Immunogenetic, pharmacological and neurodevelopmental aspects of nosocomial sepsis and meningitis in preterm infants.

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1. To identify and specify bacteria by using RT-PCR on blood and cerebrospinal fluid (CSF) in preterm infants, having nosocomial sepsis and meningitis.2. To compare RT-PCR (see aim 1) with the gold standard bacterial culture in preterm infants,...

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

Summary

ID

NL-OMON39135

Source
ToetsingOnline

Brief title
Preterms with sepsis: immunology, treatment and long term sequelae.

Condition

- Bacterial infectious disorders

Synonym
blood stream infection, sepsis

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum

Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Immunology, Pharmacology, preterm, sepsis/meningitis

Outcome measures

Primary outcome

1. Association of RT-PCR compared to culture (blood, CSF) with relation to bacterial detection (time till result, at which bacterial load does the culture become positive)

2. Immune response of the infant in relation to bacterial type and load in blood and CSF

3. Immune response of the infant in relation to specific polymorphisms

4. Association between plasma antibiotic concentrations and pharmacodynamic effects (clinical improvement, decrease in C-reactive protein, decrease in bacterial load in blood and/or CSF)

5. Study of specific co-variates (including polymorphisms) which influence pharmacokinetics and pharmacodynamics

Main study parameters/endpoints:

1. Cerebral perfusion patterns in preterm infants during (suspected) nosocomial sepsis/ meningitis (during 72 hours).

2. aEEG background patterns and presence of seizure activity in preterms during (suspected) sepsis/ meningitis (during 72 hours).

3. Development of white matter injury or cerebral hemorrhage following a confirmed bloodstream infection, related to microorganism (confirmed by

bloodculture or PCR) and/or cytokine response.

4. Neuropsychodevelopmental outcome at two years of life (corrected for prematurity).

Secondary outcome

Neuropsychological development during the first 2 years, and growth and body composition of infants who suffered a neonatal sepsis or meningitis

Study description

Background summary

Nosocomial sepsis is a major contributor to risk of death, poor neurodevelopment and growth impairment in preterm and small for gestational age (SGA) infants. The immunological basis for the increased susceptibility to severe bacterial infections in preterm infants is only partially understood. Their immature innate immune system is characterized by decreased neutrophil and monocyte activity, reduced concentrations of complement factors, and decreased production of pro-inflammatory cytokines. Furthermore, toll-like receptors (TLRs) may play an important role in recognition of microbes. Reduced expression of the TLRs surface proteins may impair VLBW infants to boost initial immune response and contribute to the susceptibility to infections with bacteria. Also, genetic variation in the innate immune system of the host may play a role in susceptibility to infection or poor outcome after infection. It is postulated that exposure of the preterm brain to inflammatory mediators during infectious episodes contributes to brain injury and poor neuropsychodevelopmental outcome, including cerebral palsy.
For the analysis of bacterial sepsis, bacterial blood culture is the gold standard for many years. Broad spectrum antibiotic therapy is given while awaiting the 48 hours preliminary result of culture. A real-time PCR with high specificity and sensitivity is currently available to identify and quantify bacterial DNA, which is a rapid diagnostic tool that even can be used to identify pathogens which are under the detection limit by culture techniques.
Most currently recommended dosing guidelines for antibiotics in neonates are not based on the level of evidence. Future prospective studies are warranted in order to improve our current knowledge on early detection of neonatal sepsis and treatment, particularly drug dosing and drug safety in preterm infants. This may not only lead to a decrease in short-term morbidity and mortality, but may also improve long-term future outcome substantially.

Supplement 27-09-2013:
Sepsis also has adverse effects on autoregulation and possibly on cerebral activity. This combined with the effects of inflammatory mediators may cause white matter injury and thereby influence longterm outcome.

Study objective

1. To identify and specify bacteria by using RT-PCR on blood and cerebrospinal fluid (CSF) in preterm infants, having nosocomial sepsis and meningitis.
2. To compare RT-PCR (see aim 1) with the gold standard bacterial culture in preterm infants, having nosocomial sepsis and meningitis.
3. To study the inflammatory response (cytokines, TLR's) of preterm infants in relation to different bacteria and bacterial load, measured by RT-PCR, and in relation to different polymorphisms.
4. To study antibiotic concentrations in plasma of preterm infants having nosocomial sepsis and/or meningitis, and to describe the relationships between plasma concentration and pharmacodynamic effects.
5. To investigate the influence of specific co-variates on pharmacodynamics and pharmacokinetics of antibiotics in preterm infants.
6. To investigate the association between nosocomial sepsis and meningitis on neuropsychodevelopmental outcome during the first 2 years of life, and growth and body composition in preterm infants.

Supplement 27-09-2013:
Objectives:
1. To investigate the changes in cerebral perfusion/ oxygenation during nosocomial sepsis/ meningitis in preterm infants.
2. To investigate the effect of nosocomial sepsis/ meningitis in preterm infants on electroencephalographic background patterns and seizure activity.
3. To relate changes in the cerebral perfusion during nosocomial sepsis/ meningitis in preterm infants to ultrasound findings (normal or abnormal).
4. To relate changes in ultrasound examination to microorganisms (by bloodculture or PCR) and/or cytokine release.
5. To relate neuropsychodevelopmental outcome at two years of age (corrected for prematurity) to changes in cerebral perfusion and the encephalographic background patterns and/ or epileptic activity in preterm infants with established nosocomial sepsis/ meningitis.

Study design

Prospective observational study during a consisting intervention.

Study burden and risks

Each participant will be studied for 2 days after the onset of the sepsis/meningitis. At fixed time points (8 in number) blood will be collected

from an indwelling arterial catheter, which is routinely inserted during sepsis/meningitis. In rare cases in which an arterial catheter is not inserted, blood will be collected by puncture, which will be combined with punctures for routine treatment if possible. In total, a minimum of 1.9 mL and a maximum of 3.9 mL of blood per patient will be collected, depending on which antibiotics are administered to the patient. Cerebrospinal fluid (CSF) is collected by lumbar puncture as a part of routine sepsis-workup. For the study 0.2 mL of extra CSF is collected during the same procedure. Buccal mucosa scraping is performed once for detection of genetic polymorphisms. After discharge from the department follow up is performed according to routine follow up of preterms in the VU University Medical Center.

Addendum 19/10/2012: to validate the PCR's on bacteria we want to use residual material from patients who are or were in the ICU Neonatology and do not participate in the study. This material (blood / CSF) is no longer used for clinical purposes and is normally discarded.

Supplement 27-09-2013:
During 72 hours 6 needle-elctrodes will be placed subcutaneously on the head and a non-invasive sensor will be placed on the forehead. This will be a minimal burden for the patient and induce no risk.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Children (2-11 years)

Inclusion criteria

1. written and informed consent from both parents or legal guardian.
2. gestational age < 32 weeks or birth weight < 1,500 gram.
3. suspicion of nosocomial blood stream infection (BSI) and/or meningitis.
Nosocomial BSI is defined according to local definitions for BSI
(Research protocol, Appendix, figure 1).

Exclusion criteria

1. syndromal or chromosomal abnormalities.
2. congenital metabolic disease.

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	01-03-2009
Enrollment:	280
Type:	Actual

Ethics review

Approved WMO Date:	09-07-2008
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-11-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-01-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	NL22434.029.08