of good practice AND/OR areas for improvement.

Please tick as appropriate.

1. Was it clear to you why your baby was being started on antibiotics?

- Yes
- No

2. Were you provided with any written information about why your baby was being started on antibiotics and what this meant for you and your baby?

- Yes
- No

3. How long on average per day were you separated from your baby because they were away from you receiving their antibiotics?

- Not separated
- 0-1 hrs
- 1-2 hrs
- 2-4 hrs
- >4 hrs

4. Please use this space to add any comments about your experience related to your baby receiving antibiotics.