Procalcitonin to guide obtaining bloodcultures in the ICU.

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The trial aims to investigate whether procalcitonin measurements can reduce the amount of blood cultures in the ICU safely and cost-effectively.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Hepatobiliary neoplasms malignant and unspecified
Study type	Observational non invasive

Summary

ID

NL-OMON39326

Source
ToetsingOnline

Brief title
ProBIC

Condition

- Hepatobiliary neoplasms malignant and unspecified

Synonym
Bloodstream infection, sepsis.

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Bloodcultures, ICU, Procalcitonin

Outcome measures

Primary outcome

1. Safety, expressed as mortality at day 28 and 90, with a mortality difference not exceeding a between groups difference of 10% by non-inferiority analysis.

2. Cost-effectiveness, expressed in euro, calculated by deducting costs of procalcitonine testing from saved blood cultures compared with standard treatment spending on blood cultures in the control group.

Secondary outcome

1. Length of stay on the ICU.

2. Length of hospital stay.

3. Positive predictive value (PPV), negative predictive value (NPV), sensitivity and specificity of procalcitonin for predicting microbial bloodstream infections.

Study description

Background summary

In health care costs have increased in total over the past decades. To cite from the 2009 report on health care related costs in the Netherlands as published by the Central Bureau of Statistics (CBS): *In de periode 1972-2008 zijn de uitgaven aan zorg jaarlijks met gemiddeld 7,3 procent gegroeid: van 6,5 miljard euro in 1972 tot 79,1 miljard euro in 2008. Dat is meer dan een verelfvoudiging. Gecorrigeerd voor prijsveranderingen zijn de uitgaven aan zorg in deze periode jaarlijks met gemiddeld 2,9 procent toegenomen. Ook als percentage van het bruto binnenlands product (bbp) zijn de uitgaven aan zorg gestegen, van 8,7 procent in 1972 naar13,3 procent in 2008. Deze toename is echter voor het grootste deel toe te rekenen aan het verschil in

prijsontwikkeling tussen het bbp en de zorguitgaven. De prijsontwikkeling van de uitgaven aan zorg lag meestal hoger dan die van het bbp*.

The Netherlands has been a country well known for a prudent use of resources. For many years the Netherlands is being ranked as one of the lowest antibiotics consuming countries or even the lowest use of antibiotics in Europe . In their 2008 publication of Nethmap , the Stichting Werkgroep Antibiotica Beleid (SWAB), a Dutch Foundation of the Working Party on Antibiotic Policy, in collaboration with the RIVM, the National Institute for Public Health and the Environment of the Netherlands, published a comprehensive and extensive insight into emerging trends in antibiotic resistance and ecological pressure. In short, pressures and resistance is on the rise in the Netherlands, despite its prudent selection of anti-microbial agents. Though this report did not report on economical aspects of antimicrobial usage, its European counterpart, the EMEA has published these effects since then. Their report claims that costs associated with antibiotic resistance should be estimated in the range of 1,5 billion euro per annum .
With no new antibiotics on the way and ever increasing costs for adequate health care, a quest has commenced to find new ways to deal with bacterial infection with still maintaining or (preferably) decreasing the current spending budget. One of these research pathways has lead to the study of biomarker usage to evaluate bacterial infections and antibiotic stewardship. The most studied biomarker in this respect is a novel acute phase reactant labeled procalcitonin. A biomarker specific for bacterial infections, procalcitonin has been tested to tailor antibiotic usage to individual patient need in targeted populations, like intensive care medicine, pulmonary medicine, the emergency room, pediatrics and general practice.

The precursor hormone of calcitonin is procalcitonin. This chain of 116 amino acids has now been studied in a high-sensitive format in no less than 13 randomized controlled trials. Though all these trials all studied different populations under different circumstances, there is common ground to be found amongst the results. One common result of these trials is that mortality never differed between the procalcitonin or the control groups, proving the procalcitonin algorithm intervention to be safe.

Another common result found across these published trials was a very large reduction in antibiotic usage. Even in low antibiotic usage countries in Western-Europe, like Switzerland and Denmark, savings of more than 23% (ICU) up to 77.9% (general practice) were published. Currently, two large validation trials in the Netherlands are underway , .

As these Dutch trials are underway, a new application for this novel biomarker is being described in two recent publications , . Being highly specific for bacterial infection, procalcitonin is being suggested to be used as a pretest evaluation for the far more expensive blood culture. Both these trials report that a cut-off of 0.25 ng/ml or less could save blood cultures in large

volumes. In the Dutch trial of urosepsis patients about 40% of all blood cultures could have been saved, while the Swiss trial on community acquired pneumonia patients reporting potential savings of up to 37% of all blood cultures. Both trials reported an accurate prediction of bacteriemia in their studied populations of about 96-97%. Other studies reported a negative predictive value of about 88-94%.

The Dutch study group in the Leids Universitair Medisch Centrum reported that using this regimen could save as much as US$36 per patient with urosepis when the procalcitonin assay was already paid for. The remarkable finding was further emphasized by the Swiss results who reported a similar amount in its cost-effectiveness analysis.

It is likely that such a regimen is usable and feasible on the ICU. We propose that this new application for procalcitonin be applied in a new trial to demonstrate its safety and economical effectiveness to reduce the number of blood cultures needed while still maintaining a high level of care without increased morbidity and mortality.

Study objective

The trial aims to investigate whether procalcitonin measurements can reduce the amount of blood cultures in the ICU safely and cost-effectively.

Study design

Multicenter cross-over clinical trial

All patients on the intensive care in whom the treating physician establishes a medical need for a blood culture are possible eligible for this trial.
The participating ICU*s (2 per medical center Erasmusmc and Maasstad ziekenhuis) will be stratified and randomized by treatment regimen into a control (standard of care) treatment and the PCT-guided treatment. Randomization is thus performed per cluster allocation, being an assigned ICU. All patients included into this trial and admitted on a participating unit will follow the regimen specified for that specific time period for that unit. Participating units will switch the allocated regimen after 3 months between the control (standard of care) treatment and the PCT-guided treatment. The washout period is 1 month, in which >95% of patients in the previous period has left the unit.

Study burden and risks

NVT

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Patients will need to be over the age of 18, be suffering from an assumed infection deemed clinically worthy for blood culturing.

Exclusion criteria

- Pregnancy.
- Neutropenia, defined as leukocyte count less then 0,5x10.000/L.
- Moribund patients.
- Predetermined illness with and expected death within 24 hours.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-01-2013
Enrollment:	1130
Type:	Actual

Ethics review

Approved WMO Date:	28-06-2012
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-09-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-05-2013
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
CCMO	NL38603.078.11