Reducing the prescription of antibiotics in newborn infants suspected for having an early onset sepsis.

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Ethical review	Approved WMO
Status	Recruiting
Health condition type	Bacterial infectious disorders
Study type	Observational invasive

Summary

ID

NL-OMON31252

Source
ToetsingOnline

Brief title
Reducing Antibiotic Prescription / RAP

Condition

- Bacterial infectious disorders
- Neonatal and perinatal conditions

Synonym
Early Onset Sepsis, Infection

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Cytokine, Diagnosis, Neonatal, Sepsis

Outcome measures

Primary outcome

Primary outcome: proven EOS

Primary parameters: cytokine levels direct post partum (umbilical cord and infant), 4 hours post partum, 24 hours post partum and 48 hours post partum.

Secondary outcome

Secundary outcome: 1.) Proven EOS, 2.) Clinical EOS, 3.) Suspected EOS but afterwards no EOS and 4.) No EOS and never suspected for an EOS.

Secundary parameters:

CRP

Gestational age

Birth weight

Gender

Number of previous pregnancies

Parity

Route of delivery

Antibiotic usage mother ante partum

Corticosteroid usage mother

Duration of rupture of membranes

Body temperature mother

Temperature delivery room

Epidural anesthesia mother

CTG

Umbilical cord pH

Meconium aspiration

Amnionitis

Intracranial bleeding

Respiratory problems

Circulatory problems

Neurological problems

Gastro-intestinal problems

Pathogen of Early Onset Sepsis

Antibiotic prescription infants (duration & type)

Outcome

Study description

Background summary

Due to suspected Early Onset Sepsis (EOS) newborn infants receive frequently antibiotics which have several side effects. EOS, defined as a sepsis starting within the first 2 days of life, is a severe and life-threatening disease. The mortality when untreated is around 100%. The first clinical symptoms of a sepsis are non-specific and may be subtle. The presence or absence of maternal risk factors like maternal fever urinary tract infection, chorioamnionitis and prolonged rupture of membranes may be related to EOS, but do not predict the occurrence of an EOS.

Common laboratory parameters are not sensitive enough to predict or exclude the diagnosis of EOS (Fowlie 1998). The golden standard to detect a neonatal sepsis is a blood culture. A positive blood culture is a definite proof of infection,

a negative blood culture has a high negative predictive value (Kaiser 2002). The result of a blood culture is definite only after 48-72 hours. Given the difficulty of a clinical diagnosis of EOS, potential fatal consequences of delayed treatment and the slow result of the blood culture, immediately starting antibiotic therapy is the recommended approach in all infants with suspected EOS. This approach will cause, in retrospect, *unnecessary* treatment in many infants. All these infants are treated with broad spectrum antibiotics for at least 2-3 days. These antibiotics are given intravenously and require that the infant is admitted at a pediatric ward.

The wide-spread use of antibiotics has drawbacks. It will lead to the emergence of resistant bacteria in the NICU (De Man 2000). In the newborn itself it may lead to an abnormal colonization (of the gastro-intestinal tract), development of resistant bacteria, and potentially to a higher incidence of yeast infections during the newborn period (Fanaro 2003, Saiman 2000). Although there is large variation in the incidence of multiresistant bacteria between several countries, the incidence has increased the previous decades and the use of antibiotics is considered as a risk factor (Quinn 1994, Burwen 1994, Asensio 2000). Restriction of the use of antibiotics can lead to a reduction of antibiotic resistant micro-organisms (White 1997, Seppala 1997).

Since the 90s promising studies with cytokines, especially IL-6 (Buck 1994, De Bont 1994, Kuster 1998, Kallman 1999, Mehr 2001, Gonzales 2003, Verboon-Maciolek 2006, Ng 2006), IL-8 (Franz 1999, Franz 2001, Nupponen 2001, Mehr 2001, Krueger 2001, Santana 2001, Franz 2004, Verboon-Maciolek 2006), IL-10 (Ng 2003, Ng 2006) and TNF-α (De Bont 1994, Ng 1997, Silveira 1999, Dollner 2001, Ng 2003), were published. The sensitivity of a single cytokine measurement direct post partum for the diagnosis of an EOS was higher than the commonly used diagnostic tests such as C-reactive protein (CRP) and white blood cell (WBC) count. However, most of the studies were limited to term infants and had a relatively small sample size. Franz et al (2004) described in a multi center randomized intervention study that with an extra IL-8 measurement directly after birth the use of antibiotics for EOS was reduced from 50% to 36% in infants suspected for an EOS.

Newborn infants have often one or more risk factors for an infection whereas in only a few infants a sepsis occurs. E.g., only one of the 100 infants who are colonized by a Group B Streptococcus (GBS) develops a GBS-sepsis. It is possible that a genetic susceptibility for EOS exists, i.e. a DNA-polymorphism, rendering some patients at risk for EOS.

Study objective

Our preliminary data shows that the prescription rate of antibiotics for suspected EOS versus blood culture proven EOS was high. We aim to develop a new diagnostic model to reduce unnecessary antibiotic treatment which can be tested in the near future.

Reducing the prescription of parenteral antibiotic therapy has several benefits for the individual infant and the neonatal intensive care unit as a whole. Antibiotic treatment induces altered colonization patterns and overgrowth of fungal and gram negative micro-organisms might occur. These changes in colonization render newborns treated with antibiotics more susceptible for gram negative and fungal infections. Broad spectrum antibiotics might select resistant micro-organisms in the NICU. Decreasing unnecessary antibiotic treatment in preterm and term infants could reduce the incidence of late onset bacterial and fungal sepsis and reduce the rates of outbreaks with multi resistant bacteria. When an infant has an infection with a (multi) resistant bacteria it has - apart from clinical consequences - logistic consequences: Intensive care wards are closed in order to reduce the risk of transmission of these multi resistant bacteria.

Due to prevention of unnecessary use of parenteral antibiotics in term infants, these infants will not be admitted at a pediatric ward and not be separated from their parents, which is an emotional and economic profit.

Study design

Non-therapeutic observational study.

1.) During a three year period infants born in participating hospitals and admitted to a pediatric or maternity ward in whom an EOS cannot be excluded will be included in this study. Direct post partum blood will be collected from cord blood (NS) and in blood taken for clinical purpose (T1) for cytokine measurements. Four hours post partum (T2), 24 hours post partum (T3) and 48 hours post partum (T4) the cytokine measurements will be repeated when blood is taken for clinical diagnostics. CRP will also be measured from the blood taken direct post partum, 24 hours post partum and 48 hours post partum. The cytokines and CRP measurements will not have influence on the antibiotic therapy. Retrospectively the course of the cytokines will be analyzed with the results of the blood culture and the clinical course. As outcome there will be 1.) proven EOS (positive blood culture), 2.) clinical EOS (sick, but negative blood culture) 3.) No EOS but suspected EOS direct post partum, 4.) No EOS. Potential confounders and clinical parameters of the mother and infant will be registered to determine their influence on the course of cytokines.
In addition, umbilical cord blood will be analyzed for DNA polymorphism, putatively involved in EOS.

If serum remains this serum will be kept anonymously for usage in a later stage for improving reference values of diagnostic tests in newborn infants.

2.) Twenty newborn infants who will be admitted direct post partum to a pediatric ward for glucose measurements and who are not suspected for an EOS will be included. Cytokine levels will be measured in cord blood and in blood taken for glucose controls direct post partum, 4 hours post partum, 24 hours

post partum and 48 hours post partum.

Study burden and risks

This research needs 0.2 ml blood on four different moments from the infant. On these moments blood is already taken on clinical grounds. The blood sample will be obtained from a central line, or via vena/ capillary puncture: in total 0.8 ml extra blood will be taken, which has no consequences for the newborn infant.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Children (2-11 years)

Inclusion criteria

1.) A newborn infant who is admitted to a pediatric or to a maternity ward and in whom an EOS cannot be excluded.;2.) A newborn infant who is admitted to a pediatric ward for glucose

controls and who is not suspected for an EOS.

Exclusion criteria

1a.) Newborn infant older than 6 hours.;2a.) Newborn infant older than 6 hours.
2b.) Newborn infant suspected for an EOS.

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	03-01-2008
Enrollment:	920
Type:	Actual

Ethics review

Approved WMO

Date:	12-10-2007
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL17658.042.07