The Effect of Focused Lung Ultrasonography on Antibiotic Prescribing in General Practice

NCT06210282

May 29, 2024

STATISTICAL ANALYSIS PLAN (SAP)

Title

The effect of focused lung ultrasonography on antibiotic prescribing in patients with acute lower respiratory tract infections in Danish general practice: A pragmatic randomized controlled trial.

The PLUS-FLUS Trial.

Study group

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1. Introduction

Antimicrobial resistance is one of the largest threats to global health, stated by The World Health Organization (WHO)[1]. Antibiotic use is the main driver of selection of resistant bacteria[2], and resistance develops quickly after any antibiotic use. Primary health care is responsible for 90% of all antibiotic prescriptions in human in Denmark[3]. General practitioners (GPs) issue 75% of these prescriptions[4] with acute lower respiratory tract infections (LRTIs) being one of the most common indications[5].

Acute LRTIs includes several different conditions with overlapping symptoms such as acute bronchitis and community-acquired pneumonia (CAP)[6]. No single symptom or specific point of care test (POCT) cut-off value, e.g. C-reactive protein (CRP), can be used to discriminate the diagnoses[7,8]. It is well known that this diagnostic uncertainty leads to overuse of antibiotics[9].

An alternative mode of diagnosing CAP is using focused lung ultrasound FLUS. Several studies have demonstrated that FLUS has an excellent accuracy for diagnosing pneumonia in hospitalised adults[10-15]. FLUS is not a common application for GPs using point-of-care ultrasonography (POCUS)[16] in general practice, even though GPs are increasingly using POCUS[17]. We do not know yet if FLUS can help discriminating between benign self-limiting acute LRTIs and bacterial CAP in general practice. **This trial aims to pragmatically determine if the addition of FLUS to usual care can effectively reduce the prescription of antibiotics** in patients presenting to general practice with an acute LRTI.

2. Study Objectives, Hypothesis and Outcomes

2.1. Primary Objective and Outcome

Primary objective: To determine if adding focused lung ultrasonography (FLUS) to usual care of patients presenting with symptoms of an acute lower respiratory tract infection (LRTI) in general practice reduces the general practitioner's (GP) antibiotic prescribing at index consultation (day 0).

The primary outcome: The proportion of participants who are prescribed antibiotics during index consultation (day 0).

The null hypothesis is that there is no difference in the proportion of participants who are prescribed antibiotics during index consultation in participants who have FLUS performed in addition to usual care compared to those who receive usual care only.

The alternative hypothesis is that FLUS, performed by the GP in addition to usual care, will lead to a significant decrease in the proportion of participants who have antibiotics prescribed during index consultation.

2.2. Secondary Objectives and Outcomes

Secondary objectives:

- To compare the clinical course of participants in terms of antibiotics prescribed up to day 28, duration and burden of LRTI symptoms, re-consultations, imaging performed, illness deterioration (hospitalization, complications, all-cause mortality), referral for and number of cancer diagnoses in review of medical records up to day 60, and spontaneously reported unintended events detected up to day 60.
- To assess participants' satisfaction with the index consultation.

Secondary outcomes:

1) Outcomes from the LRTI symptom diary:

Participants will be asked to complete a validated LRTI symptom diary every day from the day of index consultation (day 0) to day 21[18]. The recorded items include the following six symptoms of LRTI: cough, dyspnea, sputum production, well-being, sleep disturbance, and activity disturbance. The participants are asked to consider how bad each symptom has been over the past 24 hours by scoring each symptom on a 7-point Likert scale (0 = no problem, 1 = very little problem, 2 = slight problem, 3 = moderate problem, 4 = bad problem, 5 = very bad problem, and 6 = as bad as it could be). Moreover, the diary contains a social domain on cancellation of work-related or leisure activities. Only on the day of the index consultation (day 0) the diary will incorporate a question on participants' satisfaction with the consultation assessed on a 5-point Likert scale (very dissatisfied (1) to very satisfied (5)).

1.1) Daily total LRTI symptom score, calculated as the sum of the scores for six symptoms
(minimum 0 – maximum 36) (mean/median).

1.2) The number of days with symptoms rated as "moderate problem" or worse by the participant (at least one item with a score of 3 or above) (mean/median).

1.3) Number of days participants signed in sick/cancelled work-related activities or cancelled leisure activities (mean/median).

1.4) Proportion of participants who were satisfied or very satisfied (4 or 5) with the index consultation.

Outcomes 1.1, 1.2 and 1.3 from the LRTI symptom diary will be calculated for each participant every day from day 0 until the participant has scored 0 for every item, whichever comes first, or up to a maximum of 21 days.

*2) Outcomes from participants' shared medication records (*i.e.*, FMK) and on type of prescription:*

As standard care and communication method, data on changes in medicine or new prescriptions are automatically uploaded to participants' electronic shared medication record (FMK). We will review the participants' shared medication records (FMK) for outcomes on antibiotics prescribed during follow-up:

2.1) Proportion of participants who have antibiotics prescribed within 7 days after the index consultation.

2.2) Proportion of participants who have antibiotics prescribed within 28 days after the index consultation.

If antibiotics are prescribed at the index consultation (day 0), the GP is asked to report whether the prescription is an immediate or delayed prescription.

2.3) Proportion of antibiotics prescribed as delayed antibiotic prescriptions at index consultation (day 0).

As standard care and communication, GPs receive notices of health-related events, e.g., discharge and out-of-hour notices. From participants' electronic medical records, we will obtain outcomes on the clinical course during follow-up:

3) Outcomes from participants' electronic medical records:

3.1) Proportion of participants with reconsultations, defined as any primary care contact (general practice or out-of-hour services), within 28 days after the index consultation.

3.2) Proportion of participants admitted to the hospital within 28 days after the index consultation.

3.3) Proportion of participants with complications (pleural infection (defined as complicated parapneumonic effusion or empyema), lung abscess, or sepsis) during admission to hospital within 28 days after the index consultation.

3.4) Proportion of participants with imaging other than FLUS (any imaging performed in secondary health care services) performed within 28 days after the index consultation.

3.5) Other imaging methods performed within 28 days after the index consultation.

3.6) Proportion of participants referred with suspicion of cancer within 60 days after the index consultation.

3.7) Proportion of participants diagnosed with cancer within 60 days after the index consultation.

3.8) Number of spontaneously reported unintended events up to 60 days after the index consultation.

3.9) All-cause mortality up until day 28 and day 60.

2.3. Exploratory Objectives

Non-applicable.

2.4. Specification of endpoints

Primary Endpoint: The primary endpoint is at index consultation (day 0).

Secondary Endpoints: Secondary endpoints are days 0-21, 7, 28 and 60.

3. Study Design

3.1 Trial Design

The study is a pragmatic randomised controlled superiority trial, with a two-group parallel design and a participant allocation ratio of 1:1.

Control arm: Usual Care

Participants assigned to the control group will receive the GP's usual care of adults (≥ 18 years) presenting with symptoms of an acute LRTI where the GP suspects CAP. Usual care is recommended to follow applicable guidelines. Usual care does not include a FLUS examination.

Intervention arm: +FLUS

Participants assigned to the intervention group will receive a FLUS examination during the index consultation (day 0) in addition to usual care.

3.2. Randomization and Blinding

The unit of randomisation is the patient. Participants will be randomized 1:1 to either Usual Care or +FLUS group. Each general practitioner will be provided with a pile of sequentially numbered opaque sealed envelopes (SNOSE)[19]. The SNOSE piles will be prepared by a remote independent researcher, using permuted block randomization to ensure similar enrolment in both groups. Different block sizes will be used to prevent the allocation sequence from being anticipated. Details on block sizes and list lengths are unavailable to general practitioners who enroll patients and assign interventions.

Owing to the type of intervention, participants and GPs are not blinded. However, members of the research team involved in obtaining or analysing data (outcome assessors and data analysts) will be blinded to the allocation until data analyses have been finalised.

3.3. Sample Size

Based on previous audit projects in general practice in Denmark[20-21], a Danish study by Holm et al.[9] and a Dutch study on reducing antibiotic prescribing in patients with LRTI[22], we assume to detect a 15% decrease in antibiotic prescribing in patients with LRTI from 50% (usual care) to 35% (+FLUS). Using a 5% significance level and a power of 80% a total of 340 patients with 170 trial participants in each arm is needed. We assume withdrawal or discontinuation by a maximum of 10% of participants[22]. Furthermore, we increase the sample size by 5% to account for covariates in the analyses. Consequently, we plan to include a total of 390 trial participants (195 in each arm). Each GP is encouraged to include a minimum of 10 participants to account for the individual effect of FLUS on antibiotic prescribing at a GP level.

3.4 Statistical interim analyses

No interim analysis will be performed.

3.5 Timing of final analysis

All outcomes will be analysed collectively.

4. Trial Population

4.1. Eligibility

Patients

Inclusion criteria:

Patients aged ≥ 18 years with acute cough (< 28 days) and at least one other symptom of LRTI and where the GP suspects a community-acquired pneumonia (CAP).

Exclusion criteria:

- Previous antibiotic treatment for the current episode of acute LRTI.
- The patient is not listed with the GP (no medical record available).
- The patient is not capable of understanding and signing informed consent.
- The patient do not wish to participate in the study.

General practitioners

Inclusion criteria:

General practitioners who use point-of-care ultrasonography at least once a week in general practice or out-of-hour services.

4.2 Baseline characteristics

Patients

Date of enrolment, age, sex (provided from social security number), comorbidities, smoking status. Participants' symptoms and signs of acute LRTI, the results of physical examination and any POCT performed as part of usual care (e.g., CRP) in both groups. FLUS pathological findings will be reported for the +FLUS group.

General practitioners

Age, sex, region of Denmark, type of clinic, seniority as a GP, experience with POCUS, experience with FLUS, type of ultrasound device (hand-held, laptop or fixed), ultrasound brand and model, transducer(s) used, and baseline antibiotic prescribing.

Baseline characteristics	**Unit/options**	**Endpoint** (days from index consultation)					**Type of data**	**Statistical analyses**
		0	0-21	7	28	60		
General practitioners								

Age	Years	X					Ratio	Mean/Median, 95% CI
Sex	Male/Female	X					Nominal	Proportions
Region of Denmark	North/Central/Southern /Zealand/Capitol	X					Nominal	Proportions
Type of clinic	Solo/Partnership/ Collaboration/Other	X					Nominal	Proportions
Seniority as a GP	Years	X					Ratio	Mean/Median, 95% CI
Experience POCUS	Years	X					Ratio	Mean/Median, 95% CI
Experience FLUS	Years	X					Ratio	Mean/Median, 95% CI
Type of ultrasound machine system	Hand-held, Laptop, Stationary	X					Nominal	Proportions
Number of transducers available	Number	X					Ratio	Mean/Median, 95% CI
Type of transducer used for FLUS	Linear/curved/phased-array/other	X					Nominal	Proportions
Baseline antibiotic prescribing	Defined as daily doses per 1000 patients per year	X					Ratio	Mean/Median, 95% CI
Patients								
Date of enrolment	Date	X					Ordinal	Used to calculate age at date of enrolment
Date of birth	Date	X					Ordinal	Used to calculate age at date of enrolment
Age	Years	X					Ratio	Mean/Median, 95% CI, Independent samples t-test/Mann Whitney U
Sex	Male/Female	X					Nominal	Proportions, Chi^2 or Fischer's exact
List of comorbidities	Present/not present	X					Nominal	Proportions, Chi^2 or Fischer's exact
Smoking status	Smoker/former smoker/never-smoker	X					Nominal	Proportions, Chi^2 or Fischer's exact
List of symptoms	Present/not present	X					Nominal	Proportions, Chi^2 or Fischer's exact
List of clinical findings	Present/not present	X					Nominal	Proportions, Chi^2 or Fischer's exact
List of point-of-care tests	Performed/not performed	X					Nominal	Proportions, Chi^2 or Fischer's exact
Point-of-care test results	CRP: mg/L; Leukocytes: 10^9/L; Saturation: %; Pulse: Beats/min.	X					Ratio	Mean/Median, 95% CI, Independent samples t-test/Mann Whitney U

5. Statistical Principles and Analysis

All analyses described in this plan are considered *a priori* analyses as they have been defined in the protocol or in this statistical analysis plan. If any *post-hoc* analyses are conducted, they will be defined as such in the report.

5.1. Analysis set

Analyses will be performed as intention to treat (ITT) (pragmatic trial). The primary analysis population will comprise all participants, irrespective of follow-up. We will use bootstrap to handle non-normality and use a 5% significance level.

5.2. Lost to follow-up and missing data

In the case of missing data on the primary endpoint, the GP who enrolled the participant will be contacted to clarify if antibiotics were prescribed at the index consultation. If clarification is not obtained, we will consider it as if antibiotics were prescribed at the index consultation. We expect that the use of an e-CRF for GPs to complete at the time of index consultation will keep missing data on the primary outcome at a minimum. We expect that only observed data will be included in the secondary analyses.

5.3. Data validation

Data will be examined for missing values and outliers. Measures of central tendency and dispersion for continuous study parameters will be portrayed. Extreme or unexpected values will be examined individually for authenticity and data discrepancies addressed where appropriate.

5.4. Primary Outcome

The primary outcome data will be displayed in a 2x2 table comparing the dichotomous outcome variable of antibiotics prescribed at the index consultation. The primary analyses will be the proportion of patients prescribed an antibiotic at the index consultation (day 0) in the two groups. The primary analyses will also include the risk ratio (RR) presented with a 95% confidence interval (95% CI). We will test is there is a difference in the risk of having antibiotics prescribed at the index consultation between the two groups. We will consider the variation between GPs as part of the primary analyses.

Outcome	**Unit/options**	**Endpoint** (days from index consultation)	**Type of data**	**Statistical analyses**

		0	0-21	7	28	60		
Primary outcome								
Antibiotics prescribed at index consultation	Yes/No	X					Nominal	Proportions, RR, 95% CI, Chi^2

5.5. Secondary Outcomes

Table 1: All measured outcomes at different endpoints with type of data and planned statistical analyses are listed below

Outcome	**Unit/options**	**Endpoint** (days from index consultation)					**Type of data**	**Statistical analyses**
		0	0-21	7	28	60		
Secondary outcomes								
Daily total LRTI symptom score	0-36		X				Ordinal	Mean/Median, 95% CI, Chi^2 or Fischer's exact
Duration of symptoms rated 3 or above	Days		X				Ratio	Mean/Median, 95% CI, Independent samples t-test/Mann Whitney U
Cancelled work related activities	Days		X				Ratio	Mean/Median, 95% CI, Independent samples t-test/Mann Whitney U
Cancelled leisure activities	Days		X				Ratio	Mean/Median, 95% CI, Independent samples t-test/Mann Whitney U
Satisfied or very satisfied (4 or 5) with index consultation	1 (very dissatisfied), 2 (dissatisfied), 3 (nor dissatisfied or satisfied), 4 (satisfied), 5 (very satisfied)	X					Nominal	Proportions, Chi^2 or Fischer's exact
Type of antibiotic prescription at index consultation	Immediate/Delayed	X					Nominal	Proportion, RR, 95% CI, Chi^2 or Fischer's exact
Antibiotic prescribed within 7 days after index consultation	Yes/No			X			Nominal	Proportion, RR, 95% CI, Chi^2 or Fischer's exact
Antibiotic prescribed within 28 days after index consultation	Yes/No				X		Nominal	Proportion, RR, 95% CI, Chi^2 or Fischer's exact
Reconsultation within 28 days after index consultation	Yes/No				X		Nominal	Proportion, RR, 95% CI, Chi^2 or Fischer's exact
Hospitalization within 28 days after index consultation	Yes/No				X		Nominal	Proportion, RR, 95% CI, Chi^2 or Fischer's exact
Complication within 28 days after index consultation	Yes/No				X		Nominal	Proportion, RR, 95% CI, Chi^2 or Fischer's exact

Referred for suspicion of cancer (any) within 60 days after index consultation	Yes/No					X	Nominal	Proportion, RR, 95% CI, Chi^2 or Fischer's exact
Diagnosed with cancer (any) within 60 days after index consultation	Yes/No					X	Nominal	Proportion, RR, 95% CI, Chi^2 or Fischer's exact
All-cause mortality within 60 days after index consultation	Yes/No					X	Nominal	Proportion, RR, 95% CI, Chi^2 or Fischer's exact
Adverse event within 60 days after index consultation	Yes/No					X	Nominal	Proportion, RR, 95% CI, Chi^2 or Fischer's exact

5.6 Methods for additional analyses (e.g., subgroup analyses)

We will conduct subgroup analyses of the primary outcome of participants with chronic obstructive pulmonary disease (COPD), comorbid pulmonary disease in general, with a CRP concentration > 50 mg/L or aged ≥ 80 years to determine the risk of effect modification.

5.7 Statistical software

The PI, who is blinded to group allocation, will perform the statistical analyses in Stata Version 17 according to the SAP. The PI and coauthors remain blinded until after the analyses have been performed, and conclusions are drawn.

6. Implementation of Analysis Plan

Any revision of the SAP will appear from version number. The SAP will be uploaded to ClinicalTrials.gov NCT06210282 before enrolment of the last participant.

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