INTRAVENOUS-TO-ORAL ANTIBIOTIC SWITCH THERAPY FOR SUSPECTED NEONATAL BACTERIAL INFECTIONS: ;CLINICAL EFFICACY, SAFETY AND COST-EFFECTIVENESS

Published: 16-02-2017
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PRIMARY* To demonstrate the non-inferiority of intravenous-to-oral antibiotic switch therapy in clinically stable neonates with probable bacterial infection compared to a complete course of intravenous antibiotic therapySECONDARY* To describe the...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Bacterial infectious disorders
Study type	Interventional

Summary

ID

NL-OMON47298

Source
ToetsingOnline

Brief title
RAIN study

Condition

- Bacterial infectious disorders

Synonym
neonatal infection

Research involving
Human

Sponsors and support

Primary sponsor: Sint Franciscus Gasthuis
Source(s) of monetary or material Support: ZonMw Goed Gebruik Geneesmiddelen,Innovatiefonds zorgverzekeraars

Intervention

Keyword: antibiotic therapy, antimicrobial stewardship, infection, neonate

Outcome measures

Primary outcome

Bacterial (re)-infection within 28 days after finishing of antimicrobial

therapy ((defined as clinical signs and symptoms of bacterial infection and

fever (> 38.0 deg C) or undertemperature (< 36.0 deg C) and elevated

inflammatory parameters (CRP, PCT) and need for prolonged (> 48 h) antibiotic

treatment)).

Secondary outcome

* duration of hospitalization

* percentage re-admission

* total costs and cost-effectiveness

* clinical side effects of antibiotics

* pharmacokinetic profile of oral amoxicillin

* pharmacokinetic profile of oral clavulanic acid

* quality of life (painful procedures; breastfeeding; sleep quality;

gastro-intestinal symptoms; parental satisfaction)

* nosocomial infections

* gut microbial flora profile and antimicrobial resistance genes

Study description

Background summary

Neonates have a high antibiotic consumption because of their susceptibility for bacterial infections. Since the early diagnosis of bacterial infection in neonates is difficult, intravenous broad-spectrum antimicrobial therapy is usually started promptly after subtle symptoms. The majority of neonates become asymptomatic shortly after initiation; when infection is probable or proven by elevated inflammatory markers and/or a positive blood culture, intravenous antibiotics are administered for at least 7 days. However, for neonates blood culture has a limited sensitivity. Therefore, the majority of neonates with probable infection are treated for a prolonged time with intravenous broad-spectrum antimicrobial therapy.
In older children, intravenous antibiotics are often changed to oral antibiotics after cessation of symptoms and decreasing inflammatory parameters. This is not yet widely practised in neonates because of uncertainties in pharmacokinetics. Two explorative small studies from France and Italy into neonatal antibiotic switch therapy suggest that follow-up treatment with an oral antibiotic is promising; but the non-inferiority and safety was not yet properly addressed. Neonatal switch therapy, if proven to be safe and efficacious, would have a major impact on neonatal well-being, mother-to-child bonding and moreover costs.

Study objective

PRIMARY

* To demonstrate the non-inferiority of intravenous-to-oral antibiotic switch therapy in clinically stable neonates with probable bacterial infection compared to a complete course of intravenous antibiotic therapy

SECONDARY

* To describe the pharmacokinetics of oral amoxicillin/clavulanic acid in neonates
* To quantify the cost-effectiveness of oral antimicrobial switch therapy in neonates
* To study antimicrobial resistance and modification of the gut microbiome in relation to type and delivery of antibiotics.

Study design

Multicenter prospective randomized controlled non-inferiority trial.

Intervention

After informed consent has been obtained, the neonate will be allocated by a web-based randomisation tool to:

1. continue intravenous antimicrobial therapy (broad-spectrum, preferably according to the national protocol)
or
2. oral switch therapy to amoxicillin/clavulanic acid 4:1 suspension 25 mg/kg t.i.d..

Study burden and risks

If oral switch therapy in neonates is effective and safe, the implementation will have huge effects neonatal well-being (iv-drip cannulas do not need to be replaced), mother to child binding, and will finally also have huge effects on costs (saving 3-6 admission days per neonate). Safety is important; the risks will be minimalized by identification of subjects without risk factors and close follow-up. Moreover, serum levels of antibiotics will be measured. Painful procedures in the experimental group will be prevented as much as possible and do in general not exceed the number of painful procedures in the control group (1-2 x serum level of antibiotics vs. regular need for new iv-cannula*s).

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Children (2-11 years)

Inclusion criteria

Neonates, * 35+0 weeks of gestation, 0-28 days old, * 2.0 kg. ;* probable bacterial infection (clinical symptoms and/or maternal risk factors and elevated inflammatory parameters (elevated CRP and/or elevated PCT according to age-related normogram7) for which empiric broad-spectrum antimicrobial treatment was initiated and needs to be continued for > 48 hours at the discretion of the treating physician
* reassuring level and trends of inflammatory parameters 48-72 hours after initiation of antimicrobial treatment
* clinically stable
* tolerates oral feeding and/or liquids without overt vomiting
* written informed consent of parents or legal representatives;For the specific PK-study, neonates also can participate when they fulfill the inclusion criteria and are given oral amoxicillin/clavulanic acid not for this specific trial but for another reason.

Exclusion criteria

* proven bloodstream infection
* absence of blood culture (i.e. no blood culture taken)
* severe localized infection such as meningitis, osteomyelitis, necrotizing enterocolitis (except pneumonia and urinary tract infection)
* severe clinical sepsis on admission (compromised circulation; need for mechanical ventilation)
* known (maternal) colonization with resistant bacteria such as MRSA, ESBL-producing bacteria
* continuous need for central venous line (umbilical venous catheter, PICC)
* severe hyperbilirubinaemia with need for phototherapy
* clinicians* decision to continue with intravenous antibiotics because of other reasons
* parents* inability to administer medication because of social reasons or language difficulties

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Single blinded (masking used)
Control:	Active
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	08-02-2018
Enrollment:	550
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Amoxicilline / clavulaanzuur
Generic name:	Co-amoxiclav
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	16-02-2017
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	23-06-2017
Application type:	First submission

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	01-09-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	24-01-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-02-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	24-05-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	14-06-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-02-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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
EudraCT	EUCTR2016-004447-36-NL
ClinicalTrials.gov	NCT03247920
CCMO	NL51888.078.16

Study results

Date completed:	14-06-2021
Actual enrolment:	510