Reduction of antibiotic therapy by biomarkers in patients with CAP episodes

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

Summary

ID

NL-OMON45194

Source
ToetsingOnline

Brief title
REDUCE study

Condition

- Bacterial infectious disorders
- Respiratory tract infections

Synonym
Pneumonia

Research involving
Human

Sponsors and support

Primary sponsor: Medisch Centrum Alkmaar
Source(s) of monetary or material Support: Chiesi Farmaceutici,Medisch Centrum Alkmaar,Stichting Pulmoscience;Chiesi;Foreest Medical School (MCA)

Intervention

Keyword: Antibiotics, Biomarkers, Community Acquired Pneumonia, Pneumonia

Outcome measures

Primary outcome

The primary objective of this study is to determine whether the CRP and PCT strategies can be used to safely and effectively reduce the duration of antibiotic treatment in patients with CAP requiring hospitalisation.

The diagnosis CAP will be made if a non-hospitalized person presents with one or more symptoms associated with a lower respiratory tract infection and a new infiltrate on the chest radiograph. These symptoms are: temperature greater than 38°C (100.4°F); cough with or without sputum; hemoptysis; pleuritic chest pain; dyspnea; malaise or fatigue; myalgia; gastro-intestinal symptoms; rales, rhonchi or wheezing; egophony or bronchial breath sounds.

Secondary outcome

The secondary objectives of this study are to assess the length of hospital stay, clinical response, 30-day mortality, time to clinical stability and relapse rate within 30 days. A relapse is defined as new or worsening symptoms indicative of pneumonia after initial improvement on therapy. Furthermore several biomarkers and genetic polymorfisms for corticosteroid-receptors will be assessed at the end of the study.

Study description

Background summary

Community-acquired pneumonia (CAP) is a common and serious illness. In developed countries it is the most important cause of death due to an infectious disease and in the Netherlands it is the fourth leading cause of death overall. 1-3
In CAP caused by bacteria prompt initiation of antibiotic therapy is recommended, since a delay might be associated with increased mortality.4;5 The optimal duration of antibiotic therapy in bacterial CAP remains unknown.6 Most likely, it varies from patient to patient.
Current guidelines recommend treatment duration of 7-21 days, depending on illness severity and type of pathogen.2;7-9 However, adherence to guidelines is variable and physicians tend to treat longer, especially in patients with comorbidities and patients with severe CAP.10;11 Duration of treatment can be guided by clinical signs, but interpretation of the clinical response lacks standardization and is prone to interobserver variability.12
A new approach to estimate the presence of an infection and response to treatment is the use of biomarkers.13;14 Circulating levels of calcitonin precursors, including procalcitonin are elevated in bacterial infections.15;16 Procalcitonin can follow either a classic hormonal expression pathway or in the presence of an infection, a cytokine-like expression pathway.16;17
The release of procalcitonin during infection can be induced either directly by microbial toxins such as endotoxin and indirectly by humoral factors such as IL-1*, TNF-* and IL-6 or the cell-mediated host response. 16;17
Several studies have shown procalcitonin can be used as a marker for bacterial lower respiratory infections and CAP. 18-20 Some studies demonstrate procalcitonin can be used effectively and safely as a marker to initiate or discontinue treatment with antibiotics.11;21-23 However only one of these trials focuses on patients with CAP admitted to hospital. One of our objectives is to validate the procalcitonin based treatment strategy mentioned by Christ Crain et al. and Long et al. 23;24
A different way to assess the presence of (bacterial) infection is measuring the blood level of C-Reactive Protein (CRP). An elevated CRP correlates only with (systemic) inflammation and not per se infection. Several studies have attempted to use CRP as a marker in lower respiratory tract infections and CAP in a primary care setting. 25-29 Over the years several reviews have questioned the use of CRP in patients with community acquired pneumonia/lower respiratory tract infections as a marker to initiate or withhold antibiotic treatment. 27;30 There is however evidence that supports the use of consecutive measurements of CRP in follow up of antibiotic treatment in CAP. Several studies showed that a delayed normalisation of CRP within the first 3*7 days of follow-up is suggestive of inappropriate antibiotic therapy and eventually treatment failure. 31-34
Using the database from the CAPISCE study35 we retrospectively derived a CRP based treatment strategy which we believe can be used just as effectively as the PCT based strategy to discontinue antibiotic treatment in patients with CAP

admitted to hospital.
Our main goal is to determine whether the CRP and PCT guided strategies can be used to safely and effectively reduce the duration of antibiotic treatment in patients with CAP admitted to hospital.

Study objective

2.1 Primary objective(s)
The primary objective of this study is to determine whether a CRP guided and PCT guided treatment strategy (strategies mentioned below) can be used to safely and effectively reduce the duration of antibiotic treatment as compared to common clinical practice in patients with CAP requiring hospitalisation.

The diagnosis CAP will be made if a non-hospitalized person presents with one or more symptoms associated with a lower respiratory tract infection and a new infiltrate on the chest radiograph. These symptoms are: temperature greater than 38°C (100.4°F); cough with or without sputum; hemoptysis; pleuritic chest pain; dyspnea; malaise or fatigue; myalgia; gastro-intestinal symptoms; rales, rhonchi or wheezing; egophony or bronchial breath sounds.

2.2 Secondary objective(s)
The secondary objectives of this study are to assess the length of hospital stay, clinical response, 30-day mortality, time to clinical stability and relapse rate within 30 days. A relapse is defined as new or worsening symptoms indicative of pneumonia after initial improvement on therapy. Furthermore several biomarkers and genetic polymorfisms for corticosteroid-receptors will be assessed at the end of the study.

Study design

This study will be set up as a Randomised Controlled Trial with a parallel design, patients will be randomly allocated to one of 3 treatment groups. No blinding will be performed, since treating physicians will have to make a decision to continue or withhold treatment based on laboratory evaluations. In order to make the right decision they will have to know whether or not the patient is receiving antibiotics.
Patients will be included at hospital admission and the follow up period is 1 month. The control group will consist of patients getting treated according to common clinical practice.
Patients will be admitted to hospital and receive therapy according to the study protocol. They will be discharged from the hospital when their medical condition and social situation is stable. If patients are discharged and still using antibiotics, blood tests will be performed daily in the participating centre and the researcher will contact the patients by phone to inform them whether or not antibiotic treatment can be discontinued. After discharge the patient will be evaluated at an outpatient visit on day 30. In case of any

event an interim visit will be scheduled. If for some reason a patient fails to perform an outpatient blood test, antibiotics will be continued until the next blood test or for a total of 7 days and the reason for failure will be documented.
This study will be conducted in the Medical Centre Alkmaar and the Slotervaart hospital in Amsterdam.

Intervention

The 3 different treatment strategies are as follows:
1. Treatment according to common practice: often a 7 day course of antibiotics.
2. Treatment with antibiotics for at least 3 days according to current guidelines, with extension of antibiotic treatment according to procalcitonin levels. Antibiotic treatment will be discontinued if the procalcitonin level is below 0.25 mcg/L or shows a reduction to 10% of the initial value.
3. Treatment for 3 days according to current guidelines, with extension of antibiotic treatment according to CRP levels. Antibiotic treatment will be discontinued if the value is below 100 mg/L and shows a reduction to 50% of the initial value.

Study burden and risks

Low risk study according to the risk-classification as designed by the Dutch Foundation of University Medical Centres.
Risks include those associated with obtaining a blood sample and possibly worsening of the patients condition if the antibiotics happened to be stopped early, in which case antibiotic therapy can be resumed.

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

Male and female patients with a diagnosis of CAP and all criteria listed below:
1. Age 18 or above, no upper age limit will be employed.
2. Patients must require hospitalisation.
3. Clinical presentation of an acute illness with one or more of the following symptoms:
a. Temperature * 38.0 *C (100.4°F)
b. Dyspnoea
c. Cough (with or without expectoration of sputum)
d. Chest pain
e. Hemoptysis
f. Malaise or fatigue
g. Myalgia
h. Gastro-intestinal symptoms
i. Rales, rhonchi or wheezing
j. Egophony or bronchial breath sounds
4. New consolidation(s) on the chest radiograph.
5. Written informed consent obtained.
6. (Pre-event) Life expectancy > 30 days.

Exclusion criteria

Subjects presenting with any of the following will not be included in the study:
1. Severe immunosuppression (HIV infection, chemotherapy).
2. Active neoplastic disease.
3. Obstruction pneumonia (e.g. from lung cancer).
4. Aspiration pneumonia.
5. Pneumonia that developed within 8 days after hospital discharge.
6. Unable and/or unlikely to comprehend and/or follow the protocol.

7. Pregnant and/or lactating women.

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-12-2013
Enrollment:	468
Type:	Actual

Ethics review

Approved WMO Date:	15-10-2013
Application type:	First submission
Review commission:	METC Noord-Holland (Alkmaar)
Approved WMO Date:	06-10-2014
Application type:	Amendment
Review commission:	METC Noord-Holland (Alkmaar)
Approved WMO Date:	29-05-2017
Application type:	Amendment
Review commission:	METC Noord-Holland (Alkmaar)

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	NL44806.094.13