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Procalcitonin-guided antibiotic therapy and hospitalisation in patients with lower respiratory tract infections: the ProHOSP study

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Registration date 31/07/2006	**Overall study status** Completed	
Last Edited 07/07/2015	**Condition category** Respiratory	

Plain English summary of protocol
Not provided at time of registration

Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number
NCT00350987

Secondary identifying numbers
01

Study information

Scientific Title
Procalcitonin-guided antibiotic therapy and hospitalisation in patients with lower respiratory tract infections: the ProHOSP study

Acronym
ProHOSP

Study objectives
Procalcitonin (PCT) guidance will be non-inferior with at worst 7.5% higher combined failure rate as compared to standard care practice with a reduced total antibiotic (AB) use, hospitalisation rate and duration, respectively.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved by the Local Ethics Committee of Basel, Switzerland (EKBB)

Study design
Non-inferiority multicentre investigator-initiated controlled trial with an open intervention

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet

Health condition(s) or problem(s) studied
Lower respiratory tract infection (LRTI)

Interventions
Patients admitted with lower respiratory tract infection (LRTI) to hospital will be included and randomised either to standard management or to the PCT-guided prescription of AB treatment. Randomisation will be stratified by centre (the hospital) and type of LRTI (Acute bronchitis /AECOPD/CAP).

Participating physicians will receive evidence-based guidelines for the management of patients with LRTIs. Patients with LRTI will be randomised 1:1 to PCT plus guidelines (PCT group) versus PCT-guided prescription of AB treatment (control group). In patients randomised to the PCT group, the use of ABs will be more or less discouraged (less than 0.1 or less than 0.25 ug/l) or

encouraged (greater than 0.5 or greater than 0.25 ug/l), respectively. A re-evaluation after 6 to 24 hours in patients in whom antibiotics are withheld with worsening or non-improvement of vital signs, PCT (less than 0.1 or less than 0.25 ug/l) is recommended. During hospitalisation, patients with AB treatment will be reassessed at day 3, 5 and 7 and in patients randomised to the PCT group, it is recommended that AB is stopped based on PCT levels. In AB-treated outpatients or discharged patients with acute exacerbation of COPD (AECOPD) as well as CAP patients randomised to the PCT group with an uncomplicated cause, the recommended duration of AB therapy will be based on the last PCT level and will be as follows: greater than 0.5 ug/l for five days, greater than 0.25 for three days, less than 0.25 stop AB.

Intervention Type
Other

Phase
Not Specified

Primary outcome measure
To compare the risk of disease-specific failure in patients with LRTIs (pneumonic and non-pneumonic LRTI), managed with or without PCT decision making for AB prescription within 30 days following hospital-admission. The primary endpoint will be assessed by a blinded telephone interview.

Disease-specific failure (combined primary endpoint) will include death, need for intensive care unit (ICU) stay with and without the need for mechanical ventilation, microbiologically confirmed recurrence and relapse in need of AB, clinical and/or radiological recurrence in need of AB, complications from LRTI (persistence or development of pneumonia [including nosocomial], acute respiratory distress syndrome [ARDS], empyema), readmissions to hospital.
The endpoint will be assessed on day 30 (range 26 to 34) by telephone interview with the patient and the general physician, respectively. If discordant, the physician's information will be considered.
Predefined subgroup analyses will be done for CAP, acute exacerbation of COPD and acute bronchitis, respectively. An additional telephone interview after six months will be performed. The results of the six-month interview will only be included in the subgroup analysis and not for the (primary) overall comparison between the two arms.

Secondary outcome measures
1. To compare AB use for LRTIs in the presence or absence of PCT testing. Specifically, the following parameters will be evaluated in each arm:
1.1. Time to antibiotic treatment (hours) (door-to-needle time)
1.2. Prescription rate of ABs in patients with LRTI
1.3. Event-free survival days without AB until follow-up after 30 days
1.4. Duration of AB treatment (days) and defined daily doses of antimicrobial therapy in each arm
1.5. Duration of AB treatment in hospitalized patients compared to discharged patients
1.6. Rate of adequate antibiotic therapy, time to the first change in antibiotic therapy
1.7. Side-effects from AB treatment (duration and severity), including gastrointestinal signs, allergies

2. To compare hospitalisation in the presence or absence of PCT testing. Specifically, the following parameters will be measured:
2.1. Time to effective hospital discharge (days)
2.2. Time to earliest possible hospital discharge (days) based on objective criteria (possible oral

intake of food, liquids and drugs, stable vital signs greater than 24 hours [as defined below], baseline mental status, no evidence of acute serious co-morbidity that necessitates hospitalisation). This endpoint will minimise a bias due to extended hospitalisation for non-disease specific reasons (request from patients or their relatives, lack of adequate home care support, or possibility for transferal to nursery home, lack of assurance about compliance with treatment).

3. Time to clinical stability i.e. time (days) until stable vital signs for greater than 24 hours, temperature less than 38°C, heart rate per minute less than 100, spontaneous respiratory rate less than 24 per minute, systolic blood pressure greater than 90 mmHg (greater than 100 mmHg for patients diagnosed with hypertension) without vasopressor support, baseline mental status, adequate oxygenation on room air or less than 2 l of oxygen therapy (PaO2 greater than 60 mmHg or pulse oxymetry greater than 92%). For patients with chronic hypoxaemia or chronic oxygen therapy, PaO2 or pulse oximetry measurement must be at baseline.

4. Visual analogue scale, LRTI-specific disease activity score, number of days with restriction from LRTI, daily function and health state, worsening of general function and health state, all assessed at baseline and by telephone interview at follow-up after 30 days and six months. Thereby, visual analogue scale will be completed by the blinded interviewer based on the estimation of the patient on the telephone. Components of the combined primary endpoint will also be compared individually.

5. To develop prediction rules for adverse health outcomes in community-acquired LRTIs:
5.1. To assess the diagnostic and prognostic accuracy of clinical signs and symptoms for the severity and the cause of LRTI
5.2. In CAP patients the prognostic accuracy of the PSI, the CURB-65 with and without biomarkers will be compared
5.3. Rate of non-infectious differential diagnosis and time to final diagnosis in patients with suspected bacterial LRTI on admission with or without infiltrate and PCT levels of less than 0.1 and 0.25 ug/l, including congestive heart failure, pulmonary embolism, pulmonary tumor, viral infection, aspiration pneumonia, cryptogenic organising pneumonia (bronchiolitis obliterans organizing pneumonia [BOOP]), exogenous-allergic alveolitis, sarcoidosis, lymphoma
5.4. In COPD patients, the diagnostic accuracy of the Anthonisen criteria will be re-evaluated (namely sputum presence and purulence)

Overall study start date
01/10/2006

Completion date
01/05/2008

Eligibility

Key inclusion criteria
1. Patients 18 years of age or older, admitted from the community or a nursing home with acute i.e. at least for 1 day but less than 28 days) lower respiratory tract infection (LRTI) as the main diagnosis consisting of having at least two of the following: new or increased respiratory signs or symptoms (i.e. cough, sputum production, dyspnea, auscultatory findings of abnormal breath sounds and rales, pleuritic chest pain) with or without inflammatory signs (core body temperature greater than 38.0°C, leukocyte count greater than 10 or less than 4 x 10^9 cells/l). Community-acquired pneumonia (CAP) is defined by the presence of LRTI along with a new or

increased infiltrate on chest radiograph. Severity scores of CAP (pneumonia severity index [PSI] and CURB-65) will be calculated.
Chronic obstructive pulmonary disease (COPD) is defined by post-bronchodilator spirometric criteria according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines as a forced expiratory volume in one second (FEV1) or forced vital capacity (FVC) ratio below 70% and the severity categorized into mild (FEV1 =80% of predicted), moderate (50%= FEV1 <80%), severe (30%= FEV1 <50%) and very severe (FEV1 <30%), respectively. Severity of acute exacerbations of COPD will be graded as proposed.
Acute bronchitis is defined as LRTI in the absence of an underlying lung disease or focal chest signs and infiltrates on chest x-ray, respectively. Patients who are on admission judged as having a LRTI but have another final diagnosis, will be classified as 'others'.
2. Ability to understand verbal and written instructions and informed consent

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
1002

Key exclusion criteria
1. Patients unable to give written informed consent e.g. with severe dementia or patients who cannot understand German (or other local language) and where there are no translators (e.g. family members) available
2. Patients with active intravenous drug use
3. Severe immunosuppression (e.g. patients infected with human immunodeficiency virus [HIV] infection and a CD4 count below 350 x 10^9/l, patients on immunosuppressive therapy after solid organ transplantation and neutropenic patients with present neutrophil count less than 500 x 10^9/l, patients under chemotherapy with neutrophils of 500 - 1000 x 10^9/l with an expected decrease to values of less than 500 x 10^9/l), patients with cystic fibrosis, infected with Mycobacterium tuberculosis, Legionella pneumophila, Listeria spp. and hospital stay within 14 days of inclusion
4. Accompanying chronic (e.g. osteomyelitis), abscess, (e.g. brain, pleural empyema) infection or endocarditis
5. Terminal and very severe medical co-morbidity where death is imminent or is expected in current hospitalisation (e.g. due to malignancy, cardiac, renal or hepatic failure, comfort therapy)

Date of first enrolment
01/10/2006

Date of final enrolment
01/05/2008

Locations

Countries of recruitment
Switzerland

Study participating centre
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Sponsor type
University/education

ROR
https://ror.org/04k51q396

Funder(s)

Funder type
University/education

Funder Name
University Hospital of Basel (Switzerland)

Funder Name
Schweizerischer National Fund (SNF) (Switzerland)

Results and Publications

Publication and dissemination plan
Not provided at time of registration

Intention to publish date

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article	protocol	05/07/2007		Yes	No
Results article	results	13/10/2008		Yes	No
Results article	results	09/09/2009		Yes	No
Results article	results	01/07/2010		Yes	No
Results article	results	03/05/2011		Yes	No
Results article	results	15/11/2014		Yes	No