Observational multi-center, prospective study to develop a novel multi-parametric diagnostic model for hospitalized patients and patients on the Emergency Department presenting with lower respiratory tract infections and/ or sepsis.

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To develop a novel multi-parametric diagnostic model for the management of patients with LRTI and/or sepsis that will be based on novel pathogen- and host-related factors.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Observational invasive

Summary

ID

NL-OMON44266

Source
ToetsingOnline

Brief title
The TAILORED-treatment Study

Condition

- Other condition
- Bacterial infectious disorders
- Respiratory tract infections

Synonym

Lower Respiratory Tract Infection and Sepsis

Health condition

sepsis en virale infecties

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: Europese Unie: FP7 grant

Intervention

Keyword: diagnostic tool, low respiratory tract infection, sepsis

Outcome measures

Primary outcome

Sensitivity and specificity for a multi-parametric diagnostic model,

incorporating different pathogen- and host-related factors, in differentiating

between bacterial and viral etiology in patients with LRTI and/or sepsis

Secondary outcome

1) Diagnostic accuracy (sensitivity and specificity) of host-related individual

biomarkers, in differentiating bacterial or viral or fungal etiology from other

etiologies in patients with LRTI and/or sepsis

2) Diagnostic accuracy (sensitivity and specificity) of blood biomarkers, in

differentiating Gram positive or Gram negative or atypical etiology from other

disease etiologies in patients with LRTI and/or sepsis

3) Monitoring the temporal dynamics of blood biomarkers levels during the

course of disease in patients with LRTI and/or sepsis

4) A list of significant bacterial microbiome components that are associated

with poor or favorable clinical outcome in patients with LRTI and/or sepsis

5) Diagnostic accuracy (sensitivity and specificity) Sensitivity and specificity *70% for LC-MS/MS and LPI proteomics-based rapid detection technique in identifying pathogens in clinical samples of patients with LRTI and/or sepsis

6) A web-based application that recommends physicians with a preferred antimicrobial treatment based on patients clinical, molecular and biochemical data.

7)To define genetic mechanisms underlying the different host response patients with viral versus bacterial infection

Study description

Background summary

In the past 70 years antibiotics have served as the first line of defense against infectious diseases. However, antibiotics are only effective against bacterial infections and are not the solution for infections caused by viruses such as common colds or flu. Despite their contribution to healthcare, antibiotics are currently recognized as the most misused drugs in the world with global overuse estimated at 40%-70%, mostly due to the ineffectiveness of current diagnostic solutions to distinguish between bacterial and viral infections. Antibiotics misuse often causes preventable adverse events that impact patient care and lead to the emergence of antibiotic-resistant bacteria, one of the major threats to global health today. To address these challenges, novel technology is developed that relies on the best available detection system for differentiating between viruses and bacteria - the body*s own immune system. The technology employs a simple blood test that provides the physician, within two-hours, the information he needs to decide whether to treat the patient with antibiotics or not. This technology has been tested on over 1000 patients of different ages and diseases and was found to be highly accurate and safe. The current study is a non-interventional study and the participants do not receive any investigational drug nor any experimental examination or procedure. Therefore, the collected data in this study will not affect the diagnosis, prognosis, or treatment of the participants. Participation includes

the collection of a teaspoon of blood and collection of a specimen using a nasal swab. These procedures are common in the clinical practice and are widely performed and possess no significant risk. By participating in the study, the subjects impact the development of the novel technology, which is expected to enable a future faster and more accurate diagnosis of infectious diseases as well as more appropriate prescription of antibiotics. This will open the way to improve treatment decisions in millions of patients around the world.

Study objective

To develop a novel multi-parametric diagnostic model for the management of patients with LRTI and/or sepsis that will be based on novel pathogen- and host-related factors.

Study design

This is a prospective observational clinical study that will enroll 1200 pediatric and adult patients from Israel and The Netherlands. The study will be conducted in two stages: In stage A 900 patients will be enrolled with the aim of developing new multi-parametric diagnostic models as well as treatment algorithms, whereas Stage B is aimed at testing and validating the multi-parametric diagnostic models using a fresh cohort of 300 patients.
Participation in the study requires collecting demographic and clinical data as well as obtaining a blood sample (one serum tube and one plasma tube) and two nasal swabs. The blood samples will be used for protein- and/or RNA-based diagnostic biomarkers and host DNA screen. Nasal swabs will be used for several purposes: (i) a thorough microbiological and molecular investigation of the disease-causing agents using multiplex PCR assays in order to establish patient diagnosis; (ii) studying the respiratory microbiome of LRTI and/or sepsis patients; (iii) development of a mass spectrometry based detection technique for the identification of microbial pathogens and antimicrobial resistances. In addition, stool sampling will be collected in cases of diarrhea to assist in establishing a final diagnosis and identify Clostridium difficile infections.
In 830 patients (out of the 1200), one blood and two nasal swabs sampling at two sampling points (at inclusion and again after 3-5 days) will be performed for the purpose of gaining a better understanding of the temporal dynamics of the host-pathogen interactions.
Patients enrolled into the study will be managed according to the current standard of care (GCP) and per standard institutional procedures.
The investigated assay requires the measurement of multiple host- and pathogen related parameters that include: blood-based, protein and RNA biomarkers, respiratory microbiome, and pathogen proteomics and host DNA. The collected data will serve to develop and validate new diagnostic tools for differentiating between infection types, detection of pathogens types and their resistance to antibiotics, and a new treatment algorithm that integrates clinical, molecular and biochemical data.

A composite reference standard will be used in order to determine the diagnosis of each patient. Specifically, all the clinical, radiological, microbiological and laboratory data of each patient, will be recorded in a dedicated eCRF. Based on this data, the diagnosis of each patient will be determined by a panel of three independent pediatricians. Each physician will be blinded to the diagnosis of his peers and to the research data. In the current study, unanimous agreement between the experts (*consensus agreement*) will be considered as the true diagnosis for the purpose of computing the assay performance.
Both the clinical data (eCRFs) and research data (host biomarkers, microbiome analysis, pathogen profiling) will be uploaded to a central database that will be used to develop new multi-parametric model for LRTI and/or sepsis diagnosis.

Study burden and risks

Patients participating in the study do not receive any investigational drug nor any experimental examination or procedure. The participants are exposed to the minimal risk associated with the collection of one or two venous blood samples (Phlebotomy) and with two additional, non-invasive nasal swab samplings. The risk of standard phlebotomy may include infection, discomfort, pain or subcutaneous bleeding which may be caused by venous rupture. The risk in nasal swab sampling may include mainly discomfort or limited pain. The described procedures are very common in the clinical practice and are widely performed. In addition, the medical staff that will perform these procedures is highly qualified and experienced in performing these tests. The participants in the study are not expected to have any direct benefit following their enrollment to the study. Study results will not affect the diagnosis, prognosis, or treatment of the participants. Still, by participating in the study, the subjects contribute to the validation of the host-response based assay, which is aimed at differentiating between viral and bacterial infections, and is expected to enable a faster and more accurate diagnosis of infectious etiology as well as a more appropriate prescription of antibiotics.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)
Elderly (65 years and older)

Inclusion criteria

Patients (children and adults) who are at least 1 month old of age that attend the hospital or the ED due to suspected respiratory infections and/or sepsis (whose onset of symptoms began * 8 days prior of recruitment) or due to a non-infectious desease, will be eligible for inclusion.;-The LRTI disease group should fulfill the following criteria:
Presence of two or more of the following signs of respiratory distress:
-Tachypnea *
-(Chest)Cough
-Nasal flaring
-Retractions
-Rales
-Expiratory wheeze and/or decreased breath sounds;* (WHO age- specific criteria for tachypnea wil be used: a respiratory rate of more than 50 breaths per minute in infants 2-12 months of age; more than 40 breaths per minute in children 1-5 years of age; and more than 30 breaths in children older than 5 years);-The Sepsis group should fulfill the following criteria:
Sepsis will be defined as a combination of a systemic inflammatory response syndrome (SIRS) due to infectious agent. SIRS will be determined according to published criteria (the International Sepsis Definitions Conference, 2001) based on
-Heart rate (higher than 90/min)
-Respiratory rate (higher than 20/min or PaCO2 lower than 32 mmHg)
-Core body temperature (higher than 38°C or lower than 36°C)

-White blood cell count (higher than 12,000 cells/ µl or lower than 4,000/ µl);SIRS is defined as at least two of the above criteria, one of wich must be abnormal temperature or white blood cell count.;-Children with sepsis
As normal physiological variables are different for children, the SIRS criteria are defined seperately for children under 18. SIRS criteria per age group are defined according to guidelines of the International Pediatric Sepsis Consensus Conference 2005 (Pediatric Critical care Medicine , 6(1); 2-8, 2005) Protocol pag. 29-30 The criteria are also based on heart rate, respiratory rate, core body temperature and white blood cell count.
In children SIRS is also defined as at least two of the above criteria, one of wich must be abnormal temperature or white blood cell count.;The non-infectious disease group will include:
-Patients with a non-infectious disease
The non-infectious diseases group will be composed of patients that had other diseases that are not considered as infectious. These patients are expected to demonstrate inflammatory processes that are not infection-orginated (e.g. acute myocardial infarction, bone fractures ect.)
Children in this group can only be included when blood sampling for this study can be combined with blood sampling as part of standard of care.

Exclusion criteria

-An episode of febrile infection during the past 3 weeks
-A proven or suspected human immunodeficiency virus (HIV)-1, hepatitis B virus (HBV), or hepatitis C virus (HCV) infection
-Presence of obvious alternative causes of respiratory distress, such as heart failure or pneumothorax
- Patiënten met een nosocomiale LRTI (developed > 3days after hospitalization)
-Post-transplant patients
-Congenital immune deficiency (CID)
-Active hematological malignancy
-Current treatment with immune-suppressive or immune-modulating therapies including:
* -Chemotherapy
* -Radiotherapy
* -High dose steroids >1 mg/kg/day prednisone or equivalent in the past two weeks
* -Monoclonal antibody or Intravenous IgG (IVIG)
-Cyclosporine
* -Anti-TNF agents
* -Interferon (of all kinds)
-Other severe illnesses that affect life expectancy and quality of life such as:
* -Moderate to severe psychomotor retardation
-Moderate to severe congenital metabolic disorder
-In children only: Other severe illnesses affecting life expectancy less than one year.

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:	Recruitment stopped
Start date (anticipated):	17-11-2014
Enrollment:	485
Type:	Actual

Ethics review

Approved WMO Date:	10-09-2014
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	08-10-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	14-01-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	23-09-2015
Application type:	Amendment

Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	13-11-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	10-03-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

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
ClinicalTrials.gov	NCT02025699
CCMO	NL47610.041.14

Study results

Date completed:	27-06-2016
Results posted:	20-12-2018
Actual enrolment:	467

First publication
01-01-1900