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Short-course antibiotic therapy of 5 days in community-acquired pneumonia (CAP5): study protocol for a randomised controlled trial

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ABSTRACT

Introduction The optimal duration of antibiotic therapy for community-acquired pneumonia (CAP) is unsettled. Short-course therapy has proved successful in clinical trials but is not yet implemented in everyday clinical practice. Validation of results from randomised controlled trials is crucial to evaluate existing evidence and provide clinicians with assurance of using new treatment strategies. In a pragmatic framework, we aim to assess the use of short-course antibiotic therapy guided by the onset of clinical stability in patients hospitalised with CAP.

Methods and analysis This study is a randomised controlled trial with a non-inferiority design that will examine the efficacy of short-course antibiotic therapy in patients hospitalised with CAP. From six hospitals across Denmark, we plan to enrol 564 patients between 2019 and 2024. Within 3–5 days after initiating antibiotic therapy, participants will be randomised 1:1 to parallel treatment arms: (1) short-course antibiotic therapy of 5 days or (2) antibiotic therapy of at least 7 days. The primary outcome will be 90-day readmission-free survival and will be estimated as an absolute risk difference with a predefined non-inferiority margin of −6%. Secondary outcomes will comprise other safety measures including new antibiotics, adverse events, length of hospital stay and postdischarge outpatient visits. Both intention-to-treat and per-protocol analyses will be performed.

Ethics and dissemination This study has been approved by the Health Research Ethics Committee of the Capital Region of Denmark (identifier number: H-19014479). Trial data will be made available in anonymous form when the trial has ended.

Trial registration number NCT04089787, ClinicalTrials.Gov.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study is a pragmatic randomised controlled trial designed to reflect clinical practice in only intervening on the duration of antibiotic therapy and thus leaving the choice of type and dose at the discretion of the treating physicians.
⇒ The duration of antibiotic therapy is guided by the onset of clinical stability based on standard clinical measurements.
⇒ The use of objective hard endpoints to establish non-inferiority is reassuring for patients and physicians.
⇒ Eligible patients, that is, immunocompetent adults with early clinical response, represent a subpopulation of all patients hospitalised with community-acquired pneumonia which may limit the generalisability of the study.
⇒ The trial is open label for all except outcome assessors which enables a pragmatic setup but misses the advantages of blinding participants and investigators.

INTRODUCTION

Background

Community-acquired pneumonia (CAP) is a common infection that frequently leads to hospitalisation, particularly among older adults.[1] Evidence on the optimal duration of antibiotic therapy is sparse. Systematic reviews[2–4] suggest treatment for 5–7 days that is adopted by major clinical guidelines.[5–7] Of note, recent trials have reported that short-course antibiotic therapy of 3–5 days in patients with an early clinical response is sufficient and safe.[8 9]

Despite recent updates of clinical guidelines and an overall trend towards individualising treatment based on the patient's response, short-course antibiotic therapy remains underused in clinical practice.[10 11] Therefore, more evidence to support the optimal length of therapy may assist in clinical decision making of shorter durations of antibiotic therapy to a suitable subset of patients.

Previous trials have evaluated clinical cure as the primary outcome that is defined by different levels of treatment response based on improvement or resolution of symptoms and no need for additional antibiotic therapy, as proposed by the European Medicines

Agency.[12] While this outcome is highly relevant to both patients and clinicians, it does partly rely on subjective clinical assessment.

Antibiotic preferences vary internationally as reflected by other studies on treatment duration that have mainly assessed fluoroquinolones, macrolides and broad-spectrum beta-lactams.[8 9 13–15] Here, we wanted to explore these findings in a Northern European setting where narrow-spectrum beta-lactam antibiotics are preferred.[16 17] This trial, short-course antibiotic therapy of 5 days in community-acquired pneumonia (CAP5), randomises participants to two durations of antibiotic therapy, but does not dictate the type or dose of antibiotic, in order to resemble routine clinical settings. To address what we believe concerns clinicians the most, CAP5 evaluates the impact of short-course antibiotic therapy on readmissions and all-cause mortality.

Objectives

The study objective is to determine the efficacy and safety of short-course compared with standard course antibiotic therapy for adult patients hospitalised with CAP.

Trial design

The CAP5 trial is a non-inferiority randomised controlled trial with two parallel treatment arms. Participants are randomised individually with a 1:1 allocation ratio. The study is open label for participants and investigators while outcome assessors are blinded.

METHODS AND ANALYSIS

Study setting

The study is conducted at six academic hospitals across Denmark: Copenhagen University Hospitals at Amager and Hvidovre, Herlev and Gentofte, North Zealand, and Bispebjerg and Frederiksberg, Odense University Hospital and Aalborg University Hospital. The full list of the study sites can also be retrieved from ClinicalTrials.Gov NCT04089787.

Inclusion criteria

- Hospitalised with CAP, defined as new pulmonary infiltrate on chest X-ray or CT scan and at least one symptom compatible with pneumonia (cough, fever, dyspnoea and/or chest pain)
- Initiated antibiotic therapy within 12 hours of the time of the chest X-ray/CT scan with an infiltrate
- Aged ≥18 years.
- Afebrile (temperature ≤37.8°C) for 48 hours at the time of randomisation
- Achieved clinical stability at the time of randomisation, defined as systolic blood pressure ≥90 mm Hg, heart rate ≤100/min, respiratory rate ≤24/min and peripheral oxygen saturation ≥90% (without oxygen supplementation, or with the habitual level of oxygen supplementation if receiving long-term oxygen therapy).

Exclusion criteria

- Immunosuppression, defined as being HIV-positive, having neutropenia ($<1\times10^9$/L), receiving corticosteroid treatment (≥10 mg/day of prednisone or the equivalent for >30 days), having received chemotherapy within the past 90 days, having untreated terminal cancer, receiving immunosuppressive agents, being immunosuppressed after solid organ transplantation or having asplenia
- Hospitalised within the past 14 days
- Received antibiotic therapy directed at lower respiratory tract pathogens for >2 days within the past 30 days
- An uncommon bacterial aetiology requiring longer duration of antimicrobial therapy, including *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Legionella* spp, *Mycobacterium* spp or fungi
- Severe extrapulmonary infection including endocarditis, meningitis or abscess
- Pleural empyema, lung abscess or aspiration pneumonia
- Pleural effusion requiring drainage tube
- Admission to the intensive care unit before randomisation
- Pregnancy and breast feeding

Interventions

Intervention group: antibiotic therapy for 5 days, regardless of type or dose of antibiotic. The choice of drug type and dose is at the discretion of the treating physician.

Control group: antibiotic therapy for at least 7 days, regardless of type or dose of antibiotic. The choice of drug type, dose and length of therapy beyond 7 days is at the discretion of the treating physician.

Adherence to the assigned treatment duration is encouraged at reminder telephone calls and planned telephone interviews during follow-up. If participants are discharged before ending their antibiotic therapy, they will receive the remaining number of pills according to their assigned treatment duration at discharge. Adherence assessment is primarily performed at the first follow-up at 10–14 days after hospital admission.

Protocol violation will be reported if participants receive insufficient therapy corresponding to less than 80% of scheduled doses, or if participants in the intervention group receive prolonged-course antibiotic therapy despite clinical stability.

Outcomes

The primary outcome is 90-day readmission-free survival, defined as no occurrence of any readmission or all-cause death within 90 days of hospital admission.

The secondary outcome measures are assessed at 90 days after hospital admission, unless otherwise stated, and comprise the following:

- Total duration of antibiotic therapy: number of days that the participant receives antibiotic therapy for pneumonia, adding intravenous and oral therapy

- Length of hospital stay: number of days from hospital admission to discharge
- Antibiotic adverse events: number of participants with adverse events possibly related to the antibiotic therapy
- Serious adverse events: number of participants with serious adverse events in accordance with International Council of Harmonisation-Good Clinical Practice guidelines
- Major complications: number of participants with major complications, including pleural effusion, pleural empyema, lung abscess, respiratory failure, severe sepsis, renal failure, use of non-invasive or invasive ventilation, need for vasopressors and intensive care unit admission
- Use of antibiotics after hospital discharge: days of antibiotic therapy for any reason after hospital discharge
- Postdischarge follow-up visits: number of participants with medical visits after hospital discharge, including visits at the outpatient clinic and at the general practitioner
- Readmission within 30 and 90 days: number of participants with readmissions for reasons related to or unrelated to pneumonia
- All-cause mortality in-hospital, within 30 days and 90 days: number of deaths by any cause

Participant timeline

Trial eligibility is assessed within 1–5 days of hospital admission. Participants are randomised and assigned to treatment arm at days 3, 4 or 5 whichever day defines the onset of clinical stability. Follow-up is performed at planned telephone interviews 10–14 days after hospital admission (first follow-up) and 90–100 days after hospital admission (second follow-up). See figure 1 for an overview of the participant timeline.

Sample size

The target sample size was estimated based on the primary outcome composed of readmissions and deaths within 90 days of hospital admission. Previous similar studies[8 13–15 18 19] have primarily reported 30-day outcomes with readmission and mortality risks of around 2%–4% and 5%–7%, respectively. Of these, Aliberti *et al* was the only study reporting 90-day outcomes as well, with a mortality at 2% and readmission at 5%.[15] In addition, Postma *et al*, who conducted a trial comparing different empirical treatment strategies in CAP, used 90-day outcomes and reported a mortality rate of 9% in these patients hospitalised in non-ICU wards.[20] Based on these findings, we expect an event rate of the primary outcome of around 9% in both treatment arms.

We considered a non-inferiority margin of −6% as clinically relevant given the expected event rate. At a power of 80% and an alpha of 0.05, we estimated a target sample size of 564 participants in total with 282 in each arm, using the *R* package 'dani' (Design and Analysis of Non-Inferiority Trials).[21]

Recruitment

Participants are recruited during their hospital admission. The principal investigators are based in the infectious diseases departments at each study site, but participants are recruited from both emergency department and internal medicine wards. The study sites are located across Denmark.

	STUDY PERIOD														
	Enrolment		Allocation			Post-allocation									End
TIMEPOINT (days)	1	2	3	4	5	6	7	8	9	10	11	12	13	14	90
ENROLMENT															
Hospital admission	X														
Eligibility screen		X	X												
Informed consent		X	X	X	X										
Allocation			X	X	X										
INTERVENTIONS															
Short-course therapy (5 days)	♦	—	—	—	♦										
Standard therapy (7+ days)	♦	—	—	—	—	—	—	♦	·····	·····	·····	→			
ASSESSMENTS															
Demographics	X														
Comorbidities	X														
Chest X-ray	X														
Blood tests	X														
Vitals	X	X	X	X	X										
Microbiology			X	X	X									X	
Treatment adherence					X		X							X	X
Adverse events														X	X
Additional antibiotics															X
Post-discharge visits															X
Readmissions															X
Vital status															X

Figure 1 Participant timeline including screening, scheduled interventions and follow-up.

Allocation

The allocation sequence is constructed by computer-generated random numbers and stratified by study site. The sequence is generated in permuted blocks to (1) ensure equal distribution of participants in the two treatment arms and (2) avoid the sequence to be predictable for study investigators. The allocation sequence is made by an independent biostatistician without any involvement in the participant recruitment or interventions. Participants are enrolled and assigned to interventions by trained study personnel at each study site.

The allocation sequence is uploaded and stored in a secure online database unavailable for all study personnel, please refer to the Data Management section for further details.

Blinding

Outcome assessors will be blinded to treatment allocation. There is no blinding of participants, study investigators or treating physicians.

Data collection

Baseline and outcome data are primarily retrieved from the electronic medical records of the participants. Adherence to treatment allocation, adverse events and postdischarge medical visits are assessed in telephone interviews. The complete case report form is available in online supplemental material.

Data quality is promoted by setting restrictions on possible data entries, including date checks, and providing warnings when fields are left blank or incorrectly filled. In addition, regular validation of entered data is performed by assigned study personnel.

Participants that deviate from the protocol or are lost to follow-up will still have their medical records evaluated for the primary outcome and serious adverse events, unless they withdraw their consent.

If participants are unavailable for telephone interview at the planned date of follow-up, efforts to reschedule their follow-up are made.

Data management

Data are entered into a secure, web-based data capture tool (REDCap) hosted by the Capital Region of Denmark.[22 23] Here, data will be stored throughout the conduct of the trial. REDCap is accessed by study personnel via personal log-in with two-factor authentication.

Statistical methods

Primary and secondary outcomes

The main hypothesis test is a one-sided test with a significance level, alpha, at 0.05 assessing whether the null hypothesis, that is, the interventional treatment being inferior to standard treatment by more than the predetermined non-inferiority margin, can be rejected.[24] Non-inferiority is thus established if the lower limit of the 90% CI for the absolute risk difference between the interventional and standard treatment group does not exceed −6%. The primary outcome will be presented with non-inferiority plots with both 90% and 95% CIs.

Secondary outcomes will be reported separately. χ^2 test or Fisher's exact test will be used to compare categorical variables and Student's t-test or Wilcoxon rank sum test to compare continuous variables.

The primary and secondary outcomes will be analysed in both intention-to-treat and per-protocol analyses. The intention-to-treat analysis will comprise all participants that have been randomised including those who have dropped out, been lost to follow-up or violated the protocol.

In all statistical analyses other than on the primary outcome, a two-tailed p value <0.05 is considered statistically significant.

Additional analyses

Screening, enrolment, treatment allocation and follow-up data will be presented in a Consolidated Standards of Reporting Trials flow diagram.

Subgroup analyses will be performed on participants stratified by disease severity, antibiotic group and study site.

Further details on the statistical analysis plan are available from the Statistical Analysis Plan V.1.0 at ClinicalTrials.Gov NCT04089787 and in online supplemental material.

Data Safety and Monitoring Board

The Data Safety and Monitoring Board (DSMB) comprises three members including two infectious diseases specialists and one pulmonologist. The Board is an independent group advisory to the study group without any involvement in the study and free from any conflicts of interest. The role of the Board is to monitor the study safety and feasibility by evaluating the primary outcome, serious adverse events and protocol violations at the planned interim analyses.

At each meeting, the Board will discuss confidential data from the study and decide whether to remain masked to the treatment assignment. A report summarising the key points of the discussion, requests for additional information and recommendations regarding study modification, continuation or termination will be prepared by the Chair after each meeting. If concerns are raised, the report will outline the concerns, the Board's discussion of the concerns and the basis for any recommendations that the Board has made in response to the concerns.

Interim analyses

Interim analyses on the primary outcome will be performed when 100, 300 and 500 participants have completed their 90 days of follow-up. A blinded data centre statistician will carry out the data analyses and present them to the DSMB. At the first interim analysis, a sample size re-estimation will be considered by the DSMB given the observed event rates, as outlined in the Statistical Analysis Plan (online supplemental material).

Harms

Participants are interviewed on whether they have experienced any adverse events at both follow-up telephone interviews. If a participant has been readmitted to a hospital during the study period, the respective study site investigators will be notified automatically within the electronic medical records system. Adverse events will be followed until they have abated or until a stable situation has been reached.

All adverse events will be evaluated by both study investigators and sponsor to determine possible causal association with the study intervention.

Adverse events are registered in predefined case report forms individually. A report of all serious adverse events is sent to all study sites and the relevant authorities once a year. When the study has ended, a final report of the registered adverse events is drafted and submitted to the authorities.

Auditing

The overall conduct of the study is audited by an independent monitoring unit, the Good Clinical Practice Unit at Copenhagen University Hospital, Odense University Hospital, Aalborg University Hospital and Aarhus University Hospital. The frequency of monitoring visits is every 6–18 months, depending on the recruitment rate.

ETHICS AND DISSEMINATION

Research ethics approval

Ethical approval was provided by the Health Research Ethics Committee of the Capital Region of Denmark on 10 May 2019 (identifier number: H-19014479). The trial has been approved by the Danish Medicines Agency (2019-000404-15) and the Regional Data Protection Agency (P-2019-224).

Protocol amendments

All protocol amendments have been reported to and preapproved by the regional Ethics Committee and the Danish Medicines Agency before being implemented in the trial. At the time of approval of major changes, all study investigators and study personnel have been informed. All major protocol amendments and their rationale are listed in table 1.

Informed consent

Eligible patients receive both oral and written information about the study from study investigators. Informed consent is neither sought from patients with transient or persistent cognitive impairments nor from their relatives or authorised surrogates. The consent form is available in online supplemental material.

Confidentiality

Study investigators and treating physicians associated to the study identify patients eligible for inclusion during their hospital admission. Information on enrolled participants is registered and kept in electronic case report forms in REDCap. All study personnel are obliged to handle all data on participants confidentially in accordance with the Act on Processing of Personal Data.[25]

Access to data

The sponsor site will have access to the final trial dataset, while each study site will only have access to the local dataset including participants at their own site.

Table 1 Summary of major protocol amendments

Protocol version	Protocol date	Change description	Rationale
1.0	22.02.2019	Sent for review to relevant authorities	–
2.0	29.03.2019	Approved for study start	–
3.0	12.11.2019	(a) Time limit for antibiotic initiation following chest X-ray is expanded from 8 hours to 12 hours. (b) Exclusion criterium concerning the presence of multilobar infiltrates is waived.	(a) New time limit more compatible with actual timeframes (delay of administration of antibiotics due to high workload of nurses, etc). (b) More patients fulfil this criterium than expected, not included as exclusion criterium in previous similar studies.
4.0	09.01.2020	The randomisation window is expanded from only day 5 till day 3, 4 or 5 but still requires clinically stable at time of randomisation.	Patients that achieve clinical stability at day 3 or 4 of antibiotic therapy are discharged before day 5. Changes are made to secure a pragmatic trial that closely resembles everyday clinical practice.
5.0	07.09.2020	An additional study site (Herlev Hospital) is included. CT scan is accepted as method to detect new infiltrate (in addition to chest X-ray).	Some study sites prefer to use CT scan instead of chest X-ray.
6.0	02.12.2020	Patients with long-term oxygen therapy can be included if they have a peripheral saturation ≥90% with their habitual level of oxygen supplement.	To secure a pragmatic trial with diverse patients.
7.0	10.11.2021	An additional study site (Bispebjerg Hospital) is included. Study period is extended from 2022 to 2024.	To secure sufficient recruitment of participants following slow recruitment rate due to late initiation of study sites and paused recruitment during COVID-19 peaks.

Patient and public involvement

No patients were involved in the research process.

Ancillary and post-trial care

Patients participating in the trial are insured by the National Patient Insurance, according to the Act (No. 547 of 2005) respecting access to complaints and compensation within the healthcare system.[26]

Dissemination policy

Study results will be published in a peer-reviewed journal with the coordinating principal investigator as first author, the sponsor as senior author and the other principal investigators as coauthors.

All participants who have requested to be informed of the final results will receive them individually. In addition, efforts will be made to communicate the results to the public through social media or other. Finally, the results will be presented at both national and international conferences.

Data availability statement

Trial data will be made available in anonymous form at public clinical trial databases when the trial has ended. Anonymised patient-level data and other detailed information will be provided by reasonable request to the corresponding author.

Trial status

The first trial participant was enrolled in September 2019. Recruitment is expected to be completed in June 2024.

DISCUSSION

The findings from this study will add further evidence in establishing whether short-course antibiotic therapy of CAP is appropriate for patients with an early clinical response. Guiding treatment duration based on clinical measurements that are part of everyday clinical practice would facilitate clinical decision making and engage clinicians in evaluating the treatment regimen regularly.

Existing literature is mostly performed on drug-specific regimens and relies on clinical cure as the primary outcome.[8 9 13 14 18 27] When applying a non-inferiority design, it is of utmost importance that we do not risk accepting a treatment that is in fact clinically inferior to standard care. Therefore, the primary outcome should comprise the most important clinical safety measures. In our view, readmissions and mortality are of primary concern in this population while clinical cure or the prescription of new antibiotics may represent secondary measures indicating clinical failure.

In addition, settling on a non-inferiority margin is not straightforward. A recent systematic review of non-inferiority trials evaluating mortality as (part of) the primary outcome showed that non-inferiority margins were large and varied a lot.[28] Clinical trial guidelines by the European Medicines Agency propose a non-inferiority margin of −10% when evaluating the treatment response in CAP.[12] As the CAP5 trial evaluates more serious safety measures as primary outcome, we considered a narrower margin of −6% as clinically relevant when determining non-inferiority.

Overall, comparing antibiotic therapies of 5 days and 7 days does not provide a wide 'window' to detect a difference between treatment groups. However, by allowing the treating physician to extend the antibiotic therapy in the standard group, the mean treatment duration in this group will probably exceed 7 days. In the sample size estimation, we assumed that the event rate would be similar between groups, given available evidence, but we had to rely on only a few studies for the actual numbers as most studies assess 30-day rather than 90-day outcomes. Therefore, the expected event rates might have been slightly underestimated which is in line with findings from our recent study examining a CAP cohort of individuals achieving early clinical response.[29]

We chose to evaluate the primary outcome on all-cause readmissions and all-cause mortality within 90 days from admission as it would provide assurance that all severe events following the intervention were captured. In this way, study participants would have sufficient time to be readmitted or restart antibiotic therapy due to relapse, or ultimately die due to complications. Meanwhile, this is at the expense of including unrelated events and possible diluting the impact of the intervention as events occurring in more close relation to the intervention are more likely to be pneumonia related.[30]

Given the imprecision of the expected event rates, a possible sample size re-estimation was planned at the first interim analysis based on the observed event rates. However, due to extraordinary circumstances with the COVID-19 pandemic during the inclusion of the first 100 participants, the DSMB recommended to postpone this re-estimation to the second interim analysis, including the first 250 participants. Depending on the future recommendation by the DSMB, this could affect the final study size substantially.

Finally, the impact of performance bias should be considered given the open-label design. The participants in the interventional group know that they are receiving a therapy shorter than usual and could thus be more prone to contact the healthcare system for additional antibiotics if they experienced contemporary lack of or slow improvement. This could as a result potentially lead to more antibiotic prescriptions and visits to the outpatient clinic or general practitioner. Therefore, we sought to mitigate the impact of this bias by (1) using objective outcomes as primary outcomes that might be less affected than more subjective outcomes and (2) blinding the outcome assessor.

Although our study population only comprises a subgroup of the entire population with CAP, the results could still have significant impact internationally as pneumonia is a very frequent infectious disease. At best, this trial could (1) provide clinicians and patients with reassuring evidence needed for implementing the

short-course strategy, (2) spare the community for non-essential antibiotic load to help fight increasing antimicrobial resistance and (3) save patients unnecessary adverse events related to prolonged-course therapy.[31 32]

If short-course antibiotic therapy is deemed appropriate, future studies should consider designs in which treatment duration could be even more individually assigned, without a fixed date, guided by the onset of clinical stability or other everyday clinical measurements. Ideally, this strategy could be substantiated in multinational studies and across common infectious diseases requiring antibiotics.

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Contributors SBI and TB conceived the study idea. SBI and TB acquired the funding for the study. SBI, ST, LT-U and TB designed the study. SBI drafted the manuscript of the protocol. All authors critically revised the manuscript. SBI, ST, LT-U, BL, ISJ, AK, LHM, PR and TB participated in the conduct of the study. All authors have read and agreed to the final version of the manuscript.

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Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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