Effect of procalcitonin-guided decision making on duration of antibiotic therapy in suspected early-onset neonatal sepsis: multicenter prospective randomized intervention study

Published: 22-06-2009
Last updated: 06-05-2024

1. To decrease the proportion of infants treated with antibiotics for > 48 - 72 hours with possible or unlikely infection. 2. To reduce the duration of antibiotic therapy

Ethical review	Not approved
Status	Will not start
Health condition type	Bacterial infectious disorders
Study type	Interventional

Summary

ID

NL-OMON33535

Source
ToetsingOnline

Brief title
NeoPInS

Condition

- Bacterial infectious disorders

Synonym
infection in newborns

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: Brahms,de firma Brahms financiert de procalcitonine bepalingen

Intervention

Keyword: neonatal infection, procalcitonin

Outcome measures

Primary outcome

Primary endpoint is the proportion of infants treated with antibiotics for > 48

- 72 hours (efficacy of study intervention).

Co-primary endpoint is the absolute reduction of the duration of antibiotic

therapy (quantitative version of the primary endpoint for estimation of effect

size).

Secondary outcome

Safety endpoints: mortality, duration of hospitalization, recurrence of

infection necessitating antibiotic therapy within the first month of life.

Study description

Background summary

Neonatal infections are important causes of morbidity and mortalitiy in the neonatal period. The diagnosis of neonatal infections is difficult, because clinical symptoms are often non specific and can be absent when the neonate has become infected just before birth. Current laboratory tests have low positive and negative predictive values. A relatively new marker for infections in blood is procalcitonin (PCT). Multiple observational studies in neonates have been performed on the use of PCT as a parameter for bacterial infection in neonates. Compared to the conventional marker in blood for infection, CRP, sensitivity

and specificity of PCT are higher in neonatal infection. Pitfall in the use of PCT during the first days of life is the use of age-specific reference values in these neonates. The value of PCT as a marker for bacterial infection in neonates is complicated by a physiological increase of PCT during the first 3 days of life. After a peak value that is reached after 18-30 hours, PCT decreases and normalizes to reference values comparable to adults after 42-48 hours.

Based on data generated by a pilot single center intervention study in Switzerland on the use of PCT in neonatal infection, it was concluded that 1. PCT analysis is feasible in newborn infants 2. serial PCT determinations allowed to significantly reduce the duration of empiric antibiotic therapy in term and near-term infants with suspected early-onset sepsis, 3. the age-dependent PCT nomogram with a maximal threshold value of 10 ng/ml seemed to be reasonable, and 4. a multi-center study will be required to test the reliability of a PCT-based strategy in a larger cohort of neonates

To shorten the duration of administration of empiric parenteral antibiotics is important. Because of the high risk of not treating neonates with a bacterial infection, all neonates with any suspicion of infection are being treated for 7 days. Because the treatment consists of intravenously administered antibiotics, this means admission to the hospital for the neonate with separation of mother and child during these important first days of life.

Study objective

1. To decrease the proportion of infants treated with antibiotics for > 48 - 72 hours with possible or unlikely infection.
2. To reduce the duration of antibiotic therapy

Study design

A multi-center, prospective, open, randomized controlled intervention study in which serial PCT measurements will guide the treatment with intravenously administered antibiotics of neonates suspected of early-onset neonatal infection. Based on data of a pilot study in 120 neonates (60 neonates the PCT intervention arm and 60 neonates in the control arm) a poweranalysis has been performed. To answer the objectives of this study, with a power assumption of 80% and a duration of hospitalization in the pilot study of 5,4 days, 400 neonates should be enrolled.

Randomization:
Randomization to the standard therapy group (duration of intravenously administration of antibiotics based on the judgement of the attending physician), or the PCT intervention group (duration of intravenously administration of antibiotics based on serial measurements of PCT) will be done

per center as a block by opening blinded envelopes.

Laboratory parameters:
In both groups at t = 0 hours (= start antibiotics), t = 18-36 hours , t = 36-72 hours en 72-120 hours CRP and hematology screen will be done. In the PCT groep the measurement of PCT will be added, and one extra time-point (t = 12) will be added.

Based on riskfactors, patient characteristics and results from conventional laboratory parameters, patients will be divided into 4 groups: 1. infection proven, 2. infection probably, 3. infection possible, 4. infection unlikely.
The duration of antibiotic therapy in the standard group is based on the attending physician*s assessment of the probability of infection during hospitalisation: in group 1 and 2 patients, antibiotics are given for 7 - 21 days, in group 3 patients for 5 - 7 days and in group 4 patients for 2 - 3 days. In the PCT group, if infection is considered to be unlikely or possible, antibiotic therapy is discontinued when two consecutive PCT values are within the normal range. Antibiotic therapy can be continued despite fulfilled PCT criteria at the discretion of the attending physician.

Intervention

The duration of antibiotic therapy in the standard group is based on the attending physician*s assessment of the probability of infection during hospitalisation: in group 1 and 2 patients, antibiotics are given for 7 - 21 days, in group 3 patients for 5 - 7 days and in group 4 patients for 2 - 3 days. In the PCT group, if infection is considered to be unlikely or possible, antibiotic therapy is discontinued when two consecutive PCT values are within the normal range. Antibiotic therapy can be continued despite fulfilled PCT criteria at the discretion of the attending physician.

Study burden and risks

The burden is minimal, because only one extra time point for blood drawing will be done in the intervention group. For the other time points and for the children in the standard group no additional diagnostic procedures are needed. The additional burden consists of a couple of extra blood drops during routine bloodsampling.

The estimated risk is low. There is a low risk on discontinuing antibiotic treatment too early, resulting in the development of a neonatal infection with its morbidity and mortality.
Neonates will be divided in high and low risk neonates (groups 1 and 2 vs 3 and 4). Only in low risk neonates antibiotic treatment will be discontinued on the basis of PCT. In addition, a high maximal reference value will be applied to add extra safety.

Based on follow-up data of the pilot study as mentioned earlier, in 120 neonates no mortality was observed. In two children antibiotic treatment was restarted. In one neonate because of respiratory insufficiency, this neonate was born at a gestational age of 35 6/7 weeks with a clinical surfactant deficiency. The other neonate was restarted on antibiotic treatment because of Ecoli found in tracheal aspirate.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Children (2-11 years)

Inclusion criteria

Gestational age 34 weeks or more
3 or less days old
Suspected infection requiring empiric antibiotic therapy
Parental informed consent

Exclusion criteria

Surgery during the first week of life
Severe Malformations

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Diagnostic

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	200
Type:	Anticipated

Ethics review

Not approved

Date:	22-06-2009
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

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	NL24972.000.09