Study protocol

Antibiotic **E**xposure for suspected **N**eonatal **EA**rly-onset **S**epsis

AENEAS

For the ReSet (Reducing Safely Exposure to) Antibiotics Study Group

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1. Introduction

Background: Newborns are at risk of developing invasive bacterial infection (sepsis). Early-onset sepsis (EOS) presents during the first postnatal week, due to perinatal transmission of pathogens from the mother. Clinical signs are non-specific and infection can progress rapidly, leading to organ dysfunction, damage and potentially death. In consequence, antibiotics are started empirically when infection is suspected. Current approaches lead to substantial overtreatment as 40-200 newborns are treated with intravenous antibiotics for 1 case of proven infection. Over recent years, a number of studies have identified short and long term adverse outcomes related to antibiotic use in early life. Yet the level of antibiotic overtreatment for suspected EOS has not been quantified at a large scale, and at an international level. This step is essential to develop novel interventions to reduce antibiotic exposure in newborns, while safely treating infections.

Hypothesis: We hypothesize that substantial differences in antibiotic use during the first week of life exist across countries, and that these differences are influenced by strategies employed regarding the start of antibiotics.

Aim of the study: To characterize antibiotic overtreatment in late-preterm and term newborns with suspected early-onset sepsis across several countries

2. Methods

2.1. Design

International retrospective study

Patients: Infants born at a gestational age ≥ 34 weeks between 1.1.2014 and 31.12.2018

No specific exclusion criteria

Intervention/exposure: Intravenous antibiotics administered during the first week of life

Comparison between different networks & countries, which may reflect differences in guidelines, practices, and incidence of EOS

Outcomes:

- 1° outcome: *overtreatment index* (OI) = number of newborns treated for 1 case of proven sepsis
- 2° outcome: proportion of infants receiving antibiotics between birth and day 6
- 2° outcome: incidence of EOS
- 2° outcome: in hospital mortality overall and in infants with suspected and/or proven EOS
- 2° outcome[1]: total antibiotic exposure (= number of days of antibiotics per 1000 livebirths)
- 2° outcome[1]: proportion of infants hospitalized (for any reason) between birth and day 6

1. Non-mandatory secondary outcome, only for networks that are able to provide the data

2.2. Sample size calculation

Each network or country is considered to be a different group.

Overtreatment index (OI) = number of patients treated for 1 episode of culture proven sepsis; if 2% of newborns are treated and the incidence of EOS is 0.25/1'000 -> OI = 20/0.25 = 80

The approximate number of infants born ≥ 34 weeks who receive antibiotics is 2-3% in Switzerland and Norway, 5% in the Netherlands, 8-10% in England. The incidence of culture-proven EOS in infants born ≥ 34 weeks is 0.2-0.7‰ (Table 1 and recent literature).

Table 1

1st author	Berardi	Fjalstad	Kerste	Duvoisin	Sikias	Kuzniewicz	Mukhopadhyay	Duhdasia	Strunk
PMID	27872823	26368059	26948457	24964177	26299913	28241253	24446442	29666161	29514161
Date of publication	2016	2016	2016	2014	2014	2017	2014	2018	2018
Country	Italy	Norway	The Netherlands	Switzerland	France	USA	USA	USA	Australia
Region	Emilia-Romagna	nationwide	Blaricium	Lausanne	Île-de-France	California	Boston	Pensylvania	Perth
Population	Multicenter	Population based	Single Center	Single center	Multicenter	Health care system	Single Center	Single Center	Single Center
Gestational age (weeks)	≥34	>37	≥34	>34	>34	>34	≥36	≥36	≥35
Number of treated infants (n)	34	3964	111	222	48	1482	365	224	206
Number of treated infants (%)	1,6	2,3	5,3	1,9	3,9	2,6	5,2	3,7	8,2
EOS incidence (per 1000 livebirths)	0,48	0,54	0,95	0,26	**NA**	0,25	0,39	0,34	0,44
OI	**33**	**43**	**56**	**73**	**NA**	**104**	**133**	**109**	**186**
Use of EOS calculator	N	N	Y	N	N	Y	N	Y	Y

Sample size calculation was made by the Clinical Trial Unit of the University Hospital of Lausanne, Switzerland. The approach is to include enough newborns per network to be able to calculate the 1° outcome with an adequate level of precision. Considering that ± 1% precision around a proportion is acceptable, we would need 475 treated babies if the proportion of proven infection is 1.25% (1/80) among treated babies. We need a minimum sample size of 475*(100/2) = 23'750 babies in networks

that treat 2% of babies. This number goes down if more babies are treated and if the proportion of proven infection is lower. Therefore, we will aim at **25'000 babies per network**, which corresponds to approximatively 6 cases of proven EOS.

2.3. Ethics

The protocol has been evaluated positively by Swissethics, the Swiss national ethics committee on human research. A waiver of informed consent has been obtained for the patients included in Switzerland. Definitive approval is pending signature of a data transfer agreement between the Swiss centers. All documents will be made available to investigators from other countries in order to facilitate approval by their respective ethics committees, and data transfer agreements will be provided.

2.4. Data to be collected at each participating network

Data will be collected at each network, using an online REDCap database provided by the principal investigators. The general strategy is to collect 1) information to describe each network, 2) detailed information in cases of proven EOS (very few patients), 3) a simple set of data in cases of suspected EOS (larger number of patients), and 4) minimal data on annual number of births to calculate the denominator.

2.4.1. Network

A) A network is defined by a common strategy regarding the start of antibiotics for suspected EOS, and the possibility to include a minimum of 25'000 livebirths within the timeframe 2014-2018 in a single country.

B) Each network has to define itself by answering specific questions.
   1. Hospital- vs population-based network: A population-based network is capturing all births within a geographical area (including hospital and non-hospital based delivery units, and home births), defined by place of residence or place of birth (city, state, country)
   2. For population-based networks: define whether it is based on place of residence or place of birth, and define geographical area.
   3. For hospital-based networks: each hospital should be listed with its name and level of neonatal care (defined according to the American Academy of Pediatrics)

C) Obstetrical strategies used in the network to prevent EOS during the study period
   1. Use of specific guidelines
   2. Maternal screening for colonization with Group B Streptococcus (GBS)
   3. Intrapartum antibiotic prophylaxis in case of maternal GBS colonization
   4. Intrapartum antibiotic prophylaxis in case of maternal fever
   5. Intrapartum antibiotic prophylaxis in case of spontaneous preterm labor
   6. Intrapartum antibiotic prophylaxis in case of prolonged rupture of membranes
   7. Changes during the study period

D) Strategies used in the network regarding the start of antibiotics in newborns with suspected EOS during the study period
   1. Use of specific guidelines
   2. Use of the neonatal sepsis calculator
   3. Changes during the study period

2.4.2. Inclusion criteria

Three groups have been identified:

1) Proven EOS

A strict definition of EOS is important, as misclassification of even one patient can have an impact on the primary outcome. All 4 criteria need to be fulfilled:

I. Birth at a gestational age ≥ 34 weeks within the network

II. AND intravenous antibiotic treatment before postnatal day 7[1] for suspected EOS

III. AND positive blood and/or cerebrospinal fluid culture before postnatal day 7[1] (contaminated cultures are excluded, according to definition in 2.4.3)

IV. AND intent to treat with antibiotics for ≥ 5 days (= antibiotic treatment for ≥ 5 days or death before 5 days of treatment)

2) Suspected EOS

Patients will be included in this group if they fulfill the following criteria:

I. Birth at a gestational age ≥ 34 weeks within the network

II. AND intravenous antibiotic treatment before postnatal day 7[1]

III. AND does not fulfill the criteria for proven EOS

3) All livebirths ≥ 34 weeks

The number births at a gestational age ≥ 34 weeks within the network is recorded for each year of the study.

1. Means less than 7 calendar days after birth, the day of birth being day 0

2.4.3. Data collected in cases of suspected or proven EOS

- AENEAS_ID_Number: individual ID number for each patient. The link between AENEAS_ID_Number and patient identifiers (first name, last name) should be stored in a different file that remains at each study site
- Date and time of birth[1]: dd.mm.yyyy hh or dd.mm.yyyy
- Date and time of admission[1,2]: dd.mm.yyyy hh or dd.mm.yyyy
- Born in the network: birth in the network has to be confirmed
- Gestational age: in weeks and days
- Birth weight: in grams
- Sex: female or male

- Clinical signs: Yes or No

  Definition of clinical signs: fetal and delivery room distress, temperature instability, respiratory and cardio-circulatory symptoms (respiratory rate >60, grunting, flaring, use of accessory muscles, apnea, heart rate >160/min or <100/min, poor perfusion, mean arterial pressure < gestational age (mmHg)), neurologic symptoms (lethargy, poor tone, poor feeding, irritability, seizures), feeding intolerance, abdominal distension
- Positive blood culture: Yes or No
- Date and time of obtaining blood culture[1,3]: dd.mm.yyyy hh or dd.mm.yyyy
- Time to positivity of blood culture (hours)[2,3]: number of hours between placement of the blood culture bottle into the automated system and detection of a positive signal
- Pathogen(s) in blood culture[3]
- Contaminated blood culture[3]: Yes or No, defined as growth of bacteria usually considered as contaminants (eg diphtheroids, Micrococcus species) OR any Coagulase negative Staphylococci, OR blood cultures considered as a contamination by the responsible physician, implying that antimicrobial treatment is stopped after < 5 days (eg in the absence of a rise in CRP > 20 mg/L)
- Positive CSF culture: Yes or No
- Date and time of obtaining CSF culture[1,3]: dd.mm.yyyy hh or dd.mm.yyyy
- Pathogen(s) in CSF culture[3]
- Contaminated CSF culture: Yes or No
- Indication of antibiotics[2]: 1) Suspected infection, 2) Prophylaxis for urinary tract malformation, 3) Perioperative (surgical) prophylaxis, 4) Other prophylaxis
- Date and time of first dose of antibiotics[1]: dd.mm.yyyy hh or dd.mm.yyyy
- Date and time of last dose of antibiotics[1]: dd.mm.yyyy hh or dd.mm.yyyy
- Death: Yes or No
- Date of death: dd.mm.yyyy
- Cause of death: drop down menu 1) Directly sepsis related (eg respiratory or circulatory failure), 2) Indirectly sepsis related (eg intracerebral bleeding during coagulopathy), 3) Probably unrelated (eg malformation)
- Cause of death spec: free text to specify cause of death

1. Time (hours, hh) for networks that are able to provide the data
2. Non-mandatory secondary outcome, only for networks that are able to provide the data
3. Collected only in case of a positive culture

2.4.4. Births

Data from all infants born at a gestational age ≥ 34 weeks within the Network will be entered for each year separately.

- Number of livebirths
- Number of infants hospitalized before postnatal day 7[1]
- In-hospital mortality, includes 1) deaths in the delivery room, and in patients hospitalized within the first 168 hours 2) death before discharge or death at a postnatal age <28 days (for patients hospitalized beyond 28 days)

1. Means less than 7 calendar days after birth, the day of birth being day 0

3. Analysis plan and anticipated results

The incidence of the primary and secondary outcomes will be compared between different networks and countries. We expect that antibiotic exposure will be lower in countries/networks who treat infants based on clinical signs only, and higher in countries/networks treating infants based on risk factors and/or biomarkers. The incidence of EOS is likely to be influenced by obstetrical practices and baseline characteristics of mothers and infants delivering in each network. This may influence OI in different ways. This international retrospective study will provide valuable information regarding the current state of antibiotic exposure in late preterm and term infants and the incidence of EOS. This is an essential step towards designing and testing interventions aiming at safely reducing antibiotic overtreatment in early life.

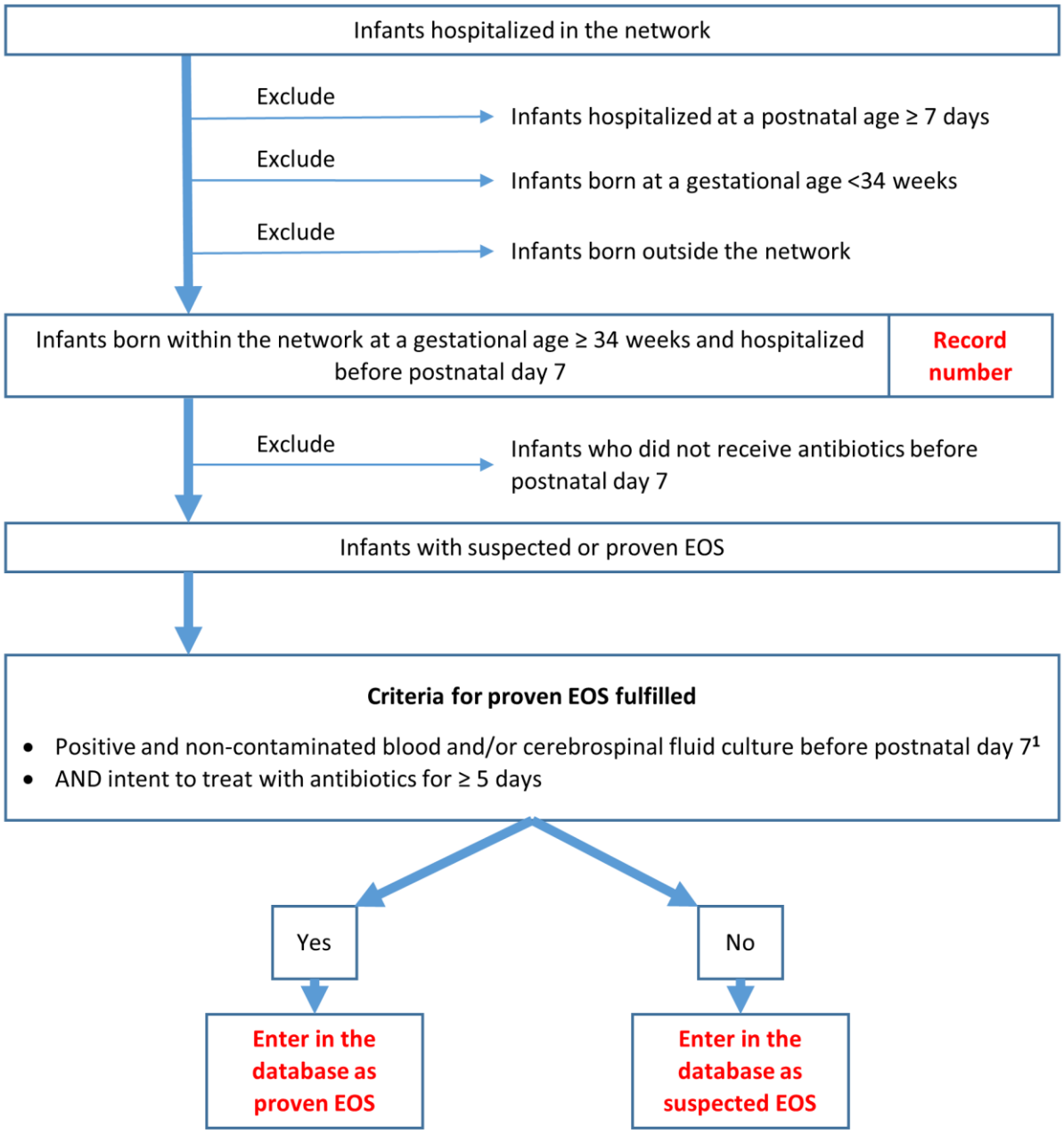
4. Potential bias and study limitations

- The 1° outcome depends both on the proportion of treated infants and the incidence of EOS. As the incidence is low, inclusion of 25'000 births will yield 5-18 cases of proven EOS per network. A strict definition of EOS is essential to reduce imprecision in the 1° outcome and variability across networks.
- Risk factors and prevention strategies influence the use of antibiotics and the incidence of EOS, potentially modifying OI in different directions. In particular, the absence of data on administration of intrapartum antibiotics to the mother is a limitation, but we believe that it is too difficult to collect reliably in a retrospective study, even in centers with clinical information systems. Instead, we will collect information on the obstetrical strategies used in each network to prevent EOS, and on the strategies used to decide when to start antibiotics for suspected EOS.
- Population-based data is preferable to hospital-based data to describe antibiotic treatment and overtreatment in a defined population. However, it is very difficult to obtain retrospectively in many countries. For feasibility reasons, we will include networks that can provide population or hospital-

based data. To take this bias into account, we will collect information describing each network. The inborn status of each included patient will be confirmed.

- Collecting data on safety outcomes is challenging, because proven EOS is rare, and adverse events due to EOS are even more rare. This is a limitation of our study. Classically, people have looked at mortality and rehospitalisation during the first week or month for suspected infection (a marker of potentially missed infections). The vast majority of newborns that die from sepsis die within 72h of onset of infection. Mortality data will be collected only for in-hospital mortality (defined in 2.4.5). Another (yet imperfect) surrogate of safety will be timing of antibiotic treatment, as it is safer to treat early. We will not collect data on rehospitalization or mortality at one month. We may look at overall neonatal mortality data obtained from national statistics.
- Practices are changing towards reducing antibiotic exposure with implementation of new guidelines or tools (neonatal sepsis calculator) or use of biomarkers (PCT)

5. Proposed flow chart for the identification of cases of suspected and proven EOS



1. Data extraction form the laboratory of microbiology can be helpful

6. References

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