ISRCTN95828556 https://doi.org/10.1186/ISRCTN95828556

Fast multiplex assay of Gram-negative rods for antibiotic stewardship in hospitalized patients

Submission date
09/05/2017

Recruitment status
No longer recruiting

Registration date
02/06/2017

Overall study status
Completed

Last Edited
27/05/2022

Condition category
Infections and Infestations

[_] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Lower respiratory tract infections are infections that affect the airways and lungs, such as pneumonia. Delays in diagnosis are a major challenge in the treatment of patients suspected of having a lower respiratory tract infection. Patients are at risk of inappropriate antibiotic treatment as the type of bacteria is not known at the start of the treatment. Patients with pneumonia and at risk of infection with Gram-negative bacteria receive broader antibiotic coverage than patients without these risk factors. Standard care includes conventional tests for bacteria and antibiotic adjustment according to the results, but results can take up to 24 to 48 hours. Bronchoalveolar lavage (BAL) is a medical procedure that is typically performed to diagnose lung disease. It involves passing a device called a bronchoscope through the mouth or nose into the lungs, where fluid is squirted into a small part of the lung and then collected for testing. The aim of this study is to find out whether a rapid test for Gram-negative bacteria in the bronchoalveolar lavage samples reduces the time the patient spends on inappropriate antibiotic treatment.

What does the study involve?
Patients aged over 18 undergoing bronchoscopy for suspicion of pneumonia and at risk of infection with Gram-negative bacteria

What does the study involve?
Participants are randomly allocated to the experimental group or the control group. In the experimental group the participants are treated according to the results of the new test, and broad coverage antibiotic treatment is stopped if the results are negative. The control group's samples are sent for conventional tests. All participants are assessed daily up to discharge from hospital as well as at 30 days to measure the amount of time they spend on inappropriate antibiotic treatment.

What are the possible benefits and risks of participating?
The new test may reduce the amount of time patients spend on inappropriate antibiotic treatment and may be more sensitive than conventional methods. As all participants are also assessed using conventional tests they are not put at any risk.

Where is the study run from?
1. University Hospital Basel (Switzerland)
2. Kantonsspital St. Gallen (Switzerland)
3. Kantonsspital Liestal (Switzerland)

When is the study starting and how long is it expected to run for?
February 2017 to April 2019

Who is funding the study?
1. University Hospital Basel (Switzerland)
2. Curetis GmbH (unrestricted grant)

Who is the main contact?
Mrs Daiana Stolz

Contact information

Type(s)
Public

Contact name
Mrs Daiana Stolz

Contact details
Petersgraben 4
Basel
Switzerland
4031

Additional identifiers

Protocol serial number
EKNZ 2017-00043

Study information

Scientific Title
Fast multiplex assay of Gram-negative rods for antibiotic stewardship in hospitalized patients (FLAGSHIP II): a randomised controlled trial

Acronym
FLAGSHIP II

Study objectives
The trialists hypothesize that the rapid identification of the causative agent by multiplex PCR in patients hospitalized with pneumonia and risk factors for Gram-negative infection will reduce the time on inappropriate antibiotic therapy compared to identification by conventional microbiologic investigations.

In this randomized, controlled intervention study, a rapid bacterial multiplex PCR from Gram-negative rods in the bronchoalveolar lavage of patients with suspicion of pneumonia and risk for infection with Gram-negative bacteria will be evaluated in its effectiveness to reduce time on inappropriate antibiotic therapy.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Ethics committee of North West Switzerland, May 2017, ref: 2017-00043

Study design
Prospective block-randomized controlled multicentre intervention study

Primary study design
Interventional

Study type(s)
Diagnostic

Health condition(s) or problem(s) studied
Pneumonia and infection with Gram-negative bacteria

Interventions
Patients hospitalized with suspicion of pneumonia and clinical indication for bronchoscopy will be screened for inclusion into the study. Patients with risk factors for infection with Gram-negative bacteria will be included in the study and randomized based on a computer-generated allocation system to the control intervention or the experimental intervention:

Control intervention: Bronchoalveolar lavage (BAL) samples will be routinely sent to the microbiologic laboratory for conventional microbiologic investigations. Results will be provided in the medical electronic records as usual or by telephone call to the treating physician according to standard in-house procedures. The treating physician will decide on antibiotic treatment and adaptations.

Experimental intervention: BAL samples will be analyzed by the Unyvero diagnostic system using the pneumonia HPN panel provided by the manufacturer Curetis in addition to conventional microbiology investigations. The results of the Gram-negative range of the panel will be reported to the treating physician of the patient and an antibiotic recommendation will be made according to the provided list. Specifically, discontinuation of broad coverage will be recommended in cases with negative multiplex bacterial PCR results for Gram-negative rods. In cases depicting a positive result for Gram-negative rods, antibiotic coverage according to results will be recommended.

Time on inappropriate antibiotic therapy will be recorded in hours daily until discharge or 30 days of follow-up. In cases depicting discordant results between conventional microbiology and the Unyvero HPN, a confirmatory microbiological examination at the Institute of medical microbiology, University Zürich (16S rDNA, RT-PCR and/or Nextera® XT) will be performed. Inappropriate antibiotic therapy is defined as antibiotic therapy
1. Not active to in-vitro susceptibility testing of the identified pathogen, or

2. Not showing a favourable clinical course in patients without identifiable pathogen, or
3. Having a spectrum too broad for the identified pathogen, or
4. If no resistance pattern is available or no identifiable pathogen, antibiotic therapy is considered too broad, when switching to an antibiotic treatment with narrower spectrum continues to show a favourable clinical course
5. With known intrinsic resistance of the identified pathogen to the given antibiotic therapy

A spectrum too broad for the identified pathogen is considered if the empirical treatment is an antibiotic with a higher spectrum (higher rank number – see list below) than the identified resistance pattern of the identified pathogen. In addition, companion drugs (e.g. to cover atypical organisms, anaerobes or resistant organisms) are considered too broad, if one single agent antibiotic treatment is possible. For the purpose of this study, antibiotic therapy for pneumococcus will be considered inappropriate if classified as rank > 2.

Optimal antibiotic therapy will be defined by the absence of inappropriate antibiotic therapy. However, antibiotic therapy for pneumococcus will be only considered optimal if classified as rank 1.

Ranking Antibiotics
5 Imipenem, Meropenem
4 Ertapenem
3 Piperacillin/tazobactam, Ceftazidime, Cefepime, Aztreonam
2 Ceftriaxone, Amoxicillin/clavulanic acid

Time to clinical stability is also recorded; clinical stability is defined as stable vital signs for 24 hours or longer with all of the following criteria to be met:
1. Temperature of ≤ 37.8 ˚C
2. Heart rate ≤ 100/min
3. Respiratory rate ≤ 24/min
4. Systolic blood pressure ≥ 90 mmHg without vasopressor support
5. Adequate oxygenation SO2 ≥90% or PO2 ≥60 mmHg(≥8kPa) on room air
6. Mental status as before diagnosis of pneumonia
7. Ability for oral intake

Intervention Type
Other

Primary outcome(s)
The time (in hours) on inappropriate antibiotic therapy based on multiplex bacterial PCR, recorded daily until discharge or 30 days follow-up

Key secondary outcome(s))
1. Time to clinical stability; vital signs recorded at inclusion and daily up to discharge or up to 30 days, whichever happens first
2. Length of hospital stay in days, measured until discharge up to 30 days
3. Mortality, measured at 30 days follow-up
4. Adverse events and their relation to antibiotic therapy, assessed daily by history taking and any examination as clinically indicated up to discharge or up to 30-day observational period
5. Diagnostic performance of the multiplex bacterial PCR (HPN Pneumonia panel) as compared to conventional microbiologic testing and to a second confirmatory multiplex PCR, measured at the BAL day for the intervention group and after completion of the study (last visit, last patient

out) for the control group
6. Diagnostic performance of multiplex PCR from BAL compared to multiplex PCR from sputa, measured after completion of the study (last visit, last patient out) for both randomized groups

Completion date
01/04/2019

Eligibility

Key inclusion criteria
1. Informed consent as documented by signature
2. Clinical indication for diagnostic bronchoscopy with bronchoalveolar lavage
3. Suspicion of pneumonia (e.g. community-acquired pneumonia (CAP); aspiration pneumonia (AP); hospital acquired pneumonia (HAP); or acute pneumonic exacerbation of COPD based on:
3.1. New pulmonary infiltrate seen on chest radiograph or CT scan plus at least one of the following:
3.2. New or increased cough with/without sputum production
3.3. Fever (documented temperature –rectal or oral- ≥ 38.3 Grad Celsius or hypothermia (documented temperature – rectal or oral - <36 Grad Celsius)
4. Evidence of systemic inflammation (such as abnormal white blood cell count – either leucocytosis (>10.0x109/l) or leukopenia (<4.0x109/l) – or C-reactive protein (CRP) or procalcitonin (PCT) values above the local upper limit
5. Risk factors for infection with Gram-negative bacteria in patients with CAP include:
5.1. Suspicion of or diagnosis of chronic alcoholism or
5.2. Chronic oral steroid administration (prednisone doses >7.5 mg/d or equivalent for more than 4 weeks) or other immunosuppressive therapy (such as in connective tissue disease, rheumatic disease or solid organ transplantation)
5.3. Suspicion of or diagnosis of underlying chronic bronchopulmonary disease such as COPD, bronchiectasis, interstitial lung disease
5.4. Suspicion of aspiration
5.5. Recent or frequent antibiotic therapy within the last 3 months
5.6. Chemotherapy within the last 3 months
5.7. Immunocompromised status due to any condition such as haematological disease, haemodialysis, HIV, solid organ or stem cell transplantation
6. Adults (age 18 – 99)

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Total final enrolment
208

Key exclusion criteria
Failure to provide informed consent

Date of first enrolment
01/06/2017

Date of final enrolment
01/04/2019

Locations

Countries of recruitment
Switzerland

Study participating centre
University Hospital Basel
Petersgraben 4
Basel
Switzerland
4031

Study participating centre
Kantonsspital St. Gallen
St. Gallen
Switzerland
9000

Study participating centre
Kantonsspital Liestal
Liestal
Switzerland
4410

Sponsor information

Organisation
University Hospital Basel

ROR
https://ror.org/04k51q396

Funder(s)

Funder type
Hospital/treatment centre

Funder Name
University Hospital Basel

Funder Name
Curetis GmbH (unrestricted grant)

Results and Publications

Individual participant data (IPD) sharing plan
The current data sharing plans for the current study are unknown and will be made available at a later date

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		23/05/2022	27/05/2022	Yes	No