Pan-London early-onset sepsis observational study

London Operational Delivery Network Task and Finish study protocol

Version 1.10

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Study management group

A Task and Finish Group will be set up in partnership with the London ODN to conduct this study.

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			KP: 10 units NICE: 16 units

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1 INTRODUCTION

1.1 Early onset sepsis and NICE guidance

Early onset sepsis (EOS) in neonates is defined as bacteraemia or bacterial meningitis occurring within 72 hours of birth (1). EOS remains a major cause of mortality and morbidity in neonates, occurring in around 0.7/1000 live births; is responsible for 5.6/1000 neonatal admissions (1) and 10% of all neonatal deaths (2). As infants can initially be asymptomatic, determining who should receive antibiotics or be kept in hospital for monitoring, can be a challenge. In the UK, the National Institute for Health and Care Excellence (NICE) guidance is based on assessment of maternal risk factors, clinical indicators and "red flags" (3) which prompt investigations and antibiotics. Taking a blood culture and monitoring without starting antibiotics is not included in the guidance.

However, there have been growing concerns that the NICE guidance has led to an unwarranted increase in painful procedures and antibiotic use, particularly among well babies on the postnatal ward, resulting in prolonged hospital stay and greater costs to the NHS (4-6). Additionally, the potential disruption of gut microbiota may have an adverse impact on long-term health outcomes (7-9). A recent NeoTRIPs study conducted across 13 London hospitals in June and July 2019 found that 12% (1062/8856) of mostly well-appearing infants ≥34 weeks' gestation on the postnatal ward received antibiotics. 7/8856 babies had a positive blood culture, making the incidence of EOS 0.8/1000 livebirths. 66% of newborns received antibiotics for maternal risk factors alone. This is not surprising given that the NICE guideline recommends all infants of mothers receiving parenteral antibiotics for confirmed or suspected invasive bacterial infection during labour to also receive antibiotics ("red flag"). However, given the imprecision of the clinical diagnosis of invasive infection, mothers are often given intravenous antibiotics for non-specific presentations e.g. a single episode of pyrexia. Often, the reason for maternal antibiotics is not communicated to the neonatal teams, making it difficult to gauge the true concern for sepsis.

Neonatal units have introduced co-ordinated quality improvement programs to promote antibiotic stewardship across neonatal services (10). The MatNeo QI project at St Mary's Hospital successfully reduced antibiotic use among infants through strong partnership between maternity and neonatal teams. Other examples for reducing hospital stay include ambulating newborn infants with paediatric outpatient parenteral antibiotic therapy (pOPAT) (11).

1.2 The Kaiser Permanente Sepsis Risk Calculator (SRC)

In search of a more objective approach based on individual risk stratification, the Kaiser Permanente (KP) Research group in the US developed a multivariate model using a nested case-control design in 608,014 newborns ≥34 weeks gestation; this is available as a web-based sepsis risk calculator (SRC) (12). The calculator contains background EOS incidence, gestational age, highest maternal antepartum temperature, duration of membrane rupture, maternal GBS status and type/timing of intrapartum antibiotics. Clinical presentation is factored in, which adjusts the 'at birth' recommendation given by the calculator depending if the baby is well appearing, equivocal or has clinical symptoms and signs. The calculator provides recommendations for: i) clinical management (routine care/blood culture/empiric antibiotics) ii) monitoring of vital signs (13-14).

A systematic review which included thirteen observational studies and 175,752 newborns found a substantially lower relative risk (range, 3%-60%) for empirical antibiotic therapy. Meta-analysis revealed a relative risk of antibiotic use of 56% (95% CI, 53%-59%) in before-after studies including newborns regardless of exposure to chorioamnionitis. Evidence on safety was limited, but proportions of missed cases of EOS were comparable between management guided by the SRC and conventional management strategies (15). This tool has been

validated against US guidelines (16-17) and endorsed by the Committee on the Fetus and Newborn of the American Academy of Pediatrics (18). Of note, the SRC was one of several evidenced-based practices promoted by the Vermont Oxford Network's "Choosing Antibiotics Wisely" internet-based Newborn Improvement Curriculum for Quality program (https://public.vtoxford.org/quality-education/universal-training/).

1.3 Implementation of SRC in the UK: an overview

Parts of the UK have been implementing SRC, including all of Wales, South West England and some London units. Studies assessing the theoretical application of the SRC reported that adoption could safely reduce antibiotic usage compared to NICE (19), but that NICE guidelines would identify more EOS cases in the asymptomatic phase (20). The SARS-CoV-2 pandemic has further accelerated the adoption of the SRC to facilitate earlier discharges. The London ODN wrote to chief executives on 4th May suggesting units should consider implementing the SRC. To date, 12 of 26 neonatal units in London (co-located with maternity) have already implemented or have plans to implement the SRC.

1.4 Uncertainties of widespread implementation of SRC in UK and rationale for proposed study

Caution is necessary when extrapolating results between countries because of differences in EOS incidence and healthcare practices. It is important to note that the SRC has not been tested with the rigour of a randomised controlled trial (RCT) and before-after studies carry an inherent risk of historical bias. Furthermore, a recent systematic review of observational data highlighted concerns of an increased risk of missed cases of EOS with SRC versus NICE (21). There is an urgent need for an adequately powered and well-designed trial to assess the safety of SRC compared to NICE. However, without secured funding, the London ODN and the study team believe that a prospective observational study should be undertaken to evaluate the impact of SRC implementation across London. It will also help test the feasibility of data collection that will inform the design of an RCT.

1.5 Important considerations for observational study design

- Some studies defined a 'missed case' as those with a positive culture and delayed treatment compared to if NICE guidance was followed. However, it is important to recognise that the low threshold for antibiotics as per NICE guidance subjects a much larger population of infants to unnecessary treatment compared to cases of true sepsis. Also, both NICE and SRC may miss cases without risk factors.
- The SRC was developed and validated using EOS confirmed by positive blood cultures. However, due to the low yield of positive blood cultures in infants, EOS can occur with a negative blood culture. Critically, although much more common, a consensus definition of culture-negative EOS is lacking.
- A red flag in NICE that mandates antibiotics for the infant is "parenteral antibiotics given to the mother for confirmed or suspected invasive bacterial infection during labour or 24 hours before/after the birth". Conversely, antepartum antibiotics lowers the EOS risk in the SRC prediction model.
- Important to note that the maternal pyrexia in the SRC relates to the highest antepartum (not postpartum) temperature. Therefore, the SRC should not be applied to infants being assessed solely because of postpartum maternal pyrexia.
- Whilst the SRC was designed to be used for all infants ≥34 weeks gestation, most London neonatal units are limiting its use to the postnatal ward; this has implications for extrapolating the results of this study to all eligible infants. We will use two denominators i) all infants ≥34 gestation including those admitted to the neonatal unit ii) excluding infants admitted to neonatal unit from labour ward.

- The SRC model was developed using data from a large number of infants prior to introduction of universal GBS screening in the US. Therefore the prediction model allows for a calculated EOS risk estimate for the individual infant when GBS status is unavailable (as per the UK without universal testing). Moreover the relative contribution of GBS as a predictive factor in the SRC model is estimated to be only 2.3% whereas, intrapartum antibiotics is found to be a greater contributor (~10%) to the risk estimate for the individual infant (13).
- Health care practices between the US and UK differ. In the UK, it is uncommon practice to take a blood culture without starting antibiotics in an infant (one of the possible SRC recommendations). A recent survey (appendix) showed that units are implementing KP in various ways e.g. restricted to postnatal ward, variable EOS incidence rates and modified interpretations of SRC recommendations such as starting antibiotics rather than take blood culture and observe.
- 'Missed cases' are rare, particularly if we only include culture-proven cases. Using existing evidence (16) we would anticipate 5-6 culture-proven 'missed cases' across London in one year. If we consider a ratio of 6:1 for culture-negative to culture-proven, we may expect approximately 70 cases of culture-proven and negative 'missed cases'. Due to the small numbers, there will insufficient power even after a year to test for a difference between KP versus NICE units. The main purpose of this study is to report the incidence of missed cases collectively and to evaluate the wider impact of implementation of the SRC which is a change of practice and deviation from national NICE guidance.

2 STUDY QUESTION AND OBJECTIVES

1) To report the proportion of 'missed cases' in neonatal units that follow NICE vs SRC. These are infants who have suffered adverse outcomes such as admission to a hospital ward or prolonged hospital stay due to delayed or no antibiotics.
2) Test the feasibility of data collection to monitor 'missed cases' that may inform the design of a randomised controlled trial.

3 STUDY DESIGN

We will adopt a pragmatic study design that will utilise London ODN and trainee networks to conduct a regional surveillance of 'missed EOS' cases in newborn infants. We will identify a common minimum dataset that will be collected across all 26 NHS neonatal units (co-located with a maternity hospital) in London.

Time period: September 2020 - September 2021, with the possibility of ongoing surveillance.

Participants: 26 neonatal units. 12 and 14 neonatal units will be following SRC and 14 NICE guidance, respectively. The decision regarding which protocol to follow (SRC/NICE) is made by individual units and is not influenced by participation in this study. Participating units may change between protocols during the study.

Definitions: Two definitions for culture-proven early onset sepsis: isolated during the first 72 hours or isolated during the first 7 days of age (where day 1 is the date of birth). Culture-negative early onset sepsis: commences antibiotics within the first 7 postnatal days and receives at least 5 days of intravenous antibiotics or where the infant dies before completing 5 days.

Method:

3.1 STUDY OUTCOME MEASURES

3.1.1 Outcomes

Incidence of 'missed' cases with adverse outcomes in units following SRC and NICE guidance.

These are infants who receive antibiotics >24 hours of age (but ≤7 days of age) with:

EOS (defined a positive culture OR negative culture treated with 5 days of intravenous antibiotics) and any of the following:

1. Death
2. Admitted to the neonatal unit during the initial hospital episode
3. Re-admitted following discharge home
4. Stayed on the postnatal ward
5. Was discharged on paediatric outpatient parenteral antibiotic therapy (pOPAT).

3.1.2 Reported outcomes

1. Incidence of culture-proven EOS
    a. with two definitions (first 72 hours or 7 days) for case ascertainment
    b. between units following NICE versus SRC

2. Number of infants having blood cultures and given antibiotics ≤ 24 hours of age.
    a. For all eligible infants
    b. For the subset of infants initially assigned postnatal care

3. Number of infants given antibiotics between 24 and up and including 72 hours of age.
    a. For all eligible infants
    b. For the subset of infants initially assigned postnatal care

4. Length of initial hospital stay

5. Maternal and infant characteristics of all 'missed cases'.

3.2 STUDY POPULATION

3.2.1 Inclusion criteria

- All inborn livebirths ≥ 34 weeks gestation at birth.

3.2.2 Exclusion criteria

- Outborn infants.
- Infants <34 weeks gestation at birth.

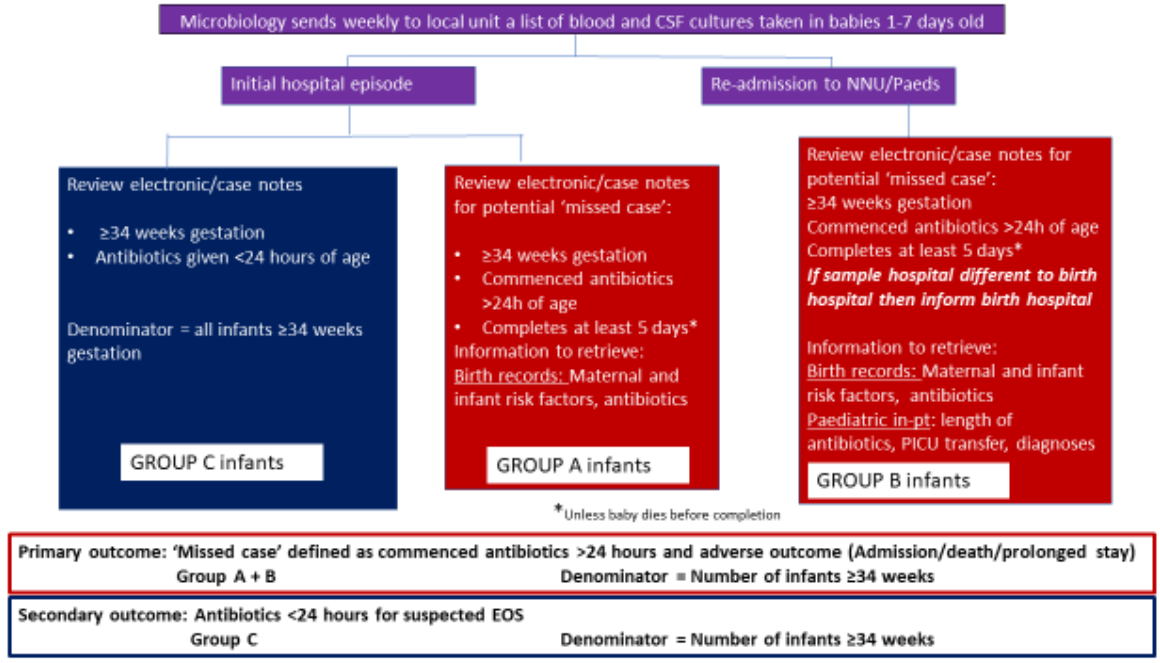
4 DATA COLLECTION

4.1 Units to collect the following information:

- Unit survey regarding practices to facilitate earlier discharge of infants and antibiotic stewardship.
- Unit protocol and EOS incidence used for KP units.
- The number of all livebirths ≥ 34 weeks per unit for the duration of the study.
- A weekly retrospective case note review will be conducted for infants who had negative or positive blood cultures taken during the first 7 postnatal days (see flow chart 1)

- A weekly retrospective case note review of blood and CSF cultures for infants taken during the first 7 postnatal days to collate the following:
    - *For each blood culture*
    - Time of each blood culture (hours of age)
    - Whether infant received empiric antibiotics and time of administration
    - Whether the infant was admitted to a neonatal unit
    - Length of stay
    - *For all culture-proven and missed cases of culture-negative EOS:*
    - Gestational age
    - Birth weight
    - Maternal risk factors (length of rupture of membrane, highest maternal antepartum temperature, GBS status, class and timing of intrapartum antibiotics)
    - Infant clinical characteristics – symptoms.
    - For KP units: EOS scores at birth and after clinical examination
    - Organism isolatedBlood stream infection, CSF, or both.
    - Length of course of antibiotics.
    - Whether this infant presented after discharge home
        - Inborn/outborn/birth hospital if outborn.

Flow chart 1



4.2 Data management

- Unit leads and trainee to retain identifiable data on NHS computers
- Anonymised data analysed centrally by study leads using a centralised spreadsheet.

5 DATA ANALYSIS

5.1 Analysis plan

- Report the incidence of 'missed cases' of EOS between units following NICE and SRC, with sub-group analyses.
- Report the incidence of culture-proven EOS using the different definitions for units following NICE, units following SRC and for Greater London as a whole.
- We will use two definitions: i) all infants ≥34 gestation including those admitted to the neonatal unit ii) excluding infants admitted to neonatal unit from labour ward.
- Report and compare the proportion of infants having blood cultures and empiric antibiotics <24 hours of age between units following NICE versus SRC.
- Report and compare the length of stay for infants having a blood culture between units following NICE versus SRC.
- Describe the maternal and infant characteristics of all 'missed cases' of EOS.

5.2 Public Health England (PHE)

PHE uses the Second Generation Surveillance System (SGSS), a national communicable disease surveillance system. SGSS collates microbiological diagnoses from laboratories across England through automated uploads and is able to provide results of positive cultures. SGSS records include information on: the laboratory, the specimen, the test method, type of infection, and patient identifiers (name, sex, DOB, NHS numbers).

Retrospective PHE data will be conducted at the end of the year to validate numbers of all culture-proven EOS cases. The strength of PHE data is the ability to capture cases that present to hospitals different to their birth hospital within the first 7 days of life, and those that are readmitted to hospitals outside of London. However, denominator data may not be restricted to ≥34 weeks due to incomplete gestation in HES.

Data linkage of EOS cases with Hospital Episode Statistics admission records (using NHS numbers) can identify the hospital where infant presented and the birth hospital.

The following information will be collated from a list of positive blood or CSF cultures taken from eligible infants < 7 days of age, born at participating hospitals:

Bacterial pathogen

Date and time of sample

Hospital where the sample was taken

Hospital episode (1, 2 or 3). If the infant was transferred to another hospital before first going home, then to consider the receiving hospital episode as the same as the transferring hospital episode.

Birth hospital

Date and time of birth

Gestation (to ensure eligibility)

Timing of antibiotic administration (from baby's time of birth to the time of first dose). If this is not possible to obtain – the age in days of administration, or whether or not antibiotics were given during that admission.

(Baby NHS number - pending approvals)

The list of participating hospitals will be shared with PHE and information on which approach was followed during each calendar month. We will also provide the total number of eligible births ≥34 weeks gestation per hospital.

This information should be able to determine the following:

1. Incidence of EOS
2. The incidence of 'missed' culture-proven EOS between the two approaches (NICE vs SRC)

5.3 Potential missing data

For infants who re-present following discharge to a hospital that was not the same as the birth hospital, the hospital informs the birth hospital as part of best practice by email NHS.net correspondence. The NeoTRIPs trainee network will play a key role to ensure missing data is minimised.

5.4 Sample size

Based on 93,790 live births ≥ 35 weeks gestation during 2018-19 (source NHS Digital) across all maternity settings within Greater London, estimate ~95,000 live births ≥ 34 weeks gestation during the study period. With an EOS incidence of 0.8/1000 livebirths (NeoTRIPs), anticipate ~80 culture-proven cases of EOS < 72 hours. Following the reported incidences of 'missed cases' of culture-proven EOS (which we align our definition with) before and after implementation of the tool by Kaiser Permenente (16), anticipate 5-6 culture-proven 'missed cases' during the study period. This will increase to approximately 60 if we include culture-negative cases.

6 REGULATORY ISSUES

6.1 Ethics approval

The opinion of the Riverside Research Ethics Committee is that this study is a service evaluation project and no formal application for approval is required. Proportionate review by Imperial College London, Joint Research Compliance Office, concluded that the study is constitutes service evaluation, is not considered research, and thus does not require review by a Research Ethics Committee.

6.2 Consent

Not applicable.

6.3 Sponsor and indemnity

Not required.

6.4 Funding

No funding is currently available for the study.

7 PUBLICATION POLICY

Results of the study will be submitted for publication in a peer reviewed journal. The manuscript will be prepared by the co-investigators and authorship will reflect the contributions.

Secondary publications and presentations will be developed to disseminate information to the neonatal community, in collaboration with the London ODN.

8 APPENDIX

8.1 London neonatal unit early onset sepsis protocols

Unit	Implemented?	If KP = take BC and observe, what is protocol?	Incidence for KP
N. central/East London			
UCLH	Yes	"Take BC and withhold antibiotics BUT take CRP, and a repeat CRP at 18-24 hours. If the CRP is significantly raised, if the baby develops signs or if the cultures are positive the baby must be commenced on antibiotics. Babies will remain on NEWTT observations until the 36 hour culture is available."	?0.5-0.8/1000 *but ongoing discussions about changing this to 0.8 though does not seem to make too much of a difference*
Royal Free	Planning to		
Barnet	Planning to		
Whipps Cross	No		
Newham	No		
Whittington	Planning to		
Royal London	No		
Homerton	No	Trialled Jan 2020- Stopped middle of Feb	
North Middlesex	No		
Queen's Romford	No		
South London			
Evelina	Yes – on PNW AND neonatal unit, on every baby + not using NICE	Take a blood culture (and no additional tests e.g. FBC, CRP) and do enhanced observations. Treat if clinical signs or blood culture is positive.	1/1000
St Georges	Yes	Take BC, hold off antibiotcs, do CRP, observe 36 hours	0.8/1000
Kingston	No		
Croydon	Planning to		
St Heliers	No		
King's College	No		
Lewisham	No		
Woolwich QE	Yes	Take BC and antibiotics	0.8/1000
Princess Royal	No		
North West London			
St Mary's	Yes	Take BC and give antibiotics	0.5/1000

Queen Charlottes	Yes	Take BC and give antibiotics	0.5/1000
Northwick Park	Yes	Take BC and hold off antibiotics, observe for 36 hours	0.8/1000
Hillingdon	Yes	Take BC and give antibiotics	0.8/1000
West Middlesex	No		
Chelsea and Westminster	No		

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