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Improved diagnostics of infectious diseases in Emergency Departments – a protocol of a multifaceted multicenter diagnostic study

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Improved diagnostics of infectious diseases in Emergency Departments

– a protocol of a multifaceted multicenter diagnostic study

Short title: Improved diagnostics of infectious diseases

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Abstract

Background: The major obstacle in prescribing an appropriate and targeted antibiotic treatment is insufficient knowledge concerning *whether* the patient has a bacterial infection, *where* the focus of infection is and *which* bacteria are the agents of the infection. A prerequisite for the appropriate use of antibiotics is timely access to accurate diagnostics such as point-of-care (POC) testing.

The study aims to evaluate diagnostic tools and working methods that support a prompt and accurate diagnosis of hospitalized patients suspected of an acute infection. We will focus on the most common acute infections; community-acquired pneumonia (CAP) and acute pyelonephritis (APN). The objectives are to investigate 1) patient characteristics and treatment trajectory of the different acute infections, 2) diagnostic and prognostic accuracy of infection markers, 3) diagnostic accuracy of POC urine flow cytometry on diagnosing and excluding bacteriuria, 4) how effective the addition of POC analysis of sputum to the diagnostic set-up for CAP is on antibiotic prescriptions, 5) diagnostic accuracy of POC ultrasound and ultralow dose (ULD) Computed Tomography (CT) on diagnosing CAP, 6) diagnostic accuracy of specialist ultrasound on diagnosing APN, 7) diagnostic accuracy of POC ultrasound in diagnosing hydronephrosis in patients suspected of APN.

Methods and analysis: It is a multifaceted multicenter diagnostic study, including 1000 adults admitted with suspicion of an acute infection. Participants will within the first 24 hours of admission undergo additional diagnostic tests including infection markers, POC urine flow cytometry, POC analysis of sputum, POC and specialist ultrasound, and ultralow dose CT. The primary reference standard is an assigned diagnosis determined by a panel of experts.

Ethics, dissemination and registration: Approved by Regional Committees on Health Research Ethics for Southern Denmark, Danish Data Protection Agency, and clinicaltrials.gov. Results will be presented in ten peer-reviewed journals, and positive, negative and inconclusive results will be published.

Key words: Acute Infection, antibiotics, diagnostic, pneumonia, pyelonephritis, sputum, point-of-care-test, ultrasound, infection marker, Ultralow dose Computed Tomography

Strengths and limitations of the study:

- It is a pragmatic study that reflects reality and has potential for substantial clinical significance
- The study combines diagnostics and knowledge from five different medical specialties
- The study is complex and contains a number of sub-studies which share the same population
- COVID-19 and the consequent societal lockdown might affect patient distribution

Introduction

Antibiotic resistance

Multi-resistant bacteria is one of the major threats to the public health(1). The incidence of multi-resistant bacteria is increasing in Denmark(2) and every 20th patient admitted to a Danish Emergency Department (ED) is colonized with multi-resistant bacteria(3). Denmark has focused on this challenge(4) by screening special patient groups for multi-resistant bacteria(5, 6), and by initiating campaigns to reduce antibiotic consumption - mainly the use of broad-spectrum antibiotics in hospitals(4, 7).

The Danish Ministry of Health has made extensive efforts targeting the use of antibiotics in hospitals. However, the major obstacle in reducing the prescription of broad-spectrum antibiotics is insufficient knowledge concerning *whether* the patient has a bacterial infection, *where* the focus of infection is and *which* bacteria are the agents of the infection(8). Uncertainty in the answers to these three questions often leads a clinician to choose a broad-spectrum antibiotic at the onset of treatment. Unfortunately, the prescription of a broad-spectrum antibiotic is rarely revised when laboratory results are available, often because the patient already has been discharged(9).

Acute infections and diagnostic tools

A prerequisite for appropriate use of antibiotics is timely access to accurate diagnostic tests, since treatment of acute infections should be initiated within a few hours to avoid serious complications such as bacteremia, sepsis, organ failure, septic shock and death(10). The most common conditions among ED patients with suspected infections are community acquired pneumonia (CAP) and acute pyelonephritis (APN)(11, 12). Diagnosing CAP and APN can be challenging as symptoms are often weak and nonspecific and the current methods for focal and etiological diagnosis have low sensitivity and specificity and often deliver results after the decision regarding antibiotic treatment has been made(9, 13, 14).

The Coronavirus Disease 2019 (COVID-19) pandemic has highlighted the need of accurate diagnostic tests. Quick and correct classification of pneumonia as COVID-19, another viral or bacterial pneumonia, or even COVID-19 complicated with bacterial pneumonia, is of vital importance to select the correct treatment (including antibiotics), and the correct infection control measures, including isolation.

In order to make the correct diagnosis and prescribe an appropriate and targeted treatment within a few hours of admission, it is important to the physician to be able to answer the following three questions: a) Is it an infection that requires antibiotic treatment (*infection marker*)? b) Where is the focus of infection (imaging *diagnosis*)? c) Which bacteria should the prescribed antibiotic target (*etiologic diagnosis*)?

Bacterial infection markers

To support the diagnosis of an infection and assess its severity, a measure of the systemic inflammatory response is useful e.g. abnormal temperature, elevated leucocyte count with neutrocytosis, or elevated C-reactive protein (CRP). Some uncertainty is associated with CRP because it has a delayed response to bacterial infection and often is elevated in non-infectious inflammatory conditions(15). A more sensitive and specific marker that can differentiate between bacterial and viral infection and reflect the severity of the infection is desired(16). Serum procalcitonin (PCT) has potential as a diagnostic tool in suspected bacterial infections(17) and can distinguish between viral and bacterial pneumonias(18). Soluble urokinase plasminogen activator receptor (suPAR) might have a potential as a marker for acute bacterial infections requiring antibiotic treatment(19). However, there are no well-conducted studies which compare simultaneously all three biomarkers diagnostic abilities for bacterial infections in general or in relation to CAP or APN (16, 20).

Imaging diagnostics

The CAP diagnosis is primarily based on clinical symptoms and findings, supplemented with chest X-ray, which has a low sensitivity and specificity (21). Identifying an improved imaging alternative with high diagnostic sensitivity and specificity and minimal risk to the patient is imperative. Computed Tomography scans (CT), e.g. high-resolution CT (HRCT) provides a detailed diagnosis of thoracic diseases, but the radiation dose is high and potentially harmful. Low-dose CT has shown promising diagnostic results, but the radiation dose is still potentially harmful (22). Ultralow dose CT (ULDCT) of the thorax could be an alternative, but has yet to be studied within an ED context. Another relevant imaging modality is ultrasound scanning (US). US of the lungs is useful to diagnose pulmonary edema and pleural effusion, but the value of US performed by a novice operator when diagnosing CAP in an ED setting needs further investigation(23).

Currently, no imaging methods are used to verify the diagnosis of APN. The diagnosis is primarily based on unspecific clinical findings (24), and is often not confirmed microbiologically (25). Complicating factors such as hydronephrosis and renal abscess can be visualized with conventional US (26). Contrast enhanced US (CEUS) seems to be a promising diagnostic imaging modality of acute renal inflammation (27, 28). The value and suitability in a clinical setting of this more advanced US investigation is unknown.

Etiological diagnostics

Sputum can be cultivated to determine the agent of CAP. However, results are often unspecific and not available until after discharge of the patient or completion of treatment(9). A point-of-care (POC) tool providing rapid microbiological results on e.g. sputum samples would therefore be useful. Systems are available today based on polymerase chain reaction (PCR) methods with results available within one hour for a variety of viral and bacterial pathogens (29). The impact of such fast diagnostic systems on antibiotic prescriptions has not been investigated in an ED context.

The diagnosis of APN is verified by significant bacteriuria in urine culture (25), but as many as half of the patients with clinical APN fails to meet this diagnostic criterion. Unfortunately, the time from sample to result for urine cultures is more than 24 hours (24, 25, 30, 31). Urine test strips are unreliable with low specificity and low predictive values(32). Therefore, a POC test is desired, which can provide rapid results and quickly identify a bacteriuria. One such tool may be urine flow cytometry (UFC), which has shown promising diagnostic value for the exclusion of bacteriuria with a high negative predictive value (33). However, better documentation for its use as an ED diagnostic screening method is needed.

Aim and objectives

Our broad hypothesis is that improved diagnostic strategies for patients in ED with suspicion of systemic infection can contribute to more rapid and accurate diagnosis. Thereby, we assume that a more appropriate antibiotic treatment can be administered to these patients.

The project aims to evaluate alternative diagnostic tools and working methods that support a prompt and accurate diagnosis of hospitalized patients suspected of an acute infection. We will focus on the most common ED infections; CAP and APN. The research objectives are to answer the following questions:

1) What are the patient characteristics and treatment trajectory of the different ED infections?
2) What is the diagnostic and prognostic accuracy of the infection markers PCT, suPAR, and CRP in patients with suspected CAP and APN?
3) What is the diagnostic accuracy of POC-UFC on diagnosing and excluding bacteuria?
4) How effective is the addition of POC-PCR analysis of sputum to the diagnostic set-up for CAP on antibiotic prescribing?
5) What is the diagnostic accuracy of POC-US and ULDCT on diagnosing CAP?
6) What is the diagnostic accuracy of CEUS on diagnosing APN?

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7) What is the diagnostic accuracy of POC-US in diagnosing hydronephrosis in patients suspected of APN?

The ultimate goal is to combine the results of all these seven objectives into a novel diagnostic model which the ED physician can apply when receiving a patient with suspicion of infection.

Methods

Study design

The study is designed as a multifaceted multicenter diagnostic study. Participants will undergo additional diagnostic tests depending on the primary suspected focus of infection.

The study protocol is reported in accordance with the SPIRIT (Standard protocol items: Recommendations for interventional trials) statement(34).

Setting

The study will recruit participants from three Danish EDs: the regional Hospital, Lillebælt Hospital in Kolding, the regional Hospital, Hospital Sønderjylland in Aabenraa, and the University Hospital, Odense University Hospital in Odense. Enrolment commences from February 8th 2021 and continues until the predefined sample size has been reached.

Six project assistants will recruit the participants and collect data. The project assistants will have a healthcare education (physicians, physiotherapists and medical students). They are certificated in focused US of kidney and lung (one-day POC-US course, 25 supervised scans, and Objective Structured Assessment of US Skills (OASUS) test) within one month from enrollment.

The study originates from the Emergency Research Unit affiliated at Hospital Sønderjylland and Department of Regional Health Research at University of Southern Denmark.

Population and eligibility criteria

Inclusion of patients is based on the receiving ED physician's initial clinical assessment of the patient. Adults aged 18 or older admitted to the ED will be invited to participate in the study, if the receiving physician suspects the patient is having an infection. Only patients able to give informed consent will be invited. Depending on primary suspected focus of infection (CAP, APN or other/unknown), the patients will be included into one of three diagnostic tracks (A, B, or C) as shown in Figure 1. In this study we define APN as a urinary tract infection with typical local symptoms and systemic affection (i.e. fever, sepsis), thus indicating ascension of infection above the bladder.

Exclusion criteria that apply to all three tracks:

- If the attending physician considers that participation will delay a life-saving treatment or directly transfer to intensive care unit
- Admission within the last 14 days to avoid hospital acquired infections
- Verified COVID-19 disease within 14 days before admission.
- Pregnant women
- Severe immunodeficiencies:
    - Primary immunodeficiencies
    - Secondary immunodeficiencies
        - Human immunodeficiency virus (HIV) positive cluster of differentiation 4 (CD4) <200
        - Patients receiving immunosuppressive treatment (Anatomical therapeutic chemical (ATC) classification L04A)

- Corticosteroid treatment (>20 mg/day prednisone or equivalent for >14 days within the last 30 days)
- Chemotherapy within 30 days

Exclusion criteria that only apply to patients with suspected CAP (track A):

- Patients <40 years old are excluded from the ULDCT and HRCT due to risk of cancer from radiation
- Patients <65 years who already participated once will be excluded from ULDCT and HRCT due to risk of cancer from radiation

Exclusion criteria that only apply to patients with suspected APN (track B):

- Patients are excluded from magnetic resonance imaging (MRI) according to common MRI exclusion criteria (e.g. contraindicating metal in the body) and claustrophobia
- Patients with known allergy to US contrast

Figure 1 Design of patient flow and diagnostic tracks

Recruitment

The study assistants will identify potential eligible patients through the local logistic system. According to the local guidelines, a medical clinical assessment of the patients is performed within half an hour from arrival at the ED(35). The study assistant will immediately after the assessment consult the receiving physician to ask if a) a systemic infection is suspected, and b) what the most likely focus is: lungs, urinary tract, elsewhere or unknown. If the patient meets eligibility criteria, the study assistant will present the study both verbally and in writing, and invite the patient to participate in the study.

Procedure

The study assistant will after obtained written consent order blood samples, urine sample, and the diagnostic tests described in the assigned track. The study assistant will collect data regarding current symptoms and signs, lifestyle factors, disease severity, vital parameters, triage at arrival, comorbidities, functional status, resident status, antibiotics prescribed during the last month, and medical history by looking in the patient record and by patient interview.

Infection markers

Blood samples will be collected by a medical laboratory technologist and transferred to the local laboratory for analysis of CRP, PCT and suPAR. Laboratory staff will be blinded to participant diagnosis and outcome. CRP and PCT results will be available to the treating physician, but the suPAR result will not be available. CRP will be measured using an immunoturbidimetric assay (Tina-quant®, Roche) on Roche/Hitachi Cobas© systems. Plasma PCT will be quantified by an automated sandwich immunoassay "ECLIA" (Elecsys®, BRAHMS PCT-analyses) on Cobas© within two hours from collection according to standard procedure. Plasma suPAR will be quantified by using the commercial available suPARnostic© Tubilatex assay reagents (ViroGates, Denmark) on Cobas© as previously validated (36). Separated plasma is kept refrigerated and analysed for suPAR within 48 hours after collection.

POC-UFC

A urine sample will be collected according to routine procedure by the study assistant. The sample will be divided into two aliquots; one half for routine urine culturing, and one half for POC-UFC analysis (UF-5000, Sysmex, Kobe, Japan). The analysis will be performed according to manufacturer's instruction and conducted by laboratory staff.

Laboratory staff will be blinded to participant diagnosis and outcome. The results of the POC-UFC analysis will not be visible to the treating physician.

POC-PCR sputum analysis

A sputum sample will be collected according to standard procedure as soon as possible after recruitment by the study assistant. This sample will be randomly assigned to one of two groups with 1:1 allocation: 1) POC-PCR analysis (Biofire® FilmArray® Pneumonia Panel plus, Biomérieux, Marcy l'Etoile, France) in accordance with manufacturer's instruction(37), and 2) Routine microbiology analysis (culturing and PCR). The randomization will be performed by the study assistants and generated electronically using Research Electronic Data Capture (RedCap) Randomization Module (38) with permuting blocks and stratified according to sites. The result of the POC-PCR will be presented by the study assistant to the treating physician within four hours upon admission. The treating physician will along with the result receive a recommended action list, developed by microbiologists.

The patients will be blinded, and the investigator will be blinded to data management and analysis. Outcome adjudicators will not be blinded.

POC-US

A POC-US (Butterfly iQ+, GM Medical) of the lungs will be performed bedside as Focused Lung US (FLUS) by study assistant within 24 hours after admission. FLUS is used to diagnose pneumothorax, pleural effusion and interstitial syndrome. Additionally, signs of pneumonia ie., liver like alveolar consolidation with shredded borders and air bronchograms will be described. Diagnostic criteria used are in accordance with international consensus(39, 40). FLUS will be conducted immediately before or after the CT scans. The FLUS result will be available to the treating physician. If a result requires immediate action, the clinician will be contacted directly by the examiner, according to standard care.

A POC-US (Butterfly iQ+) of the kidneys will be conducted bedside by a study assistant within 24 hours after admission in order to assess whether hydronephrosis is present or absent. If present, the condition will be graded in grades 1, 2, 3 or 4(41). The result will be available to the treating physician. If a result requires immediate action, the clinician will be contacted directly by the examiner, according to standard care.

ULDCT and HRCT

The ULDCT and HRCT of the thorax scans are performed in the same scanning seance, thus on the same scanner. A specially designed technical protocol is the basis of the ULDCT and will prior to inclusion through a minor pilot study be optimized at each site of inclusion to ensure uniform quality and dose. The radiological findings from ULDCT will be reported systematically using standardized assessment templates by radiologists. The HRCT will be performed according to standard protocols at each hospital, but only during inspiration to limit radiation dose. HRCT will be reference standard for FLUS and ULDCT and interpreted by lung expert radiologists. The reports from POC-US, ULDCT, and HRCT respectively will be blinded. Study consultant radiologists with experience from ED patients will post-process report the ULDCT scans systematically using specially developed research report templates. The results of ULDCT and HRCT will be available to the treating physician within a week. If a result requires immediate action, the clinician will be contacted directly by the examiner, according to standard care. If a participant is discharged before the scans have been performed, they will be offered the scan in an outpatient setting.

Specialist US and MRI

A specialist US will be performed at the Radiology Department, including conventional grayscale US and CEUS with intravenous injection of 1.5 mL ultrasound contrast (Sonovue®, Bracco). At the same time, or as close as possible, a MRI without intravenous contrast of the kidneys will be conducted. The MRI will include the following sequences: planning, Dixon, T1 mapping, T2, T2 mapping, Diffusion ADC (100, 400, 800), MRI angio (3D VIBE), and Phase Contrast. The radiological findings will be described systematically using standardized assessment templates. The report from US and MRI respectively will be blinded. A renal expert radiologist will interpret the MRI and will post-process report the imaging systematically using specially developed research report templates. Imaging from the

CEUS will be evaluated in an external postprocessing software algorithm (Vuebox, Bracco). The non-experimental results of the scans will be available to the treating physician within a week. If a result requires immediate action, the clinician will be contacted directly by the examiner, according to standard care. If a participant is discharged before the scans have been performed, they will be offered the scans in an outpatient setting.

Reference standard

Unless otherwise stated, the reference standard is the assigned diagnosis determined by a panel of experts. The panel consists of two consultants from Emergency Departments with considerable experience within emergency medicine. They will determine the final diagnosis based on all relevant information in medical records and study database available from the admission including routine blood analysis, blood/urine/sputum culturing, POC-PCR, routine and study imaging (including HRCT and MRI), and clinical information. A standardized template will be used. Conflicts will be discussed until consensus is reached.

Data collection and management

All data will be collected in RedCap. Data will be pseudoanonymized and managed and analyzed using STATA or R in collaboration with a biostatistician

For each participant information on pre-defined clinical parameters upon arrival will be obtained from the medical record including symptoms, signs, disease severity, vital parameters, triage at arrival, comorbidities, functional status, resident status, prior antibiotics prescriptions, and medical history.

Other variables from the medical record that will be registered are length of stay, re-admission, admission to intensive care unit, prescribed antibiotic treatment, in-hospital mortality, 30-days and 90-days mortality, *Clostridium difficile* infections, and chest X-ray.

Monitoring

The daily inclusion of participants will be monitored by the steering committee and the numbers of inclusion will be instantly available for all the included centers on a home page. No interim analysis will be made. The primary analysis of data will be performed by the project assistants after the last patient has been included and all analysis performed. The results will be discussed and evaluated first in the steering committee and afterwards with all the included departments.

Sample size calculation and data analysis

According to the objectives, the study has been divided into sub-studies for each the primary outcome, statistical analysis, and sample size is presented.

Patient characteristics associated to verified diagnosis, according to expert panel reference standard, will be presented with descriptive results. Logistic univariate and multivariate analysis will be carried out for selected risk indicators, including confounders in the final analysis. At least 10 variables have to be analyzed, so at least 150 patients with a particular verified diagnosis are needed (50+10 events/variable).

The diagnostic values of CRP, PCT, and suPAR in track A and B are determined using the expert panel reference standard. Diagnostic accuracy will be conducted, and an optimal cut-off value for each parameter will be identified from receiver operating characteristic (ROC) curves. The study is designed to be able to find a difference in area under the curve (AUC) from 0.7 to 0.8 between two tests, which requires 200 verified CAP cases and 200 controls (power 0.8, alpha 0.05, AUC below 0 hypothesis 0.7) and 150 verified pyelonephritis cases and 150 controls (power 0.8, alpha 0.05, AUC below 0-hypothesis 0.6) (42).

To determine the diagnostic accuracy of POC-UFC to exclude bacteriuria, the urine culture will be used as reference standard. Diagnostic accuracy will be conducted, and Youden index analysis will be used to estimate the best cut-off. Urine culture shows significant growth of uropathogenic bacterium in approximately 50% of people with suspected pyelonephritis(25). Asymptomatic bacteriuria accounts for about 20% in the elderly population, depending on gender and age (43), which among 1000 inpatients suspected of infection, of which 15% have pyelonephritis, gives a sensitivity of 50% (95% CI: 42-58 %) and a negative predictive value of 90% (95% CI: 77-83%). With the expectation of identifying at least 150 cases of pyelonephritis among our study population, an improvement in sensitivity to 70% (95% CI: 62-77%) and negative predictive value to 95% (95% CI: 93 -96%) could be found with 95% security.

To determine how effective the addition of POC-PCR analysis of sputum is on antibiotic prescription in track A (superiority randomized trial), the primary outcome is targeted versus non-targeted antibiotic treatment prescribed at four hours after admission. Targeted treatment is defined as narrow spectrum antibiotics directed against CAP, antibiotics directed against a detected respiratory pathogen or no antibiotics (e.g. in the absence of a bacterial pathogen and/or presence of a viral pathogen). Non-targeted treatment is defined as broad spectrum antibiotics not directed against a specific pathogen or antibiotics not directed against CAP. The analyses will follow the intention-to-treat principal and a hierarchical mixed effect logistic model will be utilized to analyze the primary outcome to accommodate the hierarchical structure of the random effect, which manifest according to different personnel collecting the samples and geographical variation. To achieve a power of 82% for the main analysis, 200 patients with suspected CAP must be included. To accommodate the bias presented in (44) the generalized mixed effect models will be adjusted for strong predictors. If the sample size is not sufficient for a generalized mixed effect models the corresponding univariate analysis will be conducted.

The diagnostic accuracy of POC-US and ULDCT to identify inflammatory changes in the lungs and diagnose CAP in track A is determined using the expert panel reference standard. It is assumed that the reference standard will find 98% of the patients and index test 90%. With a power of 80%, at least 132 patients with verified CAP should be included (one-sided McNemar test).

The diagnostic accuracy of specialist US to identify inflammatory changes in the kidneys compatible with APN in track B is determined using the MRI as reference standard. It is assumed that the reference standard finds 98% of patients and index test 90%. With a power of 80%, at least 132 patients must be included (one-sided McNemar test).

The diagnostic accuracy of POC-US to identify hydronephrosis in track B is determined using MRI as reference standard. It is assumed that the reference standard finds 98% of patients and index test 90%. With a power of 80%, at least 132 patients must be included (one-sided McNemar test).

Annually, 5.7% of patients admitted to an ED are diagnosed with CAP and 2.4% with APNs (data from the ED at Hospital Sønderjylland). Taking into account exclusion criteria, weekends/holidays/missing data, and experience in patient recruitment, it is estimated that at least 1000 patients admitted with suspected infection must be included in the study from the three hospitals over a 7-month period, of which at least 200 patients will be diagnosed with pneumonia and at least 150 patients with pyelonephritis.

Non-participant analysis is performed. For missing data multiple imputation is used.

Ethics and dissemination

The project was approved by the Regional Committees on Health Research Ethics for Southern Denmark (S-20200188), registered by the Danish Data Protection Agency (no. 20/60508) and by clinicaltrials.gov (NCT: 04661085, 04681963, 04667195, 04652167, 04686318, 04686292, 04651712, 04645030, and 04651244). Registration date was

November-December 2020. Signed informed consent will be obtained from all participants after information of the project has been given both in writing and orally.

Participation in track A will contain additional imaging. Patients under the age of 40 are therefore excluded from the CT due to the extra risk of developing cancer from the radiation. A local hospital physicist has helped with the following calculations: A typical HRCT gives a radiation dose of approximately 2.2 mSv which corresponds to a cancer risk of 1:9100. An X-ray gives a radiation dose of approximately 0.06 mSv which corresponds to a cancer risk of 1:333330. An ULDCT gives a radiation dose of approximately 0.1 mSv which corresponds to a cancer risk of 1:200000. Participation in track A gives each participant approximately 2.26 mSv (ULDCT and HRCT) which corresponds to a cancer risk of 1:8850(45-48). The examination time of ULDCT and HRCT is approximately 10 minutes.

Use of US contrast in rare cases cause allergic reactions; less than 1/10.000 exponents require medical treatment due to allergic reaction (49). The examination time of advanced US is approximately 20 minutes.

MRI does not provide any radiation dose to the patients and is without intravenous contrast. The examination time is approximately 45 minutes, which is aligned with normal MRI examination time.

Overall, risks related to participation in the study is considered minimal, and furthermore, chances are that the additional diagnostic imaging will inform the clinician in a favorable way before the onset of patient treatment.

Protocol amendments

Important protocol modifications like changes in eligibility criteria or outcome will be communicated to the relevant parties, i.e. sponsor, trial registry and scientific ethical committee.

Dissemination policy

The results of the study will be presented in at least ten English peer-reviewed recognized scientific journals. The results of the project will also be disseminated through participation in academic and other conferences, as well as through the printed and electronic press. The author panel will include the steering committee, project assistants, and local coordinators in accordance with the Vancouver criteria. No professional writers will be used. Positive, negative and inconclusive results will be published. Diagnostic accuracy studies will follow the guidelines for reporting diagnostic accuracy studies (STARD) (50), cross sectional studies will follow the guidelines for strengthening the reporting of observational studies in epidemiology (STROBE) (51), and randomized studies will follow the consolidated standards of reporting trials (CONSORT) (52).

Access to data

Only the members of the steering committee and project assistants will have access to the final trial dataset. Other researches may be granted access to the anonymized data for analysis on reasonable request to the corresponding authors.

Discussion

After completion of the study, a novel diagnostic algorithm will be developed. Subsequently, the plan is to test the algorithm in a national setting including at least eight EDs. The results can be implemented in daily work and routines. The study will also be able to characterize the patients, who are diagnosed at the ED with an infection of unknown origin and prescribed broad-spectrum antibiotics.

The results of the study will have both national and international interest, as the challenges are common and the solutions can easily be applied in hospitals with a similar technological context. Securing rapid and reliable diagnosis of two of the most common infections diagnosed in the ED, will encourage the reduction of broad-spectrum antibiotics and thereby the development of multi-resistant bacteria.

Declarations

Abbreviations: acute pyelonephritis (APN), Anatomical therapeutic chemical (ATC), area under the curve (AUC), community-acquired pneumonia (CAP), cluster of differentiation 4 (CD4), contrast enhanced ultrasound (CEUS), Coronavirus Disease 2019 (COVID-19), C-reactive protein (CRP), emergency department (ED), human immunodeficiency virus (HIV), high-resolution dose computed tomography (HRCT), magnetic resonance imaging (MRI), Objective Structured Assessment of US Skills (OASUS), polymerase-chain-reaction (PCR), serum procalcitonin (PCT), Point-of-care (POC), receiver operating characteristic (ROC), Soluble urokinase plasminogen activator receptor (suPAR), urine flow cytometry (UFC), ultralow dose computed tomography (ULDCT), and ultrasound (US).

Protocol version: January 25th 2021, version 1.0

Ethics approval: The project was approved by the Regional Committees on Health Research Ethics for Southern Denmark (S-20200188), registered by the Danish Data Protection Agency (20/60508) and by clinicaltrials.gov (NCT: 04661085, 04681963, 04667195, 04652167, 04686318, 04686292, 04651712, 04645030, and 04651244). Each patient provided written informed consent.

Data sharing statement: Due to Danish laws on personal data, data cannot be shared publicly. To request these data, please contact the corresponding author for more information.

Competing interests: The authors declare that they have no competing interests

Patient and Public Involvement: The patients or public were not involved in the development of the research question or the study design.

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Authors´ contributions: HS, OG, FSR, ERBP, CØ, CBL, TAS, SP, MBC, and CBM conceptualized and all authors designed the study and data collection in detail. HS, AH, MHL, MBC, and CBM reviewed the literature. AH, MHL, MBC, and MAH will recruit participants, and HS, OG, FSR, ERBP, CØ, CBL, TAS, SP, MBC, and CBM will supervise data collection and analysis. HS, AH, MHL, MBC, MAH, and CBM will carry out statistical analysis and write the first manuscripts, which will be critically reviewed by all authors, who will finally approve the manuscripts before submission.
HS and CBM are responsible for the overall content as guarantors. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Steering committee: Composed of representatives from the involved type of departments: emergency, microbiology, biochemistry, and radiology. The role of the committee is to develop the scientific framework of the study, make final decisions on major issues during the data collection and data management period. The committee is responsible for all financial issues. Members of the steering committee are HS, OG, FSR, ERBP, and CBM.

Participating departments: All departments are located in Denmark
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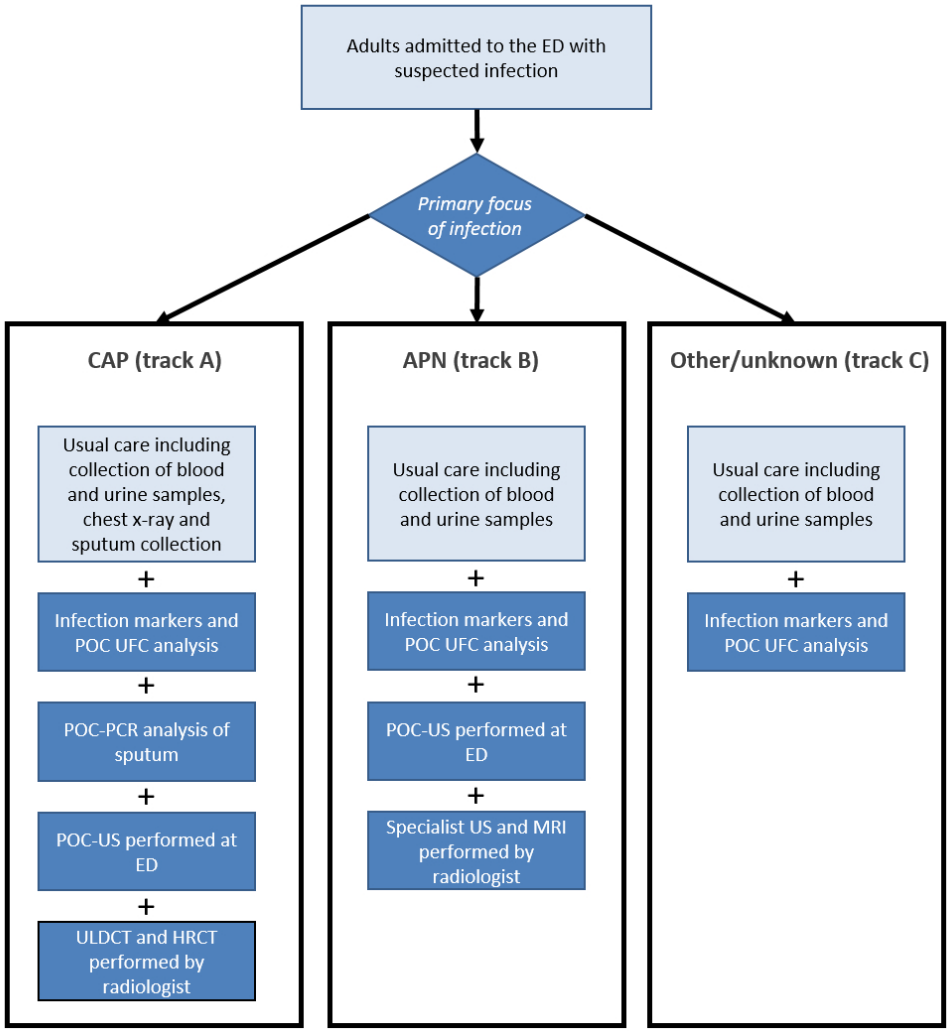

Figure 1 Design of patient flow and diagnostic tracks

170x182mm (150 x 150 DPI)

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

Completed SPIRIT checklist

Section/item	ItemNo	Description	Page in protocol
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
	2b	All items from the World Health Organization Trial Registration Data Set	-
Protocol version	3	Date and version identifier	11
Funding	4	Sources and types of financial, material, and other support	12
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	12
	5b	Name and contact information for the trial sponsor	12
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	12
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	12
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-4
	6b	Explanation for choice of comparators	3-4
Objectives	7	Specific objectives or hypotheses	4-5

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5 9-10
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5-6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7-8
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	7-8
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	-
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7-8
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8-10
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	6
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	9-10
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	77
Methods: Assignment of interventions (for controlled trials)			
Allocation:			

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	7
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	7
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	7
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	-
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	8-9
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	-
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	8-9
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	9-10
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	-
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	9-10

Methods: Monitoring

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	-
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	9
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	8
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	12

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	10
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	11
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	-
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	10
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	12
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	11
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	-

Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	11
	31b	Authorship eligibility guidelines and any intended use of professional writers	11
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	11
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Appendix I
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Appendix I

BMJ Open

Improved diagnostics of infectious diseases in Emergency Departments – a protocol of a multifaceted multicenter diagnostic study

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Primary Subject Heading:	Infectious diseases
Secondary Subject Heading:	Diagnostics, Emergency medicine, Epidemiology, Infectious diseases, Radiology and imaging
Keywords:	Diagnostic microbiology < INFECTIOUS DISEASES, MICROBIOLOGY, Computed tomography < RADIOLOGY & IMAGING, Diagnostic radiology < RADIOLOGY & IMAGING, Ultrasound < RADIOLOGY & IMAGING, ACCIDENT & EMERGENCY MEDICINE

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1

Improved diagnostics of infectious diseases in Emergency Departments

– a protocol of a multifaceted multicenter diagnostic study

Short title: Improved diagnostics of infectious diseases

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Abstract

Background: The major obstacle in prescribing an appropriate and targeted antibiotic treatment is insufficient knowledge concerning *whether* the patient has a bacterial infection, *where* the focus of infection is and *which* bacteria are the agents of the infection. A prerequisite for the appropriate use of antibiotics is timely access to accurate diagnostics such as point-of-care (POC) testing.

The study aims to evaluate diagnostic tools and working methods that support a prompt and accurate diagnosis of hospitalized patients suspected of an acute infection. We will focus on the most common acute infections; community-acquired pneumonia (CAP) and acute pyelonephritis (APN). The objectives are to investigate 1) patient characteristics and treatment trajectory of the different acute infections, 2) diagnostic and prognostic accuracy of infection markers, 3) diagnostic accuracy of POC urine flow cytometry on diagnosing and excluding bacteriuria, 4) how effective the addition of POC analysis of sputum to the diagnostic set-up for CAP is on antibiotic prescriptions, 5) diagnostic accuracy of POC ultrasound and ultralow dose (ULD) Computed Tomography (CT) on diagnosing CAP, 6) diagnostic accuracy of specialist ultrasound on diagnosing APN, 7) diagnostic accuracy of POC ultrasound in diagnosing hydronephrosis in patients suspected of APN.

Methods and analysis: It is a multifaceted multicenter diagnostic study, including 1000 adults admitted with suspicion of an acute infection. Participants will within the first 24 hours of admission undergo additional diagnostic tests including infection markers, POC urine flow cytometry, POC analysis of sputum, POC and specialist ultrasound, and ultralow dose CT. The primary reference standard is an assigned diagnosis determined by a panel of experts.

Ethics, dissemination and registration: Approved by Regional Committees on Health Research Ethics for Southern Denmark, Danish Data Protection Agency, and clinicaltrials.gov. Results will be presented in ten peer-reviewed journals, and positive, negative and inconclusive results will be published.

Key words: Acute Infection, antibiotics, diagnostic, pneumonia, pyelonephritis, sputum, point-of-care-test, ultrasound, infection marker, Ultralow dose Computed Tomography

Strengths and limitations of the study:

- It is a pragmatic study that reflects reality and has potential for substantial clinical significance
- The study combines diagnostics and knowledge from five different medical specialties
- The study is complex and contains a number of sub-studies which share the same population
- The study is only generalizable to settings with a similar technological context and trained staff
- COVID-19 and the consequent societal lockdown might affect patient distribution

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World Health Organization Trial Registration Data Set

Primary Registry and Trial Identifying Number: ClinicalTrials.gov: NCT: 04661085, 04681963, 04667195, 04652167, 04686318, 04686292, 04651712, 04645030, and 04651244.

Date of Registration in Primary Registry: December 2020

Secondary Identifying Numbers: Regional Committees on Health Research Ethics for Southern Denmark (S-20200188), and Danish Data Protection Agency (20/60508)

Source(s) of Monetary or Material Support: University Hospital of Southern Denmark and University of Southern Denmark, Aabenraa, Denmark

Primary Sponsor: Professor Christian Backer Mogensen, University Hospital of Southern Denmark and University of Southern Denmark, Aabenraa, Denmark

Secondary Sponsor(s): Associate professor Helene Skjøt-Arkil, University Hospital of Southern Denmark and University of Southern Denmark, Aabenraa, Denmark

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Public Title: Improved diagnostics of acute infectious diseases

Scientific Title: Improved diagnostics of infectious diseases in Emergency Departments

Countries of Recruitment: Denmark

Health Condition(s) or Problem(s) Studied: Infectious diseases including community-acquired pneumonia and acute pyelonphritis

Intervention(s):
Sub-study 2: Index test: infection markers (serum procalcitonin, and soluble urokinase plasminogen activator receptor
Sub-study 3: Index test: point-of-care urinary flow cytometry
Sub-study 4: Intervention: Point-of-care tool providing rapid microbiological results on sputum samples based on polymerase chain reaction. Control: routine microbiology analysis
Sub-study 5: Index test: Ultralow dose computed tomography scans / ultrasound scanning
Sub-study 6: Index test: Contrast enhanced ultrasound
Sub-study 7: Index test: Ultrasound scanning

Key Inclusion and Exclusion Criteria: Adults admitted to the Emergency Department are invited if receiving physician suspects the patient has an infection. Patients are excluded if participating will delay a life-saving treatment, if they have been admitted within 14 days, if pregnant, or if having severe immunodeficiency.

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Study Type: It is a multifaceted multicenter study, primarily diagnostic accuracy set of studies but a randomised controlled trial of sputum diagnostics embedded within it. It has been divided into seven-substudies.
Sub-study 1: Observational, descriptive study
Sub-study 2, 3, 5, 6, 7: Observational, diagnostic accuracy studies
Sub-study 4: Eksperimental, randomized controlled trial - parallel assigned, allocated 1:1 according to a computer-generated randomization schedule.

Date of First Enrollment: February 1st 2021

Sample Size
Sample Size consists of: 200 patients diagnosed with CAP and 150 patients with APN
Number of participants that the trial plans to enrol in total: 1000
Number of participants that the trial has enrolled: 460

Recruitment Status: Recruiting: participants are currently being recruited and enrolled

Primary Outcome(s):
Outcome sub-study 1: Diagnosis of community acquired pneumonia and acute pyelonephritis
Method of measurement: Expert panel consisting of emergency and infectious disease specialists (reference standard)
Timepoint: within seven days after admission

Outcome sub-study 2: Diagnosis of community acquired pneumonia and acute pyelonephritis
Method of measurement: Expert panel consisting of emergency and infectious disease specialists (reference standard)
Timepoint: within seven days after admission

Outcome sub-study 3: bacteriuria
Method of measurement: urine culturing specialists (reference standard)
Timepoint: Time of admission

Outcome sub-study: Type of prescribed antibiotic
Method of measurement: Medical record audit
Timepoint: 4 hours

Outcome sub-study 5: Diagnosis of community acquired pneumonia
Method of measurement: high-resolution computed tomography specialists (reference standard)
Timepoint: within 24 hours of admission

Outcome sub-study 6: Diagnosis of acute pyelonephritis
Method of measurement: magnetic resonance imaging specialists (reference standard)
Timepoint: within 24 hours of admission

Outcome sub-study 7: Diagnosis of acute pyelonephritis
Method of measurement: magnetic resonance imaging specialists (reference standard)
Timepoint: within 24 hours of admission

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Key Secondary Outcomes: Length of stay (medical record audit), Mortality (medical record audit and Danish National Patient Register, 30 days, 90 days, and inhospital mortality), Readmission to hospital within 30 days from day of discharge (medical record audit), Admission to intensive care (medical record audit), Antibiotic treatment at 48 hours of admission (medical record audit).

Ethics Review: The study was approved by the Regional Committees on Health Research Ethics for Southern Denmark (S-20200188) on January 7th 2021. Contact: Komite@rsyd.dk

Completion date: The last patient is expected to be included in February 2022. The final data is expected to be collected in June 2022.

IPD sharing statement: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request

Introduction

Antibiotic resistance

Multi-resistant bacteria is one of the major threats to the public health(1). The incidence of multi-resistant bacteria is increasing in Denmark(2) and every 20th patient admitted to a Danish Emergency Department (ED) is colonized with multi-resistant bacteria(3). Denmark has focused on this challenge(4) by screening special patient groups for multi-resistant bacteria(5, 6), and by initiating campaigns to reduce antibiotic consumption - mainly the use of broad-spectrum antibiotics in hospitals(4, 7).

The Danish Ministry of Health has made extensive efforts targeting the use of antibiotics in hospitals. However, the major obstacle in reducing the prescription of broad-spectrum antibiotics is insufficient knowledge concerning *whether* the patient has a bacterial infection, *where* the focus of infection is and *which* bacteria are the agents of the infection(8). Uncertainty in the answers to these three questions often leads a clinician to choose a broad-spectrum antibiotic at the onset of treatment. Unfortunately, the prescription of a broad-spectrum antibiotic is rarely revised when laboratory results are available, often because the patient already has been discharged(9).

Acute infections and diagnostic tools

A prerequisite for appropriate use of antibiotics is timely access to accurate diagnostic tests, since treatment of acute infections should be initiated within a few hours to avoid serious complications such as bacteremia, sepsis, organ failure, septic shock and death(10). The most common conditions among ED patients with suspected infections are community acquired pneumonia (CAP) and acute pyelonephritis (APN)(11, 12). Diagnosing CAP and APN can be challenging as symptoms are often weak and nonspecific and the current methods for focal and etiological diagnosis have low sensitivity and specificity and often deliver results after the decision regarding antibiotic treatment has been made(9, 13, 14).

The Coronavirus Disease 2019 (COVID-19) pandemic has highlighted the need of accurate diagnostic tests. Quick and correct classification of pneumonia as COVID-19, another viral or bacterial pneumonia, or even COVID-19 complicated with bacterial pneumonia, is of vital importance to select the correct treatment (including antibiotics), and the correct infection control measures, including isolation.

In order to make the correct diagnosis and prescribe an appropriate and targeted treatment within a few hours of admission, it is important to the physician to be able to answer the following three questions: a) Is it an infection that requires antibiotic treatment (*infection marker*)? b) Where is the focus of infection (imaging *diagnosis*)? c) Which bacteria should the prescribed antibiotic target (*etiologic diagnosis*)?

Bacterial infection markers

To support the diagnosis of an infection and assess its severity, a measure of the systemic inflammatory response is useful e.g. abnormal temperature, elevated leucocyte count with neutrocytosis, or elevated C-reactive protein (CRP). Some uncertainty is associated with CRP because it has a delayed response to bacterial infection and often is elevated in non-infectious inflammatory conditions(15). A more sensitive and specific marker that can differentiate between bacterial and viral infection and reflect the severity of the infection is desired(16). Serum procalcitonin (PCT) has potential as a diagnostic tool in suspected bacterial infections(17) and can distinguish between viral and bacterial pneumonias(18). Soluble urokinase plasminogen activator receptor (suPAR) might have a potential as a marker for acute bacterial infections requiring antibiotic treatment(19). However, there are no well-conducted studies which compare simultaneously all three biomarkers diagnostic abilities for bacterial infections in general or in relation to CAP or APN (16, 20).

Imaging diagnostics

The CAP diagnosis is primarily based on clinical symptoms and findings, supplemented with chest X-ray, which has a low sensitivity and specificity (21). Identifying an improved imaging alternative with high diagnostic sensitivity and specificity and minimal risk to the patient is imperative. Computed Tomography scans (CT), e.g. high-resolution CT (HRCT) provides a detailed diagnosis of thoracic diseases, but the radiation dose is high and potentially harmful. Low-dose CT has shown promising diagnostic results, but the radiation dose is still potentially harmful (22). Ultralow dose CT (ULDCT) of the thorax could be an alternative, but has yet to be studied within an ED context. Another relevant imaging modality is ultrasound scanning (US). US of the lungs is useful to diagnose pulmonary edema and pleural effusion, but the value of US performed by a novice operator when diagnosing CAP in an ED setting needs further investigation(23).

Currently, no imaging methods are used to verify the diagnosis of APN. The diagnosis is primarily based on unspecific clinical findings (24), and is often not confirmed microbiologically (25). Complicating factors such as hydronephrosis and renal abscess can be visualized with conventional US (26). Contrast enhanced US (CEUS) seems to be a promising diagnostic imaging modality of acute renal inflammation (27, 28). The value and suitability in a clinical setting of this more advanced US investigation is unknown.

Etiological diagnostics

Sputum can be cultivated to determine the agent of CAP. However, results are often unspecific and not available until after discharge of the patient or completion of treatment(9). A point-of-care (POC) tool providing rapid microbiological results on e.g. sputum samples would therefore be useful. Systems are available today based on polymerase chain reaction (PCR) methods with results available within one hour for a variety of viral and bacterial pathogens (29). The impact of such fast diagnostic systems on antibiotic prescriptions has not been investigated in an ED context.

The diagnosis of APN is verified by significant bacteriuria in urine culture (25), but as many as half of the patients with clinical APN fails to meet this diagnostic criterion. Unfortunately, the time from sample to result for urine cultures is more than 24 hours (24, 25, 30, 31). Urine test strips are unreliable with low specificity and low predictive values(32). Therefore, a POC test is desired, which can provide rapid results and quickly identify a bacteriuria. One such tool may be urine flow cytometry (UFC), which has shown promising diagnostic value for the exclusion of bacteriuria with a high negative predictive value (33). However, better documentation for its use as an ED diagnostic screening method is needed.

Aim and objectives

Our broad hypothesis is that improved diagnostic strategies for patients in ED with suspicion of systemic infection can contribute to more rapid and accurate diagnosis. Thereby, we assume that a more appropriate antibiotic treatment can be administered to these patients.

The project aims to evaluate alternative diagnostic tools and working methods that support a prompt and accurate diagnosis of hospitalized patients suspected of an acute infection. We will focus on the most common ED infections; CAP and APN. The research objectives are to answer the following questions:

1) What are the patient characteristics and treatment trajectory of the different ED infections?
2) What is the diagnostic and prognostic accuracy of the infection markers suPAR, and CRP in patients with suspected CAP and APN?
3) What is the diagnostic accuracy of POC-UFC on diagnosing and excluding bacteriuria?
4) How effective is the addition of POC-PCR analysis of sputum to the diagnostic set-up for CAP on antibiotic prescribing?
5) What is the diagnostic accuracy of POC-US and ULDCT on diagnosing CAP?
6) What is the diagnostic accuracy of CEUS on diagnosing APN?

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7) What is the diagnostic accuracy of POC-US in diagnosing hydronephrosis in patients suspected of APN?

The ultimate goal is to combine the results of all these seven objectives into a novel diagnostic model which the ED physician can apply when receiving a patient with suspicion of infection.

Methods

Study design

The study is designed as a multifaceted multicenter diagnostic study. Participants will undergo additional diagnostic tests depending on the primary suspected focus of infection.

The study protocol is reported in accordance with the SPIRIT (Standard protocol items: Recommendations for interventional trials) statement(34).

Setting

The study will recruit participants from three Danish EDs: the regional Hospital, Lillebælt Hospital in Kolding, the regional Hospital, Hospital Sønderjylland in Aabenraa, and the University Hospital, Odense University Hospital in Odense. Enrolment commences from February 8th 2021 and continues until the predefined sample size has been reached.

Project assistants will recruit the participants and collect data. The project assistants will have a healthcare education (physicians, physiotherapists and medical students). They are certificated in focused US of kidney and lung (one-day POC-US course, 25 supervised scans, and Objective Structured Assessment of US Skills (OASUS) test) within one month from enrollment.

The study originates from the Emergency Research Unit affiliated at University Hospital of Southern Denmark and Department of Regional Health Research at University of Southern Denmark.

Population and eligibility criteria

Inclusion of patients is based on the receiving ED physician's initial clinical assessment of the patient. Adults aged 18 or older admitted to the ED will be invited to participate in the study, if the receiving physician suspects the patient is having an infection. Only patients able to give informed consent will be invited. Depending on primary suspected focus of infection (CAP, APN or other/unknown), the patients will be included into one of three diagnostic tracks (A, B, or C) as shown in Figure 1.

Exclusion criteria that apply to all three tracks at time of recruitment

- If the attending physician considers that participation will delay a life-saving treatment or directly transfer to intensive care unit
- Admission (defined as >24 hours hospital visit) within the last 14 days to avoid hospital acquired infections
- Verified COVID-19 disease within 14 days before admission to avoid a skewed population consisting of COVID-19 patients instead of CAP patients. Patients suspected of COVID-19, at the time of recruitment, will not be excluded – nor if subsequently tested positive.
- Pregnant women, this to uniform all the studies. At the participating EDs the pregnant women represent a very small patient group, as they are admitted directly to the ward.
- Severe immunodeficiencies
    - Primary immunodeficiencies
    - Secondary immunodeficiencies

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- Human immunodeficiency virus (HIV) positive, with a cluster of differentiation 4 (CD4) cell count <200
- Patients receiving immunosuppressive treatment (Anatomical therapeutic chemical (ATC) classification L04A)
- Corticosteroid treatment (>20 mg/day prednisone or equivalent for >14 days within the last 30 days)
- Chemotherapy within 30 days

Exclusion criteria that only apply to patients with suspected CAP (track A):

- Patients <40 years old are excluded from the ULDCT and HRCT due to risk of cancer from radiation
- Patients <65 years who already participated once will be excluded from ULDCT and HRCT due to risk of cancer from radiation

Exclusion criteria that only apply to patients with suspected APN (track B):

- Patients are excluded from magnetic resonance imaging (MRI) according to common MRI exclusion criteria (e.g. contraindicating metal in the body) and claustrophobia
- Patients with known allergy to US contrast

Figure 1 Design of patient flow and diagnostic tracks

Recruitment

The study assistants will identify potential eligible patients through the local IT logistic system, which lists patients visiting the ED (Cetrea Anywhere®), According to the local guidelines, a medical clinical assessment of the patients is performed within half an hour from arrival at the ED(35). The study assistant will immediately after the assessment consult the receiving physician to ask if a) a systemic infection is suspected, and b) what the most likely focus is: lungs, urinary tract, elsewhere/unknown. If the patient meets the eligibility criteria, the study assistant will present the study both verbally and in writing, and invite the patient to participate in the study. The schedule of enrollment is illustrated in appendix III.

Procedure

The study assistant will after obtained written consent order blood samples, urine sample, and the diagnostic tests described in the assigned track. The study assistant will collect data for patient characteristic by looking in the patient record and by patient interview.

Infection markers

Blood samples will be collected by a medical laboratory technologist and transferred to the local laboratory for analysis of CRP (routine analysis), PCT and suPAR. Laboratory staff will be blinded to participant diagnosis and outcome. PCT results will be available to the treating physician, but the suPAR result will not be available. CRP will be measured using an immunoturbidimetric assay (Tina-quant®, Roche) on Roche/Hitachi Cobas© systems. Plasma PCT will be quantified by an automated sandwich immunoassay "ECLIA" (Elecsys®, BRAHMS PCT-analyses) on Cobas© within two hours from collection according to standard procedure. Plasma suPAR will be quantified by using the commercial available suPARnostic© Tubilatex assay reagents (ViroGates, Denmark) on Cobas© as previously validated (36). Separated plasma is kept refrigerated and analysed for suPAR within 48 hours after collection.

POC-UFC

A urine sample will be collected according to routine procedure by the study assistant. The sample will be divided into three aliquots; one for routine urine culturing, one for routine dipstick analysis and one half for POC-UFC analysis (UF-5000, Sysmex, Kobe, Japan). The POC-UFC analysis will be performed according to manufacturer's instruction and conducted by study assistants or laboratory staff in a point-of-care laboratory close to the department to which the transport time is less than 10 minutes. Laboratory staff will be blinded to participant diagnosis and outcome. The results of the POC-UFC analysis will not be visible to the treating physician.

The results of the dipstick analysis and the urine culturing will be available to the treating physician as part of the usual procedure (within one hour for dipstick and after up to several days for culturing).

POC-PCR sputum analysis

A sputum sample will be collected according to standard procedure as soon as possible after recruitment by the study assistant. This sample will be randomly assigned to one of two groups with 1:1 allocation: 1) POC-PCR analysis (Biofire® FilmArray® Pneumonia Panel plus, Biomérieux, Marcy l'Etoile, France) in accordance with manufacturer's instruction(37), and 2) Routine microbiology analysis (culturing and PCR). Expectorated sputum or tracheal secretions will be used for the PCR analysis. All sputum samples will be cultured. Gram stain and microscopy are not included in the analysis

The randomization will be performed by the study assistants and generated electronically using Research Electronic Data Capture (RedCap) Randomization Module (38) with permuting blocks and stratified according to sites.Allocation concealment is ensured, as randomization is performed electronically and the study assistants administering the randomization will not have access to the randomization code. The allocation is revealed after consent is obtained and sputum collection successful.

The study assistants or laboratory staff will perform the POC-PCR analysis in a point-of-care laboratory at the ED or close to the department to which the transport time is less than 10 minutes. The used POC-PCR targets 27 of the most common pathogens involved in lower respiratory tract infections (appendix IV). The result of the POC-PCR will be presented by the study assistant to the treating physician within four hours upon admission. The treating physician will along with the result receive a recommended action list (appendix V), developed by microbiologists.

The patients will be blinded, and the investigator will be blinded to data management and analysis. Outcome adjudicators will not be blinded.

POC-US

A POC-US (Butterfly iQ+, GM Medical) of the lungs will be performed bedside as Focused Lung US (FLUS) by study assistant within 24 hours after admission. FLUS is used to diagnose pneumothorax, pleural effusion and interstitial syndrome. Additionally, signs of pneumonia ie., liver like alveolar consolidation with shredded borders and air bronchograms will be described. Diagnostic criteria used are in accordance with international consensus(39, 40). FLUS will be conducted immediately before or after the CT scans. The FLUS result will not be available to the treating physician unless the result requires immediate action (pneumothorax or large pleural effusions).

A POC-US (Butterfly iQ+) of the kidneys will be conducted bedside by a study assistant within 24 hours after admission in order to assess whether hydronephrosis is present or absent. If present, the condition will be graded in grades 1, 2, 3 or 4(41). The result will not be available to the treating physician since the patient is examined by a radiologist immediately after, and the results from this examination is reported to the clinician according to standard care.

ULDCT and HRCT

The ULDCT and HRCT of the thorax scans are performed in the same scanning sequence, thus on the same scanner. A specially designed technical protocol is the basis of the ULDCT and will prior to inclusion through a minor pilot study be optimized at each site of inclusion to ensure uniform quality and dose. The radiological findings from ULDCT will be reported systematically using standardized assessment templates by radiologists. The HRCT will be performed

according to standard protocols at each hospital, but only during inspiration to limit radiation dose. HRCT will be reference standard for FLUS and ULDCT and interpreted by lung expert radiologists. The reports from POC-US, ULDCT, and HRCT respectively will be blinded. Study consultant radiologists with experience from ED patients will post-process report the ULDCT scans systematically using specially developed research report templates. The results of ULDCT and HRCT will be available to the treating physician within a week. If a result requires immediate action, the clinician will be contacted directly by the examiner (pneumothorax and large pleural effusions), according to standard care. If a participant is discharged before the scans have been performed, they will be offered the scan in an outpatient setting.

CEUS and MRI

A specialist US will be performed at the Radiology Department, including conventional grayscale US and CEUS with intravenous injection of 1.5 mL ultrasound contrast (Sonovue®, Bracco). At the same time, or as close as possible, a MRI without intravenous contrast of the kidneys will be conducted. The MRI will include the following sequences: planning, Dixon, T1 mapping, T2, T2 mapping, Diffusion ADC (100, 400, 800), MRI angio (3D VIBE), and Phase Contrast. The radiological findings will be described systematically using standardized assessment templates. The report from US and MRI respectively will be blinded. A renal expert radiologist will interpret the MRI and will post-process report the imaging systematically using specially developed research report templates. Imaging from the CEUS will be evaluated in an external postprocessing software algorithm (Vuebox, Bracco). The non-experimental results of the scans will be available to the treating physician within a week. If a result requires immediate action (suspicion of pyonephrosis or renal abcess), the clinician will be contacted directly by the examiner, according to standard care. If a participant is discharged before the scans have been performed, they will be offered the scans in an outpatient setting.

Expert panel reference standard

Unless otherwise stated, the reference standard is the assigned diagnosis determined by a panel of experts. The panel consists of two consultants: a specialist in emergency medicine and a specialist in infectious medicine with considerable experience within acute infections. They will determine the final diagnosis based on all relevant information in medical records and study database available from the admission including routine blood analysis, blood/urine/sputum culturing, POC-PCR, routine and study imaging (including HRCT and MRI), and clinical information. The final diagnosis will be based on information available within the first week after admission. A standardized template in RedCap will be used (appendix VI), and the experts will register if the patient has an infectious disease, if the focus of infection is the lungs, kidneys or other, and specify the infection by adding an ICD-10 diagnosis code. If the patient has two focal diagnoses e.g. pneumonia and APN, the assessment will be based on what is the most probable cause of infection on admission. Conflicts will be discussed until consensus is reached. In this study we define APN as a urinary tract infection with typical local symptoms and systemic affection (i.e. fever, sepsis), thus indicating ascension of infection above the bladder.

Data collection and management

All data will be collected in RedCap. Data will be pseudoanonymized and managed and analyzed using STATA or R in collaboration with a biostatistician

For each participant information on pre-defined clinical parameters upon arrival will be obtained from the medical record including symptoms, lifestyle factors signs, disease severity, vital parameters, triage at arrival, comorbidities, functional status, resident status, prior antibiotics prescriptions, and medical history.

Other variables from the medical record that will be registered are length of stay, re-admission, admission to intensive care unit, prescribed antibiotic treatment, in-hospital mortality, 30-days and 90-days mortality, *Clostridium difficile* infections, and chest X-ray.

Data monitoring

The daily inclusion of participants will be monitored by the steering committee and the numbers of inclusion will be communicated every week toemailed to the included centers. The primary analysis of data will be performed by the project assistants after the last patient has been included and all analysis performed. The results will be discussed and evaluated first in the steering committee and afterwards with all the included departments.

Process auditing

During data collection, an extern assessor will supervise the performance of all project assistants and an independent radiology expert will ensure data quality. Intraobservability on POC-US will be performed each month.

Overall risk for the participants in the randomized trial (POC-PCR sputum analysis) is minimal, as sputum collection is part of the standard care, and it will not affect the following diagnostic work-up. However the POC-PCR results may inform the clinician in a favorable way before onset of patient treatment. Any protocol deviation and/or unknown/unexpected adverse event, will be reported in RedCap, evaluated continuously by the steering committee, and reported to the treating physician and patient.

Statistical analysis and plan

According to the objectives, the study has been divided into sub-studies and for each the primary and secondary outcomes, statistical analysis, and sample size is presented.

Objective 1 - Patient characteristics and treatment trajectory

This sub-study will include all participant. Patient characteristics associated to verified diagnosis will be presented with descriptive results, and logistic univariate and multivariate analysis will be carried out for selected risk indicators, including confounders in the final analysis. The primary outcome is the diagnosis of CAP and APN determined by the expert panel reference standard). Secondary outcomes are length of stay, 30 days mortality, in-hospital mortality, admission to intensive care unit, readmission to hospital within 30 days from day of discharge.

At least 10 variables have to be analyzed, so at least 150 patients with a particular verified diagnosis are needed (50+10 events/variable).

Objective 2 - Diagnostic and prognostic accuracy of PCT and suPAR

This diagnostic accuracy study will include all participants. Index tests are the concentration of CRP, PCT, and suPAR. The expert panel is the reference standard. Diagnostic accuracy tests will be performed as primary analysis, where the test positive of the reference standard is the diagnosis of CAP, and of urinary tract infection. Secondary prognostic tests will be performed, using the reference standard of 30 and 90 days mortality, in-hospital mortality, admission to intensive care, readmission to hospital within 30 days from day of discharge, and length of stay (LOS).

The test positively cut-offs of the index tests will be determined exploratory by performing Youden index analysis to estimate the best cut-off. The CRP value will be available for the members of the expert panel, but the PCT and suPAR will not be available. The reference standard results will not be available for the index test performers.

A demographic characteristic of the study populations will be presented, and the time interval of the laboratory analysis of the biomarkers will be reported. Cross-tabulation of the index test results by the reference standard results will be made including missing results, and used to determine diagnostic and prognostic accuracy expressed as sensitivity, specificity, predictive values, and likelihood ratios reported with 95% confidence intervals where appropriate. Receiver operating characteristic (ROC) analysis will be performed. Statistical modelling will also be

performed to explore the effect of combining tests on diagnostic accuracy in order to identify the most accurate diagnostic strategy.

The study is designed to be able to find a difference in area under the curve (AUC) from 0.7 to 0.8 between two tests, which requires 200 verified CAP cases and 200 controls (power 0.8, alpha 0.05, AUC below 0 hypothesis 0.7) and 150 verified pyelonephritis cases and 150 controls (power 0.8, alpha 0.05, AUC below 0-hypothesis 0.6) (42).

Objective 3 - Diagnostic accuracy of POC-UFC on diagnosing and excluding bacteriuria

This diagnostic accuracy study will include all participants. Index test is the POC-UFC and reference standard is the urine culture. The primary outcome is bacteriuria, defined as significant growth of any bacteria. A urine culture will be considered positive with a cut-off of > 1000 CFU/ml for uropathogens and >10.000 CFU/ml for others.

A secondary diagnostic test will be performed, where the reference standard is the expert panel assessment. The outcome is urinary tract infection. The test positive of the index test is bacteuria combined with leukocytes.

The index test results will not be available for the performers of the reference standard test. The reference standard results will be available after the index test has been performed.

A demographic characteristic of the study populations will be presented. Cross-tabulation of the index test result by the reference standard results will be made including missing results, and used to determine diagnostic accuracy expressed as sensitivity, specificity, predictive values, and likelihood ratios reported with 95% confidence intervals where appropriate. Receiver operating characteristic (ROC) analysis will also be performed.

Urine culture shows significant growth of uropathogenic bacterium in approximately 50% of people with suspected APN(25). Asymptomatic bacteriuria accounts for about 20% in the elderly population, depending on gender and age (43), which among 1000 inpatients suspected of infection, of which 15% have APN, gives a sensitivity of 50% (95% CI: 42-58 %) and a negative predictive value of 90% (95% CI: 77-83%). With the expectation of identifying at least 150 cases of APN among our study population, an improvement in sensitivity to 70% (95% CI: 62-77%) and negative predictive value to 95% (95% CI: 93 -96%) could be found with 95% security.

Objective 4 – Addition of POC-PCR analysis of sputum to the diagnostic set-up for CAP on antibiotic prescribing

This RCT will include all participants in track A, who had a sputum sample collected. Intervention group: sputum samples analysed by POC-PCR. Control group: routine microbiology analysis. It is a superiority randomized trial. Primary outcome is targeted versus non-targeted antibiotic treatment prescribed at four hours after admission. Targeted treatment is defined as narrow spectrum antibiotics directed against CAP, antibiotics directed against a detected respiratory pathogen or no antibiotics (e.g. in the absence of a bacterial pathogen and/or presence of a viral pathogen) (appendix VII). Non-targeted treatment is defined as broad spectrum antibiotics not directed against a specific pathogen or antibiotics not directed against CAP. The analyses will follow the intention-to-treat principal and a hierarchical mixed effect logistic model will be utilized to analyze the primary outcome to accommodate the hierarchical structure of the random effect, which manifest according to different personnel collecting the samples and geographical variation.

Secondary outcomes are length of stay, 30 days mortality, in-hospital mortality, admission to intensive care unit, readmission to hospital within 30 days from day of discharge, and antibiotic treatment at 48 hours of admission. A reliability analysis for POC-PCR and routine culturing will be performed as secondary analysis calculating the Intra-class correlation coefficient

To achieve a power of 82% for the main analysis, 200 patients with suspected CAP must be included. To accommodate the bias presented by Gail et al (44) the generalized mixed effect models will be adjusted for strong

predictors. If the sample size is not sufficient for a generalized mixed effect models the corresponding univariate analysis will be conducted.

Objective 5 - Diagnostic accuracy of POC-US and ULDCT on diagnosing CAP

This diagnostic accuracy study will include all participants in track A, who had the HRCT performed. Index test is the POC-US, ULDCT, and chest x-ray. The reference standard is HRCT. The primary outcome is inflammatory changes in the lungs compatible with CAP.

The index test results will not be available for the performers of the reference standard test. The reference standard results will be available after the index test has been performed.

A demographic characteristic of the study populations will be presented. Cross-tabulation of the index tests result by the reference standard results will be made including missing results, and used to determine diagnostic accuracy expressed as sensitivity, specificity, predictive values, and likelihood ratios reported with 95% confidence intervals where appropriate. Receiver operating characteristic (ROC) analysis will also be performed.

It is assumed that the reference standard will find 98% of the patients and index test 90%. With a power of 80%, at least 132 patients with verified CAP should be included (one-sided McNemar test).

Objective 6 - Diagnostic accuracy of CEUS on diagnosing APN

This diagnostic accuracy study will include all participants in track B, who had both the CEUS and MRI performed. Index test is the CEUS and reference standard is MRI. The primary outcome is the presence of renal inflammatory changes compatible with APN. The reference standard will be described by an expert radiologist, who before describing will be informed of some standardized clinical and paraclinical parameters (e.g. fever, CRP, flank pain, and relevant comorbidity), but will be blinded to the results of the other imaging investigations. The CEUS will be conducted and described by a consultant radiologist. The scans will be post process evaluated in the software VueBox. Each kidney is divided into an upper, middle and lower part for each, and these regions are compared in the evaluation of diagnostic agreement.

The index test results will not be available for reference standard performer and describer. The reference standard results will not be available for the index test performers.

A demographic characteristic of the study populations will be presented, and the time interval of the two scans will be reported. Cross-tabulation of the index test result by the reference standard results will be made including missing results, and used to determine diagnostic accuracy expressed as sensitivity, specificity, predictive values, and likelihood ratios reported with 95% confidence intervals where appropriate. Receiver operating characteristic (ROC) analysis will also be performed.

It is assumed that the reference standard finds 98% of patients and index test 90%. With a power of 80%, at least 132 patients must be included (one-sided McNemar test).

Objective 7 - Diagnostic accuracy of POC-US in diagnosing hydronephrosis in patients suspected of APN

This diagnostic accuracy study will include all participants in track B, who had both the POC-US and MRI successfully conducted. Index test is the POC-US and reference standard is MRI. The primary outcome is the presence of hydronephrosis. The reference standard is described by an expert radiologist. The POC-US will be evaluated by the executive study assistants.

The index test results will not be available for reference standard evaluator. The reference standard results will not be available for the index test performers.

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A demographic characteristic of the study populations will be presented, and the time interval of the two scans will be reported. Cross-tabulation of the index test result by the reference standard results will be made including missing results, and used to determine diagnostic accuracy expressed as sensitivity, specificity, predictive values, and likelihood ratios reported with 95% confidence intervals where appropriate. Receiver operating characteristic (ROC) analysis will also be performed.

It is assumed that the reference standard finds 98% of patients and index test 90%. With a power of 80%, at least 132 patients must be included (one-sided McNemar test).

Applicable to all sub-studies

Annually, 5.7% of patients admitted to an ED are diagnosed with CAP and 2.4% with APNs (data from the ED at Hospital Sønderjylland). Taking into account exclusion criteria, weekends/holidays/missing data, and experience in patient recruitment, it is estimated that at least 1000 patients admitted with suspected infection must be included in the study, of which at least 200 patients will be diagnosed with pneumonia and at least 150 patients with APN.

No interim analysis will be made. Non-participant analysis is performed. For missing data multiple imputation is used. Any drop out during the study and the reason will be reported. It is anticipated that once the patients has consented, the drop-out rate will be minimal.

Ethics and dissemination

The project was approved by the Regional Committees on Health Research Ethics for Southern Denmark (S-20200188), registered by the Danish Data Protection Agency (no. 20/60508) and by clinicaltrials.gov (NCT: 04661085, 04681963, 04667195, 04652167, 04686318, 04686292, 04651712, 04645030, and 04651244). Registration date was November-December 2020. Signed informed consent will be obtained from all participants after information of the project has been given both in writing and orally.

Participation in track A will contain additional imaging. Patients under the age of 40 are therefore excluded from the CT due to the extra risk of developing cancer from the radiation. A local hospital physicist has helped with the following calculations: A typical HRCT gives a radiation dose of approximately 2.2 mSv which corresponds to a cancer risk of 1:9100. An X-ray gives a radiation dose of approximately 0.06 mSv which corresponds to a cancer risk of 1:333330. An ULDCT gives a radiation dose of approximately 0.1 mSv which corresponds to a cancer risk of 1:200000. Participation in track A gives each participant approximately 2.26 mSv (ULDCT and HRCT) which corresponds to a cancer risk of 1:8850(45-48). The examination time of ULDCT and HRCT is approximately 10 minutes.

Use of US contrast in rare cases cause allergic reactions; less than 1/10.000 exponents require medical treatment due to allergic reaction (49). The examination time of advanced US is approximately 20 minutes.

MRI does not provide any radiation dose to the patients and is without intravenous contrast. The examination time is approximately 45 minutes, which is aligned with normal MRI examination time.

Overall, risks related to participation in the study is considered minimal, and furthermore, chances are that the additional diagnostic imaging will inform the clinician in a favorable way before the onset of patient treatment.

The treating staff informs the patients about relevant test results. All medical records including laboratory and imaging can be assessed by the patient via the Danish public healthcare web portal (www.sundhed.dk)

Protocol amendments

Important protocol modifications like changes in eligibility criteria or outcome will be communicated to the relevant parties, i.e. sponsor, trial registry, and scientific ethical committee, and explicit described in future publications.

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Dissemination policy

The results of the study will be presented in English peer-reviewed recognized scientific journals. The results of the project will also be disseminated through participation in academic and other conferences, as well as through the printed and electronic press. The author panel will include the steering committee, project assistants, and local coordinators in accordance with the Vancouver criteria. No professional writers will be used. Positive, negative and inconclusive results will be published. Diagnostic accuracy studies will follow the guidelines for reporting diagnostic accuracy studies (STARD) (50), cross sectional studies will follow the guidelines for strengthening the reporting of observational studies in epidemiology (STROBE) (51), and randomized studies will follow the consolidated standards of reporting trials (CONSORT) (52).

Access to data

Only the members of the steering committee and project assistants will have access to the final trial dataset. Other researches may be granted access to the anonymized data for analysis on reasonable request to the corresponding authors.

Discussion

COVID-19 and the consequent societal lockdown might affect trial recruitment and patient distribution. This might lead to an extended recruitment period, as patients suspected of an infectious not related to COVID-19 may be admitted to other departments than the ED, so the ED will be able to handle the many COVID-19 patients. The lockdown may also reduce the number of infections in the society, so fewer patient will visit the hospital, and the distribution of the infections might differ since e.g. the airborne transmitted infections will be reduced. This challenge will especially sub-study 1 be aware of when presenting the results.

After completion of the study, a novel diagnostic algorithm will be developed. Subsequently, the plan is to test the algorithm in a national setting including at least eight EDs. The results can be implemented in daily work and routines. The study will also be able to characterize the patients, who are diagnosed at the ED with an infection of unknown origin and prescribed broad-spectrum antibiotics.

The study is only generalisable to settings where appropriately trained staff and equipment can perform POC-US, and well-resourced settings where a rapid POC-PCR and POC-UFC service is available.

The results of the study will have both national and international interest, as the challenges are common and the solutions can easily be applied in hospitals with a similar technological context. Securing rapid and reliable diagnosis of two of the most common infections diagnosed in the ED, will encourage the reduction of broad-spectrum antibiotics and thereby the development of multi-resistant bacteria.

Declarations

Abbreviations: acute pyelonephritis (APN), Anatomical therapeutic chemical (ATC), area under the curve (AUC), community-acquired pneumonia (CAP), cluster of differentiation 4 (CD4), contrast enhanced ultrasound (CEUS), Coronavirus Disease 2019 (COVID-19), C-reactive protein (CRP), emergency department (ED), human immunodeficiency virus (HIV), high-resolution dose computed tomography (HRCT), magnetic resonance imaging (MRI), Objective Structured Assessment of US Skills (OASUS), polymerase-chain-reaction (PCR), serum procalcitonin (PCT), Point-of-care (POC), receiver operating characteristic (ROC), Soluble urokinase plasminogen activator receptor (suPAR), urine flow cytometry (UFC), ultralow dose computed tomography (ULDCT), and ultrasound (US).

Protocol version: January 25th 2021, version 1.0

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Ethics approval: The project was approved by the Regional Committees on Health Research Ethics for Southern Denmark (S-20200188), registered by the Danish Data Protection Agency (20/60508) and by clinicaltrials.gov (NCT: 04661085, 04681963, 04667195, 04652167, 04686318, 04686292, 04651712, 04645030, and 04651244). Each patient provided written informed consent.

Data sharing statement: Due to Danish laws on personal data, data cannot be shared publicly. To request these data, please contact the corresponding author for more information.

Competing interests: The authors declare that they have no competing interests

Patient and Public Involvement: The patients or public were not involved in the development of the research question or the study design.

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Authors´ contributions: HS, OG, FSR, ERBP, CØ, CBL, TAS, SP, MBC, and CBM conceptualized and all authors designed the study and data collection in detail. HS, AH, MHL, MBC, and CBM reviewed the literature. AH, MHL, MBC, and MAH will recruit participants, and HS, OG, FSR, ERBP, CØ, CBL, TAS, SP, MBC, and CBM will supervise data collection and analysis. HS, AH, MHL, MBC, MAH, and CBM will carry out statistical analysis and write the first manuscripts, which will be critically reviewed by all authors, who will finally approve the manuscripts before submission.
HS and CBM are responsible for the overall content as guarantors. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Steering committee: Composed of representatives from the involved type of departments: emergency, microbiology, biochemistry, and radiology. The role of the committee is to develop the scientific framework of the study, make final decisions on major issues during the data collection and data management period. The committee is responsible for all financial issues. Members of the steering committee are HS, OG, FSR, ERBP, and CBM.

Roles and responsibilities: CBM is the legal sponsor and the study chief investigator (Christian.Backer.Mogensen@rsyd.dk). HSA is the principal investigator.

Participating departments: All departments are located in Denmark
Emergency Department, Hospital Sønderjylland, Aabenraa. Emergency Department, Hospital Lillebælt, Kolding. Emergency Department, Odense University Hospital, Odense.
Radiology Department, Hospital Sønderjylland, Aabenraa. Radiology Department, Hospital Lillebælt, Kolding. Radiology Department, Odense University Hospital, Odense.
Department of Microbiology, Hospital Sønderjylland, Sønderborg. Department of Clinical Microbiology, Lillebælt Hospital, Vejle. Department of Clinical Microbiology, Odense University Hospital, Odense.
Bloodsamples, Biochemistry and Immunology, Hospital Sønderjylland, Aabenraa. Biochemistry and Immunology, Lillebælt Hospital, Kolding and Vejle. Clinical Biochemistry and Pharmacology, Odense University Hospital, Odense.

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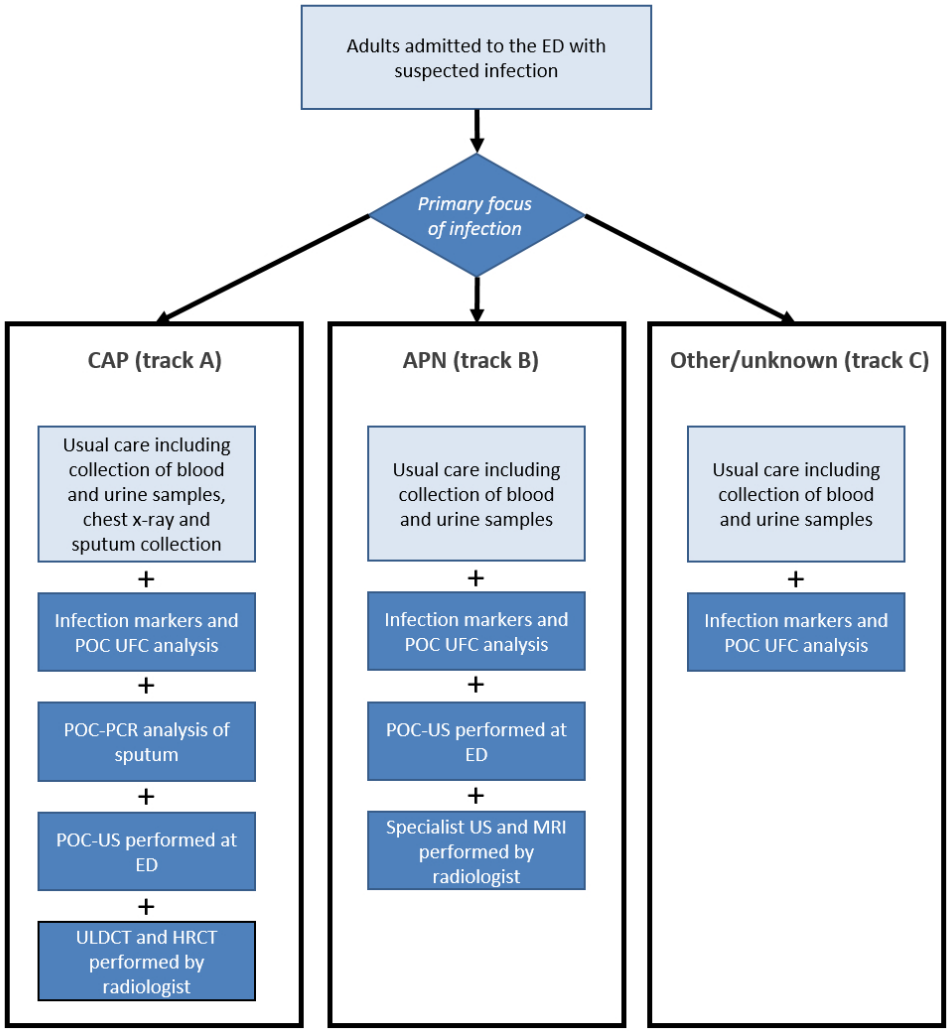


Figure 1 Design of patient flow and diagnostic tracks

170x182mm (150 x 150 DPI)

Appendix

I. Informed consent materials
II. Biological specimens
III. Schedule of enrollment, interventions, and assessments
IV. Targets in POC-PCR
V. Recommended action list
VI. Template for reference standard
VII. Algorithm for antibiotic prescription

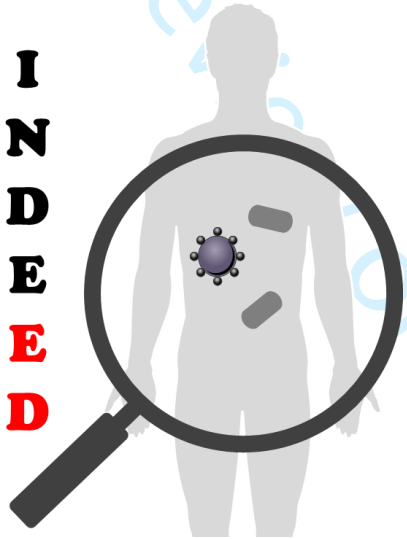
Appendix I - Informed consent materials

Informed consent materials given to the participants has been developed in three versions – track A, B, and C, respectively. The written consent form can be found at the end of appendix I. It is all in Danish.

Participant information - Track A

Deltagerinformation om deltagelse i videnskabeligt forskningsprojekt for personer, der indlægges akut med mistanke om lungebetændelse

Forbedret diagnostik af akutte infektioner



Infectious Diagnostics in Emergency Departments (INDEED study)

Et samarbejdsprojekt på tværs af specialer på Sygehus Sønderjylland, Sygehus Lillebælt og Odense Universitetshospital med udgangspunkt i Akutafdelingerne

Vi vil spørge, om du vil deltage i et videnskabeligt projekt?

Projektet handler om at blive bedre til at diagnosticere lungebetændelse på Akutafdelingen, så en målrettet behandling kan igangsættes så hurtigt som muligt.

Før du beslutter, om du vil deltage i projektet, skal du fuldt ud forstå, hvad projektet går ud på, og hvorfor vi gennemfører det. Vi vil derfor bede dig om at læse denne deltagerinformation grundigt.

Hvis du beslutter dig for at deltage, vil vi bede dig om at underskrive en samtykkeerklæring. Husk, at du har ret til at rådføre dig hos familie, venner eller bekendte. Du har også ret til betænkningstid før du underskriver, men da der er tale om en akut infektion, som kræver hurtig behandling, beder vi om, at du beslutter dig inden for 30 minutter.

Det er frivilligt at deltage i projektet. Du kan når som helst og uden at give en grund trække dit samtykke tilbage. Hvis du trækker dit samtykke om deltagelse i projektet tilbage, vil det ikke få konsekvenser for din videre behandling.

Projektets mål

De redskaber og undersøgelser, der eksisterer i dag til at diagnosticere lungebetændelse, har mange begrænsninger. Det udfordrer lægen i at stille en sikker diagnose inden for kort tid og igangsætte en målrettet behandling. Det kan få konsekvenser for den enkelte persons indlæggelsesforløb. Hvis man behandler med antibiotika som dækker flere bakterier end nødvendigt vil det også bidrage til udviklingen af bakterier, som er modstandsdygtige over for mange antibiotika.

Projektet har derfor til formål at finde bedre redskaber, som kan hjælpe lægen til at stille en sikker diagnose inden for få timer for personer, indlagt akut med mistanke om lungebetændelse.

Det undersøger projektet

Projektet vil undersøge

- hvilke symptomer, tegn og forhold, der kendetegner lungebetændelse og sygdomsgraden
- hvilke markører for infektion i blodet, der bedst kan identificere en lungebetændelse og sygdomsgraden
- om en ny metode til at måle bakterier i urinen er nyttig
- om en ny metode til at identificere bakterier i sekret fra lungerne er nyttigt
- om ultralydsundersøgelse og CT-skanning med meget lav strålingsrisiko kan bruges til at diagnosticere lungebetændelse

Plan for projektet

Projektet foregår på Fælles Akutmodtagelsen i Aabenraa, Sygehus Sønderjylland, på Akutafdelingen i Kolding, Sygehus Lillebælt, og på Fælle Akut Modtagelsen i Odense, Odense Universitetshospital. Fra

februar 2021 til vinteren 2021/22 vil 500 voksne personer, som indlægges akut med mistanke om lungebetændelse på de tre akutafdelinger, blive inviteret til at deltage.

Personalet vil i forbindelse med din indlæggelse opsøge og informere dig om projektet, og tilbyde deltagelse i projektet. Da det er vigtigt at en akut infektion bliver behandlet hurtigt, vil vi bede dig om at tilkendegive din beslutning inden for en halv time.

Det indebærer deltagelse i projektet for dig

Deltagelse i projektet betyder, at du vil modtage den normale behandling, afdelingen tilbyder, og derudover få foretaget ekstra undersøgelser.

Vi vil stille dig nogle spørgsmål omkring dine symptomer, tidligere og aktuelle sygdomme, og hvordan du har det. Vi beder i den forbindelse adgang til din patientjournal, for at følge op på eventuelle tidligere indlæggelser, den aktuelle indlæggelse, og eventuelle indlæggelser inden for den næste måned efter du er udskrevet.

Vi vil tage 14mL ekstra blod svarende til 2 ekstra rør, når du alligevel får taget blodprøve, og hjælpe dig med at aflevere en urinprøve.

Af det sekret fra lungerne, som der bliver taget ifølge normal behandling, vil vi tage en lille del fra nogle af projektpersonerne, og undersøge det med en ny metode.

Det blod, urin og sekret fra lungerne, der indhentes til projektet, vil blive destrueret, når projektet er afsluttet.

Hvis du vælger at deltage, skal du have taget to ekstra skanninger af lungerne. 1) Ultralydsskanning som foretages på akutafdelingen og tager 5 min. 2) En CT-skanning som består af en skanning med meget lav strålingsrisiko, og en højopløselig CT-skanning, som er den mest præcise skanning, der benyttes på lungerne i dag. CT-skanningen vil i alt tage 10 min.

Dit samtykke vil give den forsøgsansvarlige, sponsor og dennes repræsentant direkte adgang til relevante helbredsoplysninger i journalen for at kunne gennemføre, overvåge og kontrollere projektet. I projektet vil behandlingen af personoplysninger følge databeskyttelsesloven og databeskyttelsesforordningen. Efter indsamling af de ønskede informationer vil dine persondata blive fjernet fra vores registreringssystem, og dit personnummer vil blive erstattet af en kode (pseudo-anonymisering).

Bivirkninger, risici, komplikationer og ulemper

Der er ingen eller kun få kendte risici eller bivirkninger ved at deltage i projektet. Alle prøvetagningsmetoder er velkendte og almindeligt anvendte procedurer, som vi har stor erfaring med og kendskab til. Der kan dog være risici ved undersøgelserne, som vi endnu ikke kender. Vi beder dig derfor om at fortælle, hvis du oplever problemer i forbindelse med prøvetagning og undersøgelser. Hvis vi opdager bivirkninger, som vi ikke allerede har fortalt dig om, vil du naturligvis blive orienteret med det samme, og du vil skulle tage stilling til, om du ønsker at fortsætte med prøvetagning og undersøgelser.

De ekstra blodprøver til projektet tages i forbindelse med de blodprøver, der alligevel tages ved indlæggelse. Risici og bivirkninger ved at få taget en blodprøver kan være ubehageligt, lette smerter og/eller blå mærker, og i nogle tilfælde besvimelse. I sjældne tilfælde kan der opstå en mindre blodansamling eller betændelse ved indstiksstedet.

Urinprøven kan som regel afleveres i et bæger, opsamlet ved toiletbesøg. Er du kateterbærer eller på grund af sygdom ikke selv kan lade vandet, kan det blive nødvendigt at hjælpe vandladningen på vej med et kateter, som er et tyndt plastikrør til indførsel i blæren via urinrøret. Denne procedure kan give let ubehag og eventuelt kortvarig mindre blødning fra slimhinderne.

Skanningerne er ikke forbundet med smerte, men du kan eventuelt opleve ubehag ved flytningen til CT-skanneren. Væsentligste risiko i forbindelse med deltagelse i projektet er den ekstra stråledosis som CT-skanningen medfører. Den ekstra stråledosis, du udsættes for, udgør i alt lidt mindre end den baggrundsstråling, som du normalt udsættes for i løbet af et år. Strålingen fra skanningen medfører en let øget risiko for udvikling kræft på ca. 0,01-0,1% og svarer til, at den samlede livstidsrisiko for kræft stiger fra 25% til 25,1%. Denne risiko vurderes dog betydningsløs i forhold til de risici, der i øvrigt er ved din aktuelle indlæggelse.

Dine prøvesvar

Ønsker du svar på de almindelige blod- og urinundersøgeler, kan du se det på www.sundhed.dk. Svar på de ekstra blod- og urinundersøgelser i projektet vil ikke fremkomme her, da vi ikke kender betydningen af resultaterne endnu. Har svarene et alarmerende resultat, vil den behandlende læge få besked og vil vurdere, om det har betydning for din behandling. Resultatet af den ekstra undersøgelse af sekret fra lungerne, som der vil kunne blive lavet i projektet, vil lægen, der behandler dig, blive orienteret om.

Skanningsresultaterne vil være synlige for lægerne, der behandler dig, og indgå i deres vurdering og behandling. Hvis vi skulle opdage noget, der kunne give os mistanke om andre sygdomme (f.eks. kræft), vil vi via din læge kontakte dig og tilbyde yderligere udredning. Bidrager skanningerne ikke med viden, der ændrer på din behandling eller diagnose, hører du ikke nærmere til skanningsresultatet.

Nytte ved projektet

Projektet er vigtigt for at vi fremadrettet kan gøre indlæggelsesforløbet for personer, der indlægges akut med mistanke om lungebetændelse, bedre. Projektet vil have en afgørende betydning for praksis på akutafdelingerne, og formentligt hvilken type antibiotika lægen ordinerer. Et mere målrettet antibiotikaforbrug vil bidrage til reduktion af bakterier, der er modstandsdygtige over for antibiotika, og dermed sikre at infektioner i fremtiden også kan behandles med antibiotika.

For dig personligt, vil deltagelse ikke umiddelbart have en betydning for dit behandlingsforløb. Hvis der skulle ske at være nogle særlige komplikationer til din aktuelle sygdom relateret til lungerne, vil vi dog med de ekstra scanninger formentlig hurtigere erkende dette.

Udelukkelse fra undersøgelse

Du vil udgå af dele af projektet, hvis nogle af undersøgelserne mislykkes af fx tekniske grunde eller hvis din behandlende læge vurderer, at det er for risikabelt for dig at deltage.

Adgang til projektets resultater

Projektets samlede resultater vil blive offentliggjort 2024 i videnskabelige tidsskrifter samt på sygehusenes hjemmesider. Resultater med relevans for beslutningstagere i sundhedsvæsenet vil blive offentliggjort i danske medier og tidsskrifter. Det sikres, at ingen deltagere kan genkendes i det, som offentliggøres. Har du interesse i at vide mere om projektets resultater, kan du efter offentliggørelse opsøge dem via http://www.sygehussonderjylland.dk/wm521282.

Vi håber, at du med denne information har fået tilstrækkeligt indblik i, hvad det vil sige at deltage i projektet, og at du føler dig rustet til at tage beslutningen om din eventuelle deltagelse. Hvis du vil vide mere, er du meget velkommen til at kontakte os. Information om dine rettigheder er vedlagt denne deltagerinformation sidst i dokumentet (Bilag 1).

Hvis du beslutter dig for at deltage i projektet, vil vi bede dig om at underskrive samtykkeerklæringen. Du kan vælge om du vil give samtykke til hele projektet eller kun dele af projektet. Det er frivilligt at deltage i projektet, og du kan når som helst og uden at give en grund trække dit samtykke tilbage. Det vil ikke få konsekvenser for den videre behandling.

Yderligere oplysninger kan fås ved henvendelse til

Professor og overlæge Christian Backer Mogensen
Fælles Akutmodtagelsen, Sygehus Sønderjylland
Kresten Philipsens Vej 15 - 6200 Aabenraa
Christian.Backer.Mogensen@rsyd.dk
Tlf: 79971123

Initiativtagere til projektet

Projektet er primært udarbejdet i samarbejde mellem Akutafdeling, Biokemisk Afdeling og Mikrobiologisk Afdeling, og Radiologisk Afdeling på Sygehus Sønderjylland, Sygehus Lillebælt og Odense Universitets Hospital. Projektet er forankret på Sygehus Sønderjylland og Institut for Regional Sundhedsforskning på Syddansk Universitet, som er ansøgnings- og bevillingsansvarlige.

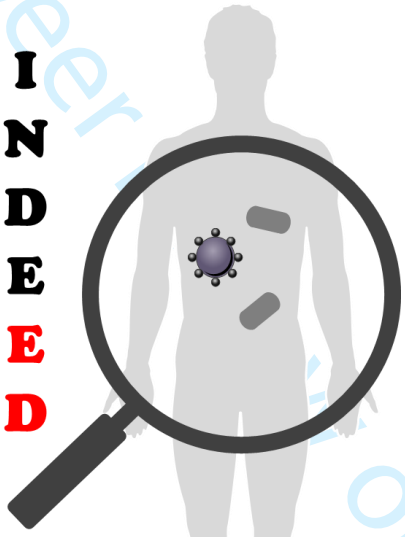
Økonomisk støtte til projektet

Projektet har fået økonomisk støttet i form af ph.d. stipendiater fra Syddansk Universitet (1.650.000kr), ph.d.-stipendiater fra Sygehus Sønderjylland (4.800.000kr) samt støtte til drift fra Region Syddanmark (500.000kr). Forsøgsansvarlige har ingen økonomisk tilknytning til støttegivere eller andre interessenter i forsøget. Der vil ikke være en økonomisk kompensation til patienter, der deltager i projektet.

Participant information - Track B

Deltagerinformation om deltagelse i videnskabeligt forskningsprojekt for personer, der indlægges akut med mistanke om nyrebækkenbetændelse

Forbedret diagnostik af akutte infektioner



Infectious Diagnostics in Emergency Departments (INDEED study)

Et samarbejdsprojekt på tværs af specialer på Sygehus Sønderjylland, Sygehus Lillebælt og Odense Universitetshospital med udgangspunkt i Akutafdelingerne

Vi vil spørge, om du vil deltage i et videnskabeligt projekt?

Projektet handler om at blive bedre til at diagnosticere akut nyrebækkenbetændelse på Akutafdelingen, så en målrettet behandling kan igangsættes så hurtigt som muligt.

Før du beslutter, om du vil deltage i projektet, skal du fuldt ud forstå, hvad projektet går ud på, og hvorfor vi gennemfører det. Vi vil derfor bede dig om at læse denne deltagerinformation grundigt.

Hvis du beslutter dig for at deltage, vil vi bede dig om at underskrive en samtykkeerklæring. Husk, at du har ret til at rådføre dig hos familie, venner eller bekendte. Du har også ret til betænkningstid før du underskriver, men da der er tale om en akut infektion, som kræver hurtig behandling, beder vi om, at du beslutter dig inden for 30 minutter.

Det er frivilligt at deltage i projektet. Du kan når som helst og uden at give en grund trække dit samtykke tilbage. Hvis du trækker dit samtykke om deltagelse i projektet tilbage, vil det ikke få konsekvenser for din videre behandling.

Projektets mål

De redskaber og undersøgelser, der eksisterer i dag til at diagnosticere nyrebækkenbetændelse, har mange begrænsninger. Det udfordrer lægen i at stille en sikker diagnose inden for kort tid og igangsætte en målrettet behandling. Det kan få konsekvenser for den enkelte persons indlæggelsesforløb. Hvis man behandler med antibiotika som dækker flere bakterier end nødvendigt vil det også bidrage til udviklingen af bakterier, som er modstandsdygtige over for mange antibiotika.

Projektet har derfor til formål at finde bedre redskaber, som kan hjælpe lægen til at stille en sikker diagnose inden for få timer for personer, indlagt akut med mistanke om akut nyrebækkenbetændelse.

Det undersøger projektet

Projektet vil undersøge

- hvilke symptomer, tegn og forhold, der kendetegner nyrebækkenbetændelse og sygdomsgraden
- hvilke markører for infektion i blodet, der bedst kan identificere en nyrebækkenbetændelse og sygdomsgraden
- om en ny metode til at måle bakterier i urinen er nyttig
- om ultralydsundersøgelse med og uden kontrastvæske kan bidrage til at diagnosticere nyrebækkenbetændelse

Plan for projektet

Projektet foregår på Fælles Akutmodtagelsen i Aabenraa, Sygehus Sønderjylland, på Akutafdelingen i Kolding, Sygehus Lillebælt, og på Fælle Akut Modtagelsen i Odense, Odense Universitetshospital. Fra februar 2021 til vinteren 2021/22 vil 300 voksne personer, som indlægges akut med mistanke om nyrebækkenbetændelse på de tre akutafdelinger, blive inviteret til at deltage.

Personalet vil i forbindelse med din indlæggelse opsøge og informere dig om projektet, og tilbyde deltagelse i projektet. Da det er vigtigt at en akut infektion bliver behandlet hurtigt, vil vi bede dig om at tilkendegive din beslutning inden for en halv time.

Det indebærer deltagelse i projektet for dig

Deltagelse i projektet betyder, at du vil modtage den normale behandling, afdelingen tilbyder, og derudover få foretaget ekstra undersøgelser.

Vi vil stille dig nogle spørgsmål omkring dine symptomer, tidligere og aktuelle sygdomme, og hvordan du har det. Vi beder i den forbindelse adgang til din patientjournal, for at følge op på eventuelle tidligere indlæggelser, den aktuelle indlæggelse, og eventuelle indlæggelser inden for den næste måned efter du er udskrevet.

Vi vil tage 14mL ekstra blod svarende til 2 ekstra rør, når du alligevel får taget blodprøve, og hjælpe dig med at aflevere en urinprøve.

Det blod og urin, der indhentes til projektet, vil blive destrueret, når projektet er afsluttet.

Vi vil tilbyde dig tre ekstra skanninger af nyrerne. 1) Ultralydsskanning som foretages på akutafdelingen og tager 5 min. 2) Ultralydsskanning, hvor der sprøjtes kontrastvæske ind i dine blodåre, og som foretages af en røntgenlæge. Skanningen tager 20 min. 3) MR-skanning af røntgenlægen, og som tager 45 min. Det tilstræbes, at skanningerne foretages i forbindelse med din indlæggelse. Hvis du udskrives før, kan det være nødvendigt, at du møder op til skanningerne dagen efter.

Dit samtykke vil give den forsøgsansvarlige, sponsor og denne repræsentant direkte adgang til relevante helbredsoplysninger i journalen for at kunne gennemføre, overvåge og kontrollere projektet. I projektet vil behandlingen af personoplysninger følge databeskyttelsesloven og databeskyttelsesforordningen. Efter indsamling af de ønskede informationer vil dine persondata blive fjernet fra vores registreringssystem, og dit personnummer vil blive erstattet af en kode (pseudo-anonymisering).

Bivirkninger, risici, komplikationer og ulemper

Der er ingen eller kun få kendte risici eller bivirkninger ved at deltage i projektet. Alle prøvetagningsmetoder er velkendte og almindeligt anvendte procedurer, som vi har stor erfaring med og kendskab til. Der kan dog være risici ved undersøgelserne, som vi endnu ikke kender. Vi beder dig derfor om at fortælle, hvis du oplever problemer i forbindelse med prøvetagning og undersøgelser. Hvis vi opdager bivirkninger, som vi ikke allerede har fortalt dig om, vil du naturligvis blive orienteret med det samme, og du vil skulle tage stilling til, om du ønsker at fortsætte med prøvetagning og undersøgelser.

De ekstra blodprøver til projektet tages i forbindelse med de blodprøver, der alligevel tages ved indlæggelse. Risici og bivirkninger ved at få taget en blodprøver kan være ubehageligt, lette smerter og/eller blå mærker, og i nogle tilfælde besvimelse. I sjældne tilfælde kan der opstå en mindre blodansamling eller betændelse ved indstiksstedet.

Urinprøven kan som regel afleveres i et bæger, opsamlet ved toiletbesøg. Er du kateterbærer eller på grund af sygdom ikke selv kan lade vandet, kan det blive nødvendigt at hjælpe vandladningen på vej med et

kateter, som er et tyndt plastikrør til indførsel i blæren via urinrøret. Denne procedure kan give let ubehag og eventuelt kortvarig mindre blødning fra slimhinderne.

Det kontraststof, der bruges til ultralydsskanningen, består overvejende af små luftbobler. Det er ikke farligt for kroppen. Der kan opstå milde, kortvarige bivirkninger som fx hovedpine, svimmelhed, ændret smags- og lugtesans. Dette ses hos 0,5-5 %. I meget sjældne tilfælde kan man udvikle en allergisk reaktion, når stoffet sprøjtes ind i blodårerne. Disse alvorlige reaktioner er beskrevet hos mindre end 1/16.500. Du vil derfor blive observeret i 20 minutter efter skanningen, for at se om der skulle opstå bivirkninger eller allergisk reaktion.

MR-skanningen kan godt føles som lang tid. Skanningen er larmende og du har derfor høreværn på. Der er *ingen* strålebelastning eller andre påvirkninger af kroppen forbundet med en MR-skanning.

Dine prøvesvar

Ønsker du svar på de almindelige blod- og urinundersøgeler, kan du se det på www.sundhed.dk. Svar på de ekstra blod- og urinundersøgelser i projektet vil ikke fremkomme her, da vi ikke kender betydningen af resultaterne endnu. Har svarene et alarmerende resultat, vil den behandlende læge få besked og vil vurdere, om det har betydning for din behandling.

Skanningsresultaterne vil være synlige for lægerne, der behandler dig, og indgå i deres vurdering og behandling. Hvis vi skulle opdage noget, der kunne give os mistanke om andre sygdomme (f.eks. kræft), vil vi via din læge kontakte dig og tilbyde yderligere udredning. Bidrager skanningerne ikke med viden, der ændrer på din behandling eller diagnose, hører du ikke nærmere til skanningsresultatet.

Nytte ved projektet

Projektet er vigtigt for at vi fremadrettet kan gøre indlæggelsesforløbet for personer, der indlægges akut med mistanke om nyrebækkenbetændelse, bedre. Projektet vil have en afgørende betydning for praksis på akutafdelingerne, og formentligt hvilken type antibiotika lægen ordinerer. Et mere målrettet antibiotikaforbrug vil bidrage til reduktion af bakterier, der er modstandsdygtige over for antibiotika, og dermed sikre at infektioner i fremtiden også kan behandles med antibiotika.

For dig personligt, vil deltagelse ikke umiddelbart have en betydning for dit behandlingsforløb. Hvis der skulle ske at være nogle særlige komplikationer til din aktuelle sygdom relateret til nyrerne, vil vi dog med de ekstra skanninger formentlig hurtigere erkende dette.

Udelukkelse fra undersøgelse

Du vil udgå af dele af projektet, hvis nogle af undersøgelserne mislykkes af fx tekniske grunde eller hvis din behandlende læge vurderer, at det er for risikabelt for dig at deltage.

Adgang til projektets resultater

Projektets samlede resultater vil blive offentliggjort 2024 i videnskabelige tidsskrifter samt på sygehusenes hjemmesider. Resultater med relevans for beslutningstagere i sundhedsvæsenet vil blive offentliggjort i danske medier og tidsskrifter. Det sikres, at ingen deltagere kan genkendes i det, som offentliggøres. Har du interesse i at vide mere om projektets resultater, kan du efter offentliggørelse opsøge dem via http://www.sygehussonderjylland.dk/wm521282.

Vi håber, at du med denne information har fået tilstrækkeligt indblik i, hvad det vil sige at deltage i projektet, og at du føler dig rustet til at tage beslutningen om din eventuelle deltagelse. Hvis du vil vide mere, er du meget velkommen til at kontakte os. Information om dine rettigheder er vedlagt denne deltagerinformation sidst i dokumentet (Bilag 1).

Hvis du beslutter dig for at deltage i projektet, vil vi bede dig om at underskrive samtykkeerklæringen. Du kan vælge om du vil give samtykke til hele projektet eller kun dele af projektet. Det er frivilligt at deltage i projektet, og du kan når som helst og uden at give en grund trække dit samtykke tilbage. Det vil ikke få konsekvenser for den videre behandling.

Yderligere oplysninger kan fås ved henvendelse til

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Initiativtagere til projektet

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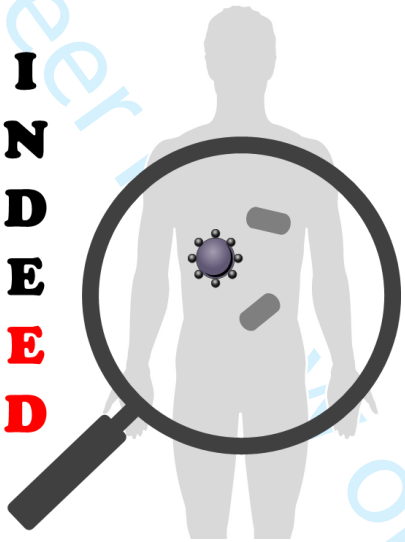
Økonomisk støtte til projektet

Projektet har fået økonomisk støttet i form af ph.d. stipendiater fra Syddansk Universitet (1.650.000kr), ph.d.-stipendiater fra Sygehus Sønderjylland (4.800.000kr) samt støtte til drift fra Region Syddanmark (500.000kr). Forsøgsansvarlige har ingen økonomisk tilknytning til støttegivere eller andre interessenter i forsøget. Der vil ikke være en økonomisk kompensation til patienter, der deltager i projektet.

Participant information - Track C

Deltagerinformation om deltagelse i videnskabeligt forskningsprojekt for personer, der indlægges akut med mistanke om infektion

Forbedret diagnostik af akutte infektioner



Infectious Diagnostics in Emergency Departments (INDEED study)

Et samarbejdsprojekt på tværs af specialer på Sygehus Sønderjylland, Sygehus Lillebælt og Odense Universitetshospital med udgangspunkt i Akutafdelingerne

Vi vil spørge, om du vil deltage i et videnskabeligt projekt?

Projektet handler om at blive bedre til at diagnosticere akutte infektioner på Akutafdelingen, så en målrettet behandling kan igangsættes så hurtigt som muligt.

Før du beslutter, om du vil deltage i projektet, skal du fuldt ud forstå, hvad projektet går ud på, og hvorfor vi gennemfører det. Vi vil derfor bede dig om at læse denne deltagerinformation grundigt.

Hvis du beslutter dig for at deltage, vil vi bede dig om at underskrive en samtykkeerklæring. Husk, at du har ret til at rådføre dig hos familie, venner eller bekendte. Du har også ret til betænkningstid før du underskriver, men da der er tale om en akut infektion, som kræver hurtig behandling, beder vi om, at du beslutter dig inden for 30 minutter.

Det er frivilligt at deltage i projektet. Du kan når som helst og uden at give en grund trække dit samtykke tilbage. Hvis du trækker dit samtykke om deltagelse i projektet tilbage, vil det ikke få konsekvenser for din videre behandling.

Projektets mål

De redskaber og undersøgelser, der eksisterer i dag til at finde ud af, hvilken type infektion, der er skyld i indlæggelsen på Akutmodtagelsen, har mange begrænsninger. Det udfordrer lægen i at stille en sikker diagnose inden for kort tid og igangsætte en målrettet behandling. Det kan få konsekvenser for den enkelte persons indlæggelsesforløb Hvis man behandler med antibiotika som dækker flere bakterier end nødvendigt vil det også bidrage til udviklingen af bakterier, som er modstandsdygtige over for mange antibiotika.

Projektet har derfor til formål at finde bedre redskaber, som kan hjælpe lægen til at stille en sikker diagnose inden for få timer for personer, indlagt akut med mistanke om infektion.

Det undersøger projektet

Projektet vil undersøge

- hvilke symptomer, tegn og forhold, der kendetegner de forskellige typer af infektioner og sygdomsgraden
- hvilke markører for infektion i blodet, der bedst kan angive typen af infektion og sygdomsgraden
- om en ny metode til at måle bakterier i urinen er nyttig

Plan for projektet

Projektet foregår på Fælles Akutmodtagelsen i Aabenraa, Sygehus Sønderjylland, på Akutafdelingen i Kolding, Sygehus Lillebælt, og på Fælle Akut Modtagelsen i Odense, Odense Universitetshospital. Fra februar 2021 til vinteren 2021/22 vil 1000 voksne personer, som indlægges akut med mistanke om infektion på de tre akutafdelinger, blive inviteret til at deltage.

Personalet vil i forbindelse med din indlæggelse opsøge og informere dig om projektet, og tilbyde deltagelse i projektet. Da det er vigtigt at en akut infektion bliver behandlet hurtigt, vil vi bede dig om at tilkendegive din beslutning inden for en halv time.

Det indebærer deltagelse i projektet for dig

Deltagelse i projektet betyder, at du vil modtage den normale behandling, afdelingen tilbyder, og derudover få foretaget ekstra undersøgelser.

Vi vil stille dig nogle spørgsmål omkring dine symptomer, tidligere og aktuelle sygdomme, og hvordan du har det. Vi beder i den forbindelse adgang til din patientjournal, for at følge op på eventuelle tidligere indlæggelser, den aktuelle indlæggelse, og eventuelle indlæggelser inden for den næste måned efter du er udskrevet.

Vi vil tage 14mL ekstra blod svarende til 2 ekstra rør, når du alligevel får taget blodprøve, og hjælpe dig med at aflevere en urinprøve.

Det blod og urin, der indhentes til projektet, vil blive destrueret, når projektet er afsluttet.

Dit samtykke vil give den forsøgsansvarlige, sponsor og denne repræsentant direkte adgang til relevante helbredsoplysninger i journalen for at kunne gennemføre, overvåge og kontrollere projektet. I projektet vil behandlingen af personoplysninger følge databeskyttelsesloven og databeskyttelsesforordningen. Efter indsamling af de ønskede informationer vil dine persondata blive fjernet fra vores registreringssystem, og dit personnummer vil blive erstattet af en kode (pseudo-anonymisering).

Bivirkninger, risici, komplikationer og ulemper

Der er ingen eller kun få kendte risici eller bivirkninger ved at deltage i projektet. Alle prøvetagningsmetoder er velkendte og almindeligt anvendte procedurer, som vi har stor erfaring med og kendskab til. Der kan dog være risici ved undersøgelserne, som vi endnu ikke kender. Vi beder dig derfor om at fortælle, hvis du oplever problemer i forbindelse med prøvetagning og undersøgelser. Hvis vi opdager bivirkninger, som vi ikke allerede har fortalt dig om, vil du naturligvis blive orienteret med det samme, og du vil skulle tage stilling til, om du ønsker at fortsætte med prøvetagning og undersøgelser.

De ekstra blodprøver til projektet tages i forbindelse med de blodprøver, der alligevel tages ved indlæggelse. Risici og bivirkninger ved at få taget en blodprøver kan være ubehageligt, lette smerter og/eller blå mærker, og i nogle tilfælde besvimelse. I sjældne tilfælde kan der opstå en mindre blodansamling eller betændelse ved indstiksstedet.

Urinprøven kan som regel afleveres i et bæger, opsamlet ved toiletbesøg. Er du kateterbærer eller på grund af sygdom ikke selv kan lade vandet, kan det blive nødvendigt at hjælpe vandladningen på vej med et kateter, som er et tyndt plastikrør til indførsel i blæren via urinrøret. Denne procedure kan give let ubehag og eventuelt kortvarig mindre blødning fra slimhinderne.

Dine prøvesvar

Ønsker du svar på de almindelige blod- og urinundersøgeler, kan du se det på www.sundhed.dk. Svar på de ekstra blod- og urinundersøgelser i projektet vil ikke fremkomme her, da vi ikke kender betydningen af resultaterne endnu. Har svarene et alarmerende resultat, vil den behandlende læge få besked og vil vurdere, om det har betydning for din behandling.

Nytte ved projektet

Projektet er vigtigt for at vi fremadrettet kan gøre indlæggelsesforløbet for personer, der indlægges akut med mistanke om infektion, bedre. Projektet vil have en afgørende betydning for praksis på akutafdelingerne, og formentligt hvilken type antibiotika lægen ordinerer. Et mere målrettet antibiotikaforbrug vil bidrage til reduktion af bakterier, der er modstandsdygtige over for antibiotika, og dermed sikre at infektioner i fremtiden også kan behandles med antibiotika.

For dig personligt, vil deltagelse ikke have en betydning for dit behandlingsforløb, da resultaterne af undersøgelserne først vil blive evalueret når projektet er afsluttet på akutafdelingen.

Udelukkelse fra undersøgelse

Du vil udgå af dele af projektet, hvis nogle af undersøgelserne mislykkes af fx tekniske grunde

Adgang til projektets resultater

Projektets samlede resultater vil blive offentliggjort 2024 i videnskabelige tidsskrifter samt på sygehusenes hjemmesider. Resultater med relevans for beslutningstagere i sundhedsvæsenet vil blive offentliggjort i danske medier og tidsskrifter. Det sikres, at ingen deltagere kan genkendes i det, som offentliggøres. Har du interesse i at vide mere om projektets resultater, kan du efter offentliggørelse opsøge dem via http://www.sygehussonderjylland.dk/wm521282.

Vi håber, at du med denne information har fået tilstrækkeligt indblik i, hvad det vil sige at deltage i projektet, og at du føler dig rustet til at tage beslutningen om din eventuelle deltagelse. Hvis du vil vide mere, er du meget velkommen til at kontakte os. Information om dine rettigheder er vedlagt denne deltagerinformation sidst i dokumentet (Bilag 1).

Hvis du beslutter dig for at deltage i projektet, vil vi bede dig om at underskrive samtykkeerklæringen. Du kan vælge om du vil give samtykke til hele projektet eller kun dele af projektet. Det er frivilligt at deltage i projektet, og du kan når som helst og uden at give en grund trække dit samtykke tilbage. Det vil ikke få konsekvenser for den videre behandling.

Yderligere oplysninger kan fås ved henvendelse til

Professor og overlæge Christian Backer Mogensen
Fælles Akutmodtagelsen, Sygehus Sønderjylland
Kresten Philipsens Vej 15 - 6200 Aabenraa
Christian.Backer.Mogensen@rsyd.dk
Tlf: 79971123

Initiativtagere til projektet

Projektet er primært udarbejdet i samarbejde mellem Akutafdeling, Biokemisk Afdeling og Mikrobiologisk Afdeling, og Radiologisk Afdeling på Sygehus Sønderjylland, Sygehus Lillebælt og Odense Universitets Hospital. Projektet er forankret på Sygehus Sønderjylland og Institut for Regional Sundhedsforskning på Syddansk Universitet, som er ansøgnings- og bevillingsansvarlige.

Økonomisk støtte til projektet

Projektet har fået økonomisk støttet i form af ph.d. stipendiater fra Syddansk Universitet (1.650.000kr), ph.d.-stipendiater fra Sygehus Sønderjylland (4.800.000kr) samt støtte til drift fra Region Syddanmark (500.000kr). Forsøgsansvarlige har ingen økonomisk tilknytning til støttegivere eller andre interessenter i forsøget. Der vil ikke være en økonomisk kompensation til patienter, der deltager i projektet.

Bilag 1: Forsøgspersoners rettigheder i et sundhedsvidenskabeligt forskningsprojekt

Som deltager i et sundhedsvidenskabeligt forskningsprojekt skal du vide, at:

- din deltagelse i forskningsprojektet er helt frivillig og kun kan ske efter, at du har fået både skriftlig og mundtlig information om forskningsprojektet og underskrevet samtykkeerklæringen.
- du til enhver tid mundtligt, skriftligt eller ved anden klar tilkendegivelse kan trække dit samtykke til deltagelse tilbage og udtræde af forskningsprojektet. Såfremt du trækker dit samtykke tilbage påvirker dette ikke din ret til nuværende eller fremtidig behandling eller andre rettigheder, som du måtte have.
- du har ret til at tage et familiemedlem, en ven eller en bekendt med til informationssamtalen.
- du har ret til betænkningstid, før du underskriver samtykkeerklæringen.
- oplysninger om dine helbredsforhold, øvrige rent private forhold og andre fortrolige oplysninger om dig, som fremkommer i forbindelse med forskningsprojektet, er omfattet af tavshedspligt. behandling af oplysninger om dig, herunder oplysninger i dine blodprøver og væv, sker efter reglerne i databeskyttelsesforordningen, databeskyttelsesloven samt sundhedsloven. Den dataansvarlige i forsøget skal orientere dig nærmere om dine rettigheder efter databeskyttelsesreglerne.
- der er mulighed for at få aktindsigt i forsøgsprotokoller efter offentlighedslovens bestemmelser. Det vil sige, at du kan få adgang til at se alle papirer vedrørende forsøgets tilrettelæggelse, bortset fra de dele, som indeholder forretningshemmeligheder eller fortrolige oplysninger om andre.
- der er mulighed for at klage og få erstatning efter reglerne i lov om klage- og erstatningsadgang inden for sundhedsvæsenet. Hvis der under forsøget skulle opstå en skade kan du henvende dig til Patienterstatningen, se nærmere på www.patienterstatningen.dk.

Dette tillæg er udarbejdet af det Videnskabsetiske komitésystem og kan vedhæftes den skriftlige information om det sundhedsvidenskabelige forskningsprojekt. Spørgsmål til et konkret projekt skal rettes til projektets forsøgsansvarlige. Generelle spørgsmål til forsøgspersoners rettigheder kan rettes til den komité, som har godkendt projektet.

Revideret 21. september 2019

Written consent form – track A, B, and C

Informeret samtykke til at deltage i et sundhedsvidenskabeligt projekt

Forbedret diagnostik af akutte infektioner

- Infectious Diseases in Emergency Departments (INDEED study)

Erklæring fra forsøgspersonen:
Jeg har fået skriftlig og mundtlig information, og jeg ved nok om formål, metode, fordele og ulemper til at sige ja til at deltage.

Jeg ved, at det er frivilligt at deltage, og jeg altid kan trække mit samtykke tilbage uden at miste mine nuværende eller fremtidige rettigheder til behandling.

Jeg giver hermed samtykke til at deltage i projektet og har fået en kopi af dette samtykkeark samt en kopi af den skriftlige information om projektet til eget brug.

Forsøgspersonens navn: _____

Forsøgspersonens Cpr-nummer: _____

Dato: _____ Underskrift: _____

Hvis der kommer nye væsentlige helbredsoplysninger frem om dig i forskningsprojektet vil du blive informeret. Vil du **frabede** dig information om nye væsentlige helbredsoplysninger, som kommer frem i forskningsprojektet, bedes du markere her: _____ (sæt x)

Erklæring fra den, der afgiver information:

Jeg erklærer, at forsøgspersonen har modtaget mundtlig og skriftlig information om forsøget.

Efter min overbevisning er der givet tilstrækkelig information til, at der kan træffes beslutning om deltagelse i forsøget.

Navnet på den, der har afgivet information:

Dato: _____ Underskrift:_____

Appendix II - Biological specimens

In this study, blood will be collected for analysis of serum procalcitonin (PCT) and Serum soluble urokinase plasminogen activator receptor (suPAR) and for a research biobank to store blood until analysis is feasible.

	Blood for analysis of PCT and suPAR	**Blood for research biobank**
Collection	The blood will be collected in an EDTA plasma tube.	Biobank blood is only collected for patient in track A and includes one tube of EDTA plasma and one tube of LiHeparin plasma.
Storage	At two of the sites, the analysis will be performed within is tested within two hours from the collection of the blood sample. At the third site, samples will be stored locally in a -80 °C freezer. The samples are pseudonymized with a code to protect the identity of the participants. All samples and code lists are stored safely and separately to prevent unauthorized access.	All samples will be stored locally in a -80 °C freezer. The samples are pseudonymized with a code to protect the identity of the participants. All samples and code lists are stored safely and separately to prevent unauthorized access.
Sample analysis	*Serum procalcitonin (PCT)* Serum PCT concentration is quantified with an automated sandwich immunoassay "ECLIA" (Elecsys®, BRAHMS PCT-analyses) on Cobas e801. Calibration is performed after Cobas e pack has been registered in the instrument and is standardized to the BRAHMS PCT LIA assay. The correlation of Elecsys BRAHMS PCT analyses has been compared to BRAHMS PCT LIA and to BRAHMS PCT sensitive KRYPTOR with similar results of r=0.981 and r=0.988 respectively. Quality control is performed after each calibration and regularly following the standard procedure. The manufacture states a lower limit of detection 0.02 µg/L up to 100 µg/L. The functional assay sensitivity is identified at ≤ 0.06 ng/mL. In this study a range from 0.06 µg/L to 100 µg/L will be measured. Normal healthy individuals have a PCT concentration < 0.1 µg/L. All plasma samples are screened for potential interfering substances like bilirubin, hemoglobin and lipids and no	Molecular analysis for future use in ancillary studies will take place after all samples have been collected.

	results will be included with significant interference. There is no hook-effect in PCT concentrations measured up to 1000 µg/L. The precision of PCT assay is expected to be <3% CV or similar. This is estimated from the internal quality controls using PC PCT1 (lot.419495) and PC PCT2 (lot.419497) at target PCT levels 0.49 and 9.44 ng/L showing a precision of 2.67 % CV and 2.63 % CV, respectively.	
	Serum soluble urokinase plasminogen activator receptor (suPAR) Serum suPAR is measured using suPARnostic© Tubilatex assay reagents (validated on Cobas© c111) protocol for Cobas© c702 and c502 applying the Multi-Pack cassettes (Roche Diagnostics, Mannheim, Germany) (42). Calibration is performed at least once a month or in connection to a new batch of TurbiLatex reagents, after calibration a quality control is performed. Measure range of the suPARnostic© Tubilatex assay is 1.8 µg/L to 16.0 µg/L on Cobas© c502 analyzer. The assay's limit of blank, limit of detection and limit of quantification are 1.0 µg/L, 1.2 µg/L and 1.2 µg/L respectively. Expected values for patients attending ED's range from 3-6 µg/L and can reach double digits in patients with severe disease related to poor prognosis. High concentration of SuPAR above 20 µg/L may be false positive results related with interference used by high concentration of hemoglobin, lipids or bilirubin. There is no identified interference in concentrations of bilirubin >350 µmol/L, triglycerides > 3.3g/L, hemoglobin > 1.4 g/L or rheumatoid factor > 440 IU/mL. The highest concentration of suPAR is tested at 47.5 µg/L without hook-effect and the linearity is from 1.8 µg/L to 26.6 µg/L. The mean value of precision of the test is 3.4 µg/L, 7.1 µg/L, 10.2 µg/L for low, middle and high concentrations of SuPAR respectively. The accuracy of suPARnostic© Tubilatex is compared with suPARnostic© ELISA with similar results < 15 % of difference. The precision of suPAR assay is expected to be < 5% CV or similar. This is estimated from external quality assessment material, HK 19 (Product code 2226 DK, Lot. No.	

	201808) analyzed repeatedly during five different days on c502 and c702 and the mean content of suPAR determined by turbidimetry was 2.15 mg/ L and 2.03 mg/L (CV% 4.56 and 5.52) for the Cobas c502 and c702 instruments, respectively.	
Evaluation	The results will be saved in a study database and not be visible for the physician in the medical journal.	The results will be saved in a study database. The expiry date of the research biobank is expected to be October 2022. After expiry date, the remaining material in the research bank will be destroyed.
Location	Samples will be located at Bloodsamples, Biochemistry and Immunology, University Hospital of Southern Denmark, Aabenraa, Denmark	Samples will be located at: - Bloodsamples, Biochemistry and Immunology, University Hospital of Southern Denmark, Aabenraa, Denmark - Biochemistry and Immunology, University Hospital of Southern Denmark, Kolding, Denmark - Clinical Biochemistry and Pharmacology, Odense University Hospital, Odense, Denmark

Appendix III - Schedule of enrollment, interventions and assessments

	STUDY PERIOD										
	RECRUITMENT	ALLOCATION	POST-ALLOCATION							CLOSE-OUT	
TIMEPOINT (h=hours, d=days)	**-½h**	**0h**	<1h	<4h	<24h	<48h	<5d	<7d	<14d	30d	90d
ENROLMENT											
Eligibility screeen	x										
Informed consent	x										
Physician assessment	x										
Allocation		x									
INTERVENTIONS – all tracks											
Collection of blood sample			x								
• PCT analysis									x		
• suPAR analysis									x		
Collection of urine sample				x							

• POC-UFC analysis				x							
INTERVENTIONS – track A											
Collection of sputum sample			x								
• POC-PCR analysis and presented to the treating physician				x							
POC-US					x						
ULDCT and HRCT					x						
INTERVENTIONS – track B											
CEUS					x						
POC-US					x						
MRI					x						
ASSESSMENTS											
Collection of patient characteristic (patient interview and look up in medical record)				x							
CRP results				x							
Dipstick result				x							
Urine routine culturing result								x			

Sputum routine culturing and PCR result								x			
Antibiotic prescription				x		x	x				
Expert panel reference standard								x			
Length of stay											x
Mortality											x
Admission to ICU and readmission											x

Appendix IV - Targets in POC-PCR

The BIOFIRE® FILMARRAY® Pneumonia plus Panel is testing for 27 of the most common pathogens involved in Lower respiratory tract infections and 7 genetic markers of antibiotic resistance.

Bacteria (semi quantitative)	Antibiotic Resistance Genes
Acinetobacter calcoaceticus-baumannii complex *Enterobacter cloacae* *Escherichia coli* *Haemophilus influenzae* *Klebsiella aerogenes* *Klebsiella oxytoca* *Klebsiella pneumoniae group* *Moraxella catarrhalis* *Proteus spp.* *Pseudomonas aeruginosa* *Serratia marcescens* *Staphylococcus aureus* *Streptococcus agalactiae* *Streptococcus pneumoniae* *Streptococcus pyogenes*	**ESBL** CTX-M **Carbapenemases** KPC NDM Oxa48-like VIM IMP **Methicilin Resistance** mecA/mecC and MREJ

Atypical Bacteria (Qualitative)	Viruses
Legionella pneumophila *Mycoplasma pneumoniae* *Chlamydia pneumoniae*	Influenza A Influenza B Adenovirus Coronavirus Parainfluenza virus Respiratory Syncytial virus Human Rhinovirus/Enterovirus Human Metapneumovirus Middle East Respiratory Syndrome Coronavirus (MERS-CoV)

Appendix V – recommended action list

Guidance of results from POC-PCR *FilmArray® Pneumonia Panel plus*

This guidance is developed to the INDEED-study (Infectious diseases in Emergency Department).

Emergency department physicians from Hospital Sønderjylland in Aabenraa, Hospital Lillebælt in Kolding, and Odense University Hospital in Odense, will receive this action card along with the results from sputum sample analyses.

In case of doubt in the interpretation of the results, the physician is encouraged to contact the local clinical microbiologist.

Agens	Association with CAP[#]	Remarks	Antibiotics	
			First choice	Penicillin allergy
*Streptococcus pneumoniae**	Frequent and likely pathogen	Part of the normal microbiota in upper respiratory tract. May be contamination with pharyngeal microbiota.	Benzylpenicillin 1.2g (2 mill.IE) x4 i.v. *or* Phenoxymethylpenicillin 0.6g (1 mill.IE) x4 oral	Cefuroxime 1.5g x 3 i.v. *or* Roxithromycin 300mg x1 oral
*Haemophilus influenza**	Frequent and likely pathogen		Ampicillin 2g x4 i.v. *or* Benzylpenicillin 1.2g (2 mill. IE) x4 i.v. *or* Piv-ampicillin 1g x3 oral *or* Amoxicillin 1g x3 oral	Cefuroxime 1.5g x 3 i.v. *or* Doxycycline 100mg x2 first 24 hours oral followed by 100mg x1 oral
*Streptococcus pyogenes**	Probable, but rare phatogen	Part of the normal microbiota in upper respiratory tract. These pathogens relatively often represent contamination with pharyngeal microbiota. Infection caused by *Streptococcus pyogenes* or *Staphylococcus aureus* will usually results in severe pneumonia.	Benzylpenicillin 1.2g (2 mill. IE) x4 i.v.	Cefuroxime 1.5g x3 i.v.
*Streptococcus agalactiae**	Rare phatogen in adults		Benzylpenicillin 1.2g (2 mill. IE) x4 i.v.	Cefuroxime 1.5g x3 i.v.
*Staphylococcus aureus**	Probable, but rare phatogen		Cloxacillin 1g x4 i.v.	Cefuroxime 1.5g x3 i.v.
*Moraxella catarrhalis**	Probrable phatogen		Piperacillin-tazobactam 4/0.5g x3 i.v. *or* amoxicillin-clavulanic acid 500/125mg x3 oral	Cefuroxime 1.5g x3 i.v. *or* Roxithromycin 300mg x1 oral *or* Azithromycin 500mg x1 oral
Legionella pneumophila *Mycoplasma pneumonia*	Likely causative phatogen	Is not a part of the normal respiratory microbiota.	Azithromycin 500mg x1 i.v./oral	
Chlamydia pneumoniae	Probrable causative phatogen	Is not a part of the normal respiratory microbiota Will usually cause mild infections. In case of severe infection, other pathogens / superinfection should be considered.	Azithromycin 500mg x1 i.v./oral	

Agens	Association with CAP[#]	Remarks	Antibiotics
*Pseudomonas aeruginosa** *Acinetobacter calcoaceticus-baumannii complex** *Enterobacter cloacae** *Escherichia coli** *Klebsiella (Enterobacter) aerogenes** *Klebsiella oxytoca** *Klebsiella pneumoniae group** *Proteus spp.** *Serratia marcescens**	Very rare causative phatogens	These findings usually represents colonization.	These findings should typically not lead to adjustment of empirical antimicrobial treatment.
Influenza A Influenza B	Frequent pathogens	Is not a part of the normal respiratory microbiota Bacterial superinfection can occur.	Consider whether the patient's pneumonia symptoms can be explained by viral infection, and whether antibiotic treatment is necessary / indicated.
Parainfluenza virus Respiratory Syncytial Adenovirus Coronavirus *(does not include SARS-CoV-2)* Human Rhinovirus/Enterovirus Human Metapneumovirus	Probrable pathogens	Usually causes mild infections. In case of severe infection, other pathogens / superinfection should be considered. May be an accidental finding due to previous /recent / asymptomatic infection.	
Not detected *(POC-PCR(FilmArray) is negative)*	A negative result does not rule out pneumonia, but means that CAP caused by the most common pathogens is less likely. Consider whether the pneumonia diagnosis is correct and consider investigation for rare causes of pneumonia (e.g. tubeculosis or *Chlamydia psittaci*).		

#CAP: Community-Acquired Pneumonia

*: Concentration (copies/mL) is reported in the POC-PCR (FilmArray) result

Most bacterial causative pathogens of CAP are also part of the normal respiratory microbiota or may colonize the upper respiratory tract, and the clinical relevance of these findings must always be assessed carefully.

For the bacterial agents marked with "*", a concentration (copies/mL) is reported in the POC-PCR (FilmArray) result. There is a reasonable correlation between copies/mL and the culture-based measure "CFU/mL", however, "copies/mL" is typically a factor of 10-100 higher than the corresponding "CFU/mL".

The limits of significance are not well established and depend probably on the agent, the quality of the sample and the clinical context - and must therefore be used with caution. The Infectious Diseases Society of America and the American Society of Microbiology[1] propose the following culture-based limits for hospital-acquired pneumonia:

Culture-based measure	POC-PCR (FilmArray) concentration	Interpretation (caution)
$< 10^4$ CFU/mL	≈ $< 10^5$ copies/mL	Indicates mixture with normal flora
$10^4 – 10^5$ CFU/mL	≈ 10^5-10^6 copies/mL	Gray zone
$> 10^5$ CFU/mL	≈ $>10^6$ copies/mL	Indicates real findings

Developed by microbiologist Flemming Rosenvinge, Department of Clinical Microbiology, Odense University Hospital in Odense, and microbiologist Claus Østergaard, Department of Clinical Microbiology, Hospital Lillebælt in Kolding, Denmark

Version 1.1 – February 7th 2021

[1] *Miller, J. M., Binnicker, M. J., Campbell, S., et al. A Guide to Utilization of the Microbiology Laboratory for Diagnosis of Infectious Diseases: 2018 Update by the Infectious Diseases Society of America and the American Society for Microbiology. Clinical Infectious Diseases, 67(6), e1–e94. https://doi.org/10.1093/cid/ciy381*

Appendix VI - Template for expert panel reference standard

The template for the expert panel reference standard is illustrated in the table:

<table>
<tr><th>Main question</th><th>Sub-question</th></tr>
<tr><td rowspan="2">Does the patient has an infection?
❑ Yes ❑ No</td><td>If yes, what was the focus of infection?
❑ Respiratory ❑ Urinary tract ❑ Other</td></tr>
<tr><td>If yes, was the focus of infection identified within 48 hours?
❑ Yes ❑ No</td></tr>
<tr><td colspan="2">If focus is respiratory infection</td></tr>
<tr><td colspan="2">What type of respiratory infection was the patient primarily hospitalized with?
❑ Covid-19 pneumonia
❑ CAP
❑ COPD – exacerbation
❑ Aspiration pneumonia
❑ Other – please specify (by using a list of ICD-10 diagnosis): _____</td></tr>
<tr><td colspan="2">If focus is urinary tract infection (UTI)</td></tr>
<tr><td>What type of UTI was the patient primarily hospitalized with?
❑ UTI without systemic effects (cystitis)
❑ UTI with systemic effects (pyelonephritis/urosepsis)</td><td>If UTI with systemic effects, please specify
❑ Pyolonephritis (local symptoms + fever + increased CRP)
❑ Urosepsis (UTI + 2 qSOFA or relevant bacteremia)
❑ Cannot be further specified
❑ Other – please specify (by using a list of ICD-10 diagnosis): _____</td></tr>
<tr><td colspan="2">If focus of infection is other than respiratory and urinary tract infection</td></tr>
<tr><td colspan="2">What type of infection was the patient primarily hospitalized with?
❑ Unknown focus ❑ Soft tissue abscess
❑ Erysipelas ❑ Cholecystitis
❑ Tonsillitis ❑ Diverticulitis
❑ Gastroenteritis ❑ Pancreatitis
❑ Endocarditis ❑ Appendicitis
❑ Meningitis
❑ Other – please specify (by using a list of ICD-10 diagnosis): _____</td></tr>
</table>

Appendix VII - Algorithm for antibiotic treatment

The algorithm specify if the antibiotic treatment is targeted or non-targeted. Targeted treatment is defined as narrow spectrum antibiotics directed against CAP, antibiotics directed against a detected respiratory pathogen or no antibiotics (e.g. in the absence of a bacterial pathogen and/or presence of a viral pathogen. Non-targeted treatment is defined as broad spectrum antibiotics not directed against a specific pathogen or antibiotics not directed against CAP.

Narrow spectrum antibiotics (NS) is defined in table 1. Targeted treatment (TT) for the different types of agens is defined in table 2. Treatment with other antibiotics (not listed as NS or TT in table 1 and 2) is classified non-targeted treatment (NT).

Table 1 Narrow spectrum antibiotis

Antibiotic treatment – narrow spectrum	
No penicillin allergy	Penicillin allergy
Benzylpenicillin Phenoxymethylpenicillin	Benzylpenicillin Phenoxymethylpenicillin Clindamycin Macrolide Cefuroxime

Table 2 Targeted treatment

	Antibiotic treatment - targeted	
Agens	No penicillin allergy	Penicillin allergy
Streptococcus pneumonia, pyogenes, or agalactiae	Benzylpenicillin Phenoxymethylpenicillin	Benzylpenicillin Phenoxymethylpenicillin Clindamycin Macrolide Cefuroxime
H. influenzae	Benzylpenicillin Ampicillin Piv-ampicillin Amoxicillin Amoxicillin-clavulanate Piperacillin/Tazobactam Cefuroxime Doxycycline Ciprofloxacin	Benzylpenicillin Ampicillin Piv-ampicillin Amoxicillin Amoxicillin-clavulanate Piperacillin/Tazobactam Cefuroxime Doxycycline Ciprofloxacin
Moraxella catarrhalis	Amoxicillin-clavulanate Piperacillin/Tazobactam Cefuroxime or Macrolide	Amoxicillin-clavulanate Piperacillin/ Tazobactam Cefuroxime Macrolide
Staphylococcus aureus	Cloxacillin	Benzylpenicillin

	Dicloxacillin	Phenoxymethyl-penicillin Macrolid Cefuroxime Cloxacillin Dicloxacillin Clindamycin Macrolide Cefuroxime
Legionella pneumophila	Macrolide Ciprofloxacin Moxifloxacin Doxycycline Tetracycline	Macrolide Ciprofloxacin Moxifloxacin Doxycycline Tetracycline
Mycoplasma pneumoniae or Chlamydia pneumoniae	Macrolide Moxifloxacin Doxycycline Tetracycline	Macrolide Moxifloxacin Doxycycline Tetracycline

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

Completed SPIRIT checklist

Section/item	ItemNo	Description	Page in protocol
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	3
Protocol version	3	Date and version identifier	17
Funding	4	Sources and types of financial, material, and other support	17
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	17
	5b	Name and contact information for the trial sponsor	3+18
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	18
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	18
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	6-7
	6b	Explanation for choice of comparators	6-7
Objectives	7	Specific objectives or hypotheses	7-8

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	8
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8-9
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9-11
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	15
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	12
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7-8
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	12-15
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	9+appendix III
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	12-15
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	12
Methods: Assignment of interventions (for controlled trials)			
Allocation:			

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	10
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	10
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	10
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	10
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	-
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	12-15
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	-
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	12-15
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	12-15
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	12-15
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	12-15

Methods: Monitoring

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	11-12
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	15
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	12
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	12

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	15-16
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	16
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	9
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	-
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	15-16
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	17
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	16
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	-

Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	16
	31b	Authorship eligibility guidelines and any intended use of professional writers	16
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	16
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Appendix I
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Appendix II

BMJ Open

Improved diagnostics of infectious diseases in Emergency Departments – a protocol of a multifaceted multicenter diagnostic study

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Improved diagnostics of infectious diseases in Emergency Departments

– a protocol of a multifaceted multicenter diagnostic study

Short title: Improved diagnostics of infectious diseases

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Abstract

Background: The major obstacle in prescribing an appropriate and targeted antibiotic treatment is insufficient knowledge concerning *whether* the patient has a bacterial infection, *where* the focus of infection is and *which* bacteria are the agents of the infection. A prerequisite for the appropriate use of antibiotics is timely access to accurate diagnostics such as point-of-care (POC) testing.

The study aims to evaluate diagnostic tools and working methods that support a prompt and accurate diagnosis of hospitalized patients suspected of an acute infection. We will focus on the most common acute infections; community-acquired pneumonia (CAP) and acute pyelonephritis (APN). The objectives are to investigate 1) patient characteristics and treatment trajectory of the different acute infections, 2) diagnostic and prognostic accuracy of infection markers, 3) diagnostic accuracy of POC urine flow cytometry on diagnosing and excluding bacteriuria, 4) how effective the addition of POC analysis of sputum to the diagnostic set-up for CAP is on antibiotic prescriptions, 5) diagnostic accuracy of POC ultrasound and ultralow dose (ULD) Computed Tomography (CT) on diagnosing CAP, 6) diagnostic accuracy of specialist ultrasound on diagnosing APN, 7) diagnostic accuracy of POC ultrasound in diagnosing hydronephrosis in patients suspected of APN.

Methods and analysis: It is a multifaceted multicenter diagnostic study, including 1000 adults admitted with suspicion of an acute infection. Participants will within the first 24 hours of admission undergo additional diagnostic tests including infection markers, POC urine flow cytometry, POC analysis of sputum, POC and specialist ultrasound, and ultralow dose CT. The primary reference standard is an assigned diagnosis determined by a panel of experts.

Ethics, dissemination and registration: Approved by Regional Committees on Health Research Ethics for Southern Denmark, Danish Data Protection Agency, and clinicaltrials.gov. Results will be presented in peer-reviewed journals, and positive, negative and inconclusive results will be published.

Key words: Acute Infection, antibiotics, diagnostic, pneumonia, pyelonephritis, sputum, point-of-care-test, ultrasound, infection marker, Ultralow dose Computed Tomography

Strengths and limitations of the study:

- It is a pragmatic study that reflects reality and has potential for substantial clinical significance
- The study combines diagnostics and knowledge from five different medical specialties
- The study is complex and contains a number of sub-studies which share the same population
- The study is only generalizable to settings with a similar technological context and trained staff
- COVID-19 and the consequent societal lockdown might affect patient distribution

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World Health Organization Trial Registration Data Set

Primary Registry and Trial Identifying Number: ClinicalTrials.gov: NCT: 04661085, 04681963, 04667195, 04652167, 04686318, 04686292, 04651712, 04645030, and 04651244.

Date of Registration in Primary Registry: December 2020

Secondary Identifying Numbers: Regional Committees on Health Research Ethics for Southern Denmark (S-20200188), and Danish Data Protection Agency (20/60508)

Source(s) of Monetary or Material Support: University Hospital of Southern Denmark and University of Southern Denmark, Aabenraa, Denmark

Primary Sponsor: Professor Christian Backer Mogensen, University Hospital of Southern Denmark and University of Southern Denmark, Aabenraa, Denmark

Secondary Sponsor(s): Associate professor Helene Skjøt-Arkil, University Hospital of Southern Denmark and University of Southern Denmark, Aabenraa, Denmark

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Public Title: Improved diagnostics of acute infectious diseases

Scientific Title: Improved diagnostics of infectious diseases in Emergency Departments

Countries of Recruitment: Denmark

Health Condition(s) or Problem(s) Studied: Infectious diseases including community-acquired pneumonia and acute pyelonphritis

Intervention(s):
Sub-study 2: Index test: infection markers (serum procalcitonin, and soluble urokinase plasminogen activator receptor
Sub-study 3: Index test: point-of-care urinary flow cytometry
Sub-study 4: Intervention: Point-of-care tool providing rapid microbiological results on sputum samples based on polymerase chain reaction. Control: routine microbiology analysis
Sub-study 5: Index test: Ultralow dose computed tomography scans / ultrasound scanning
Sub-study 6: Index test: Contrast enhanced ultrasound
Sub-study 7: Index test: Ultrasound scanning

Key Inclusion and Exclusion Criteria: Adults admitted to the Emergency Department are invited if receiving physician suspects the patient has an infection. Patients are excluded if participating will delay a life-saving treatment, if they have been admitted within 14 days, if pregnant, or if having severe immunodeficiency.

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Study Type: It is a multifaceted multicenter study, primarily diagnostic accuracy set of studies but a randomised controlled trial of sputum diagnostics embedded within it. It has been divided into seven-substudies.
Sub-study 1: Observational, descriptive study
Sub-study 2, 3, 5, 6, 7: Observational, diagnostic accuracy studies
Sub-study 4: Eksperimental, randomized controlled trial - parallel assigned, allocated 1:1 according to a computer-generated randomization schedule.

Date of First Enrollment: February 1st 2021

Sample Size
Sample Size consists of: 200 patients diagnosed with CAP and 150 patients with APN
Number of participants that the trial plans to enrol in total: 1000
Number of participants that the trial has enrolled: 460

Recruitment Status: Recruiting: participants are currently being recruited and enrolled

Primary Outcome(s):
Outcome sub-study 1: Diagnosis of community acquired pneumonia and acute pyelonephritis
Method of measurement: Expert panel consisting of emergency and infectious disease specialists (reference standard)
Timepoint: within seven days after admission

Outcome sub-study 2: Diagnosis of community acquired pneumonia and acute pyelonephritis
Method of measurement: Expert panel consisting of emergency and infectious disease specialists (reference standard)
Timepoint: within seven days after admission

Outcome sub-study 3: bacteriuria
Method of measurement: urine culturing specialists (reference standard)
Timepoint: Time of admission

Outcome sub-study: Type of prescribed antibiotic
Method of measurement: Medical record audit
Timepoint: 4 hours

Outcome sub-study 5: Diagnosis of community acquired pneumonia
Method of measurement: high-resolution computed tomography specialists (reference standard)
Timepoint: within 24 hours of admission

Outcome sub-study 6: Diagnosis of acute pyelonephritis
Method of measurement: magnetic resonance imaging specialists (reference standard)
Timepoint: within 24 hours of admission

Outcome sub-study 7: Diagnosis of acute pyelonephritis
Method of measurement: magnetic resonance imaging specialists (reference standard)
Timepoint: within 24 hours of admission

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Key Secondary Outcomes: Length of stay (medical record audit), Mortality (medical record audit and Danish National Patient Register, 30 days, 90 days, and inhospital mortality), Readmission to hospital within 30 days from day of discharge (medical record audit), Admission to intensive care (medical record audit), Antibiotic treatment at 48 hours of admission (medical record audit).

Ethics Review: The study was approved by the Regional Committees on Health Research Ethics for Southern Denmark (S-20200188) on January 7th 2021. Contact: Komite@rsyd.dk

Completion date: The last patient is expected to be included in February 2022. The final data is expected to be collected in June 2022.

IPD sharing statement: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request

Introduction

Antibiotic resistance

Multi-resistant bacteria is one of the major threats to the public health(1). The incidence of multi-resistant bacteria is increasing in Denmark(2) and every 20th patient admitted to a Danish Emergency Department (ED) is colonized with multi-resistant bacteria(3). Denmark has focused on this challenge(4) by screening special patient groups for multi-resistant bacteria(5, 6), and by initiating campaigns to reduce antibiotic consumption - mainly the use of broad-spectrum antibiotics in hospitals(4, 7).

The Danish Ministry of Health has made extensive efforts targeting the use of antibiotics in hospitals. However, the major obstacle in reducing the prescription of broad-spectrum antibiotics is insufficient knowledge concerning *whether* the patient has a bacterial infection, *where* the focus of infection is and *which* bacteria are the agents of the infection(8). Uncertainty in the answers to these three questions often leads a clinician to choose a broad-spectrum antibiotic at the onset of treatment. Unfortunately, the prescription of a broad-spectrum antibiotic is rarely revised when laboratory results are available, often because the patient already has been discharged(9).

Acute infections and diagnostic tools

A prerequisite for appropriate use of antibiotics is timely access to accurate diagnostic tests, since treatment of acute infections should be initiated within a few hours to avoid serious complications such as bacteremia, sepsis, organ failure, septic shock and death(10). The most common conditions among ED patients with suspected infections are community acquired pneumonia (CAP) and acute pyelonephritis (APN)(11, 12). Diagnosing CAP and APN can be challenging as symptoms are often weak and nonspecific and the current methods for focal and etiological diagnosis have low sensitivity and specificity and often deliver results after the decision regarding antibiotic treatment has been made(9, 13, 14).

The Coronavirus Disease 2019 (COVID-19) pandemic has highlighted the need of accurate diagnostic tests. Quick and correct classification of pneumonia as COVID-19, another viral or bacterial pneumonia, or even COVID-19 complicated with bacterial pneumonia, is of vital importance to select the correct treatment (including antibiotics), and the correct infection control measures, including isolation.

In order to make the correct diagnosis and prescribe an appropriate and targeted treatment within a few hours of admission, it is important to the physician to be able to answer the following three questions: a) Is it an infection that requires antibiotic treatment (*infection marker*)? b) Where is the focus of infection (imaging *diagnosis*)? c) Which bacteria should the prescribed antibiotic target (*etiologic diagnosis*)?

Bacterial infection markers

To support the diagnosis of an infection and assess its severity, a measure of the systemic inflammatory response is useful e.g. abnormal temperature, elevated leucocyte count with neutrocytosis, or elevated C-reactive protein (CRP). Some uncertainty is associated with CRP because it has a delayed response to bacterial infection and often is elevated in non-infectious inflammatory conditions(15). A more sensitive and specific marker that can differentiate between bacterial and viral infection and reflect the severity of the infection is desired(16). Serum procalcitonin (PCT) has potential as a diagnostic tool in suspected bacterial infections(17) and can distinguish between viral and bacterial pneumonias(18). Soluble urokinase plasminogen activator receptor (suPAR) might have a potential as a marker for acute bacterial infections requiring antibiotic treatment(19). However, there are no well-conducted studies which compare simultaneously all three biomarkers diagnostic abilities for bacterial infections in general or in relation to CAP or APN (16, 20).

Imaging diagnostics

The CAP diagnosis is primarily based on clinical symptoms and findings, supplemented with chest X-ray, which has a low sensitivity and specificity (21). Identifying an improved imaging alternative with high diagnostic sensitivity and specificity and minimal risk to the patient is imperative. Computed Tomography scans (CT), e.g. high-resolution CT (HRCT) provides a detailed diagnosis of thoracic diseases, but the radiation dose is high and potentially harmful. Low-dose CT has shown promising diagnostic results, but the radiation dose is still potentially harmful (22). Ultralow dose CT (ULDCT) of the thorax could be an alternative, but has yet to be studied within an ED context. Another relevant imaging modality is ultrasound scanning (US). US of the lungs is useful to diagnose pulmonary edema and pleural effusion, but the value of US performed by a novice operator when diagnosing CAP in an ED setting needs further investigation(23).

Currently, no imaging methods are used to verify the diagnosis of APN. The diagnosis is primarily based on unspecific clinical findings (24), and is often not confirmed microbiologically (25). Complicating factors such as hydronephrosis and renal abscess can be visualized with conventional US (26). Contrast enhanced US (CEUS) seems to be a promising diagnostic imaging modality of acute renal inflammation (27, 28). The value and suitability in a clinical setting of this more advanced US investigation is unknown.

Etiological diagnostics

Sputum can be cultivated to determine the agent of CAP. However, results are often unspecific and not available until after discharge of the patient or completion of treatment(9). A point-of-care (POC) tool providing rapid microbiological results on e.g. sputum samples would therefore be useful. Systems are available today based on polymerase chain reaction (PCR) methods with results available within one hour for a variety of viral and bacterial pathogens (29). The impact of such fast diagnostic systems on antibiotic prescriptions has not been investigated in an ED context.

The diagnosis of APN is verified by significant bacteriuria in urine culture (25), but as many as half of the patients with clinical APN fails to meet this diagnostic criterion. Unfortunately, the time from sample to result for urine cultures is more than 24 hours (24, 25, 30, 31). Urine test strips are unreliable with low specificity and low predictive values(32). Therefore, a POC test is desired, which can provide rapid results and quickly identify a bacteriuria. One such tool may be urine flow cytometry (UFC), which has shown promising diagnostic value for the exclusion of bacteriuria with a high negative predictive value (33). However, better documentation for its use as an ED diagnostic screening method is needed.

Aim and objectives

Our broad hypothesis is that improved diagnostic strategies for patients in ED with suspicion of systemic infection can contribute to more rapid and accurate diagnosis. Thereby, we assume that a more appropriate antibiotic treatment can be administered to these patients.

The project aims to evaluate alternative diagnostic tools and working methods that support a prompt and accurate diagnosis of hospitalized patients suspected of an acute infection. We will focus on the most common ED infections; CAP and APN. The research objectives are to answer the following questions:

1) What are the patient characteristics and treatment trajectory of the different ED infections?
2) What is the diagnostic and prognostic accuracy of the infection markers suPAR, and CRP in patients with suspected CAP and APN?
3) What is the diagnostic accuracy of POC-UFC on diagnosing and excluding bacteriuria?
4) How effective is the addition of POC-PCR analysis of sputum to the diagnostic set-up for CAP on antibiotic prescribing?
5) What is the diagnostic accuracy of POC-US and ULDCT on diagnosing CAP?
6) What is the diagnostic accuracy of CEUS on diagnosing APN?

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7) What is the diagnostic accuracy of POC-US in diagnosing hydronephrosis in patients suspected of APN?

The ultimate goal is to combine the results of all these seven objectives into a novel diagnostic model which the ED physician can apply when receiving a patient with suspicion of infection.

Methods

Study design

The study is designed as a multifaceted multicenter diagnostic study. Participants will undergo additional diagnostic tests depending on the primary suspected focus of infection.

The study protocol is reported in accordance with the SPIRIT (Standard protocol items: Recommendations for interventional trials) statement(34). Informed consent materials can be found in appendix I, Biological specimens in appendix II, and Schedule of enrollment, interventions, and assessments in appendix III.

Setting

The study will recruit participants from three Danish EDs: the regional Hospital, Lillebælt Hospital in Kolding, the regional Hospital, Hospital Sønderjylland in Aabenraa, and the University Hospital, Odense University Hospital in Odense. Enrolment commences from February 8th 2021 and continues until the predefined sample size has been reached.

Project assistants will recruit the participants and collect data. The project assistants will have a healthcare education (physicians, physiotherapists and medical students). They are certificated in focused US of kidney and lung (one-day POC-US course, 25 supervised scans, and Objective Structured Assessment of US Skills (OASUS) test) within one month from enrollment.

The study originates from the Emergency Research Unit affiliated at University Hospital of Southern Denmark and Department of Regional Health Research at University of Southern Denmark.

Population and eligibility criteria

Inclusion of patients is based on the receiving ED physician's initial clinical assessment of the patient. Adults aged 18 or older admitted to the ED will be invited to participate in the study, if the receiving physician suspects the patient is having an infection. Only patients able to give informed consent will be participating in the study. Depending on primary suspected focus of infection (CAP, APN or other/unknown), the patients will be included into one of three diagnostic tracks (A, B, or C) as shown in Figure 1.

Exclusion criteria that apply to all three tracks at time of recruitment

- If the attending physician considers that participation will delay a life-saving treatment or directly transfer to intensive care unit
- Admission (defined as >24 hours hospital visit) within the last 14 days to avoid hospital acquired infections
- Verified COVID-19 disease within 14 days before admission to avoid a skewed population consisting of COVID-19 patients instead of CAP patients. Patients suspected of COVID-19, at the time of recruitment, will not be excluded – nor if subsequently tested positive.
- Pregnant women, this to uniform all the studies. At the participating EDs the pregnant women represent a very small patient group, as they are admitted directly to the ward.
- Severe immunodeficiencies
    - Primary immunodeficiencies
    - Secondary immunodeficiencies

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- Human immunodeficiency virus (HIV) positive, with a cluster of differentiation 4 (CD4) cell count <200
- Patients receiving immunosuppressive treatment (Anatomical therapeutic chemical (ATC) classification L04A)
- Corticosteroid treatment (>20 mg/day prednisone or equivalent for >14 days within the last 30 days)
- Chemotherapy within 30 days

Exclusion criteria that only apply to patients with suspected CAP (track A):

- Patients <40 years old are excluded from the ULDCT and HRCT due to risk of cancer from radiation
- Patients <65 years who already participated once will be excluded from ULDCT and HRCT due to risk of cancer from radiation

Exclusion criteria that only apply to patients with suspected APN (track B):

- Patients are excluded from magnetic resonance imaging (MRI) according to common MRI exclusion criteria (e.g. contraindicating metal in the body) and claustrophobia
- Patients with known allergy to US contrast

Figure 1 Design of patient flow and diagnostic tracks

Recruitment

The study assistants will identify potential eligible patients through the local IT logistic system, which lists patients visiting the ED (Cetrea Anywhere®), According to the local guidelines, a medical clinical assessment of the patients is performed within half an hour from arrival at the ED(35). The study assistant will immediately after the assessment consult the receiving physician to ask if a) a systemic infection is suspected, and b) what the most likely focus is: lungs, urinary tract, elsewhere/unknown. If the patient meets the eligibility criteria, the study assistant will present the study both verbally and in writing, and invite the patient to participate in the study.

Procedure

The study assistant will after obtained written consent order blood samples, urine sample, and the diagnostic tests described in the assigned track. The study assistant will collect data for patient characteristic by looking in the patient record and by patient interview.

Infection markers

Blood samples will be collected by a medical laboratory technologist and transferred to the local laboratory for analysis of CRP (routine analysis), PCT and suPAR. Laboratory staff will be blinded to participant diagnosis and outcome. PCT results will be available to the treating physician, but the suPAR result will not be available. CRP will be measured using an immunoturbidimetric assay (Tina-quant®, Roche) on Roche/Hitachi Cobas© systems. Plasma PCT will be quantified by an automated sandwich immunoassay "ECLIA" (Elecsys®, BRAHMS PCT-analyses) on Cobas© within two hours from collection according to standard procedure. Plasma suPAR will be quantified by using the commercial available suPARnostic© Tubilatex assay reagents (ViroGates, Denmark) on Cobas© as previously validated (36). Separated plasma is kept refrigerated and analysed for suPAR within 48 hours after collection.

POC-UFC

A urine sample will be collected according to routine procedure by the study assistant. The sample will be divided into three aliquots; one for routine urine culturing, one for routine dipstick analysis and one half for POC-UFC

analysis (UF-5000, Sysmex, Kobe, Japan). The POC-UFC analysis will be performed according to manufacturer's instruction and conducted by study assistants or laboratory staff in a point-of-care laboratory close to the department to which the transport time is less than 10 minutes. Laboratory staff will be blinded to participant diagnosis and outcome. The results of the POC-UFC analysis will not be visible to the treating physician.

The results of the dipstick analysis and the urine culturing will be available to the treating physician as part of the usual procedure (within one hour for dipstick and after up to several days for culturing).

POC-PCR sputum analysis

A sputum sample will be collected according to standard procedure as soon as possible after recruitment by the study assistant. This sample will be randomly assigned to one of two groups with 1:1 allocation: 1) POC-PCR analysis (Biofire® FilmArray® Pneumonia Panel plus, Biomérieux, Marcy l'Etoile, France) in accordance with manufacturer's instruction(37), and 2) Routine microbiology analysis (culturing and PCR). Expectorated sputum or tracheal secretions will be used for the PCR analysis. All sputum samples will be cultured. Gram stain and microscopy are not included in the analysis

The randomization will be performed by the study assistants and generated electronically using Research Electronic Data Capture (RedCap) Randomization Module (38) with permuting blocks and stratified according to sites.Allocation concealment is ensured, as randomization is performed electronically and the study assistants administering the randomization will not have access to the randomization code. The allocation is revealed after consent is obtained and sputum collection successful.

The study assistants or laboratory staff will perform the POC-PCR analysis in a point-of-care laboratory at the ED or close to the department to which the transport time is less than 10 minutes. The used POC-PCR targets 27 of the most common pathogens involved in lower respiratory tract infections (appendix IV). The result of the POC-PCR will be presented by the study assistant to the treating physician within four hours upon admission. The treating physician will along with the result receive a recommended action list (appendix V), developed by microbiologists.

The patients will be blinded, and the investigator will be blinded to data management and analysis. Outcome adjudicators will not be blinded.

POC-US

A POC-US (Butterfly iQ+, GM Medical) of the lungs will be performed bedside as Focused Lung US (FLUS) by study assistant within 24 hours after admission. FLUS is used to diagnose pneumothorax, pleural effusion and interstitial syndrome. Additionally, signs of pneumonia ie., liver like alveolar consolidation with shredded borders and air bronchograms will be described. Diagnostic criteria used are in accordance with international consensus(39, 40). FLUS will be conducted immediately before or after the CT scans. The FLUS result will not be available to the treating physician unless the result requires immediate action (pneumothorax or large pleural effusions).

A POC-US (Butterfly iQ+) of the kidneys will be conducted bedside by a study assistant within 24 hours after admission in order to assess whether hydronephrosis is present or absent. If present, the condition will be graded in grades 1, 2, 3 or 4(41). The result will not be available to the treating physician since the patient is examined by a radiologist immediately after, and the results from this examination is reported to the clinician according to standard care.

ULDCT and HRCT

The ULDCT and HRCT of the thorax scans are performed in the same scanning sequence, thus on the same scanner. A specially designed technical protocol is the basis of the ULDCT and will prior to inclusion through a minor pilot study be optimized at each site of inclusion to ensure uniform quality and dose. The radiological findings from ULDCT will be reported systematically using standardized assessment templates by radiologists. The HRCT will be performed according to standard protocols at each hospital, but only during inspiration to limit radiation dose. HRCT will be reference standard for FLUS and ULDCT and interpreted by lung expert radiologists. The reports from POC-US,

ULDCT, and HRCT respectively will be blinded. Study consultant radiologists with experience from ED patients will post-process report the ULDCT scans systematically using specially developed research report templates. The results of ULDCT and HRCT will be available to the treating physician within a week. If a result requires immediate action, the clinician will be contacted directly by the examiner (pneumothorax and large pleural effusions), according to standard care. If a participant is discharged before the scans have been performed, they will be offered the scan in an outpatient setting.

CEUS and MRI

A specialist US will be performed at the Radiology Department, including conventional grayscale US and CEUS with intravenous injection of 1.5 mL ultrasound contrast (Sonovue®, Bracco). At the same time, or as close as possible, a MRI without intravenous contrast of the kidneys will be conducted. The MRI will include the following sequences: planning, Dixon, T1 mapping, T2, T2 mapping, Diffusion ADC (100, 400, 800), MRI angio (3D VIBE), and Phase Contrast. The radiological findings will be described systematically using standardized assessment templates. The report from US and MRI respectively will be blinded. A renal expert radiologist will interpret the MRI and will post-process report the imaging systematically using specially developed research report templates. Imaging from the CEUS will be evaluated in an external postprocessing software algorithm (Vuebox, Bracco). The non-experimental results of the scans will be available to the treating physician within a week. If a result requires immediate action (suspicion of pyonephrosis or renal abcess), the clinician will be contacted directly by the examiner, according to standard care. If a participant is discharged before the scans have been performed, they will be offered the scans in an outpatient setting.

Expert panel reference standard

Unless otherwise stated, the reference standard is the assigned diagnosis determined by a panel of experts. The panel consists of two consultants: a specialist in emergency medicine and a specialist in infectious medicine with considerable experience within acute infections. They will determine the final diagnosis based on all relevant information in medical records and study database available from the admission including routine blood analysis, blood/urine/sputum culturing, POC-PCR, routine and study imaging (including HRCT and MRI), and clinical information. The final diagnosis will be based on information available within the first week after admission. A standardized template in RedCap will be used (appendix VI), and the experts will register if the patient has an infectious disease, if the focus of infection is the lungs, kidneys or other, and specify the infection by adding an ICD-10 diagnosis code. If the patient has two focal diagnoses e.g. pneumonia and APN, the assessment will be based on what is the most probable cause of infection on admission. Conflicts will be discussed until consensus is reached. In this study we define APN as a urinary tract infection with typical local symptoms and systemic affection (i.e. fever, sepsis), thus indicating ascension of infection above the bladder.

Data collection and management

All data will be collected in RedCap. Data will be pseudoanonymized and managed and analyzed using STATA or R in collaboration with a biostatistician

For each participant information on pre-defined clinical parameters upon arrival will be obtained from the medical record including symptoms, lifestyle factors signs, disease severity, vital parameters, triage at arrival, comorbidities, functional status, resident status, prior antibiotics prescriptions, and medical history.

Other variables from the medical record that will be registered are length of stay, re-admission, admission to intensive care unit, prescribed antibiotic treatment, in-hospital mortality, 30-days and 90-days mortality, *Clostridium difficile* infections, and chest X-ray.

Data monitoring

The daily inclusion of participants will be monitored by the steering committee and the numbers of inclusion will be communicated every week toemailed to the included centers. The primary analysis of data will be performed by the project assistants after the last patient has been included and all analysis performed. The results will be discussed and evaluated first in the steering committee and afterwards with all the included departments.

Process auditing

During data collection, an extern assessor will supervise the performance of all project assistants and an independent radiology expert will ensure data quality. Intraobservability on POC-US will be performed each month.

Overall risk for the participants in the randomized trial (POC-PCR sputum analysis) is minimal, as sputum collection is part of the standard care, and it will not affect the following diagnostic work-up. However the POC-PCR results may inform the clinician in a favorable way before onset of patient treatment. Any protocol deviation and/or unknown/unexpected adverse event, will be reported in RedCap, evaluated continuously by the steering committee, and reported to the treating physician and patient.

Statistical analysis and plan

According to the objectives, the study has been divided into sub-studies and for each the primary and secondary outcomes, statistical analysis, and sample size is presented.

Objective 1 - Patient characteristics and treatment trajectory

This sub-study will include all participant. Patient characteristics associated to verified diagnosis will be presented with descriptive results, and logistic univariate and multivariate analysis will be carried out for selected risk indicators, including confounders in the final analysis. The primary outcome is the diagnosis of CAP and APN determined by the expert panel reference standard). Secondary outcomes are length of stay, 30 days mortality, in-hospital mortality, admission to intensive care unit, readmission to hospital within 30 days from day of discharge.

At least 10 variables have to be analyzed, so at least 150 patients with a particular verified diagnosis are needed (50+10 events/variable).

Objective 2 - Diagnostic and prognostic accuracy of PCT and suPAR

This diagnostic accuracy study will include all participants. Index tests are the concentration of CRP, PCT, and suPAR. The expert panel is the reference standard. Diagnostic accuracy tests will be performed as primary analysis, where the test positive of the reference standard is the diagnosis of CAP, and of urinary tract infection. Secondary prognostic tests will be performed, using the reference standard of 30 and 90 days mortality, in-hospital mortality, admission to intensive care, readmission to hospital within 30 days from day of discharge, and length of stay (LOS).

The test positively cut-offs of the index tests will be determined exploratory by performing Youden index analysis to estimate the best cut-off. The CRP value will be available for the members of the expert panel, but the PCT and suPAR will not be available. The reference standard results will not be available for the index test performers.

A demographic characteristic of the study populations will be presented, and the time interval of the laboratory analysis of the biomarkers will be reported. Cross-tabulation of the index test results by the reference standard results will be made including missing results, and used to determine diagnostic and prognostic accuracy expressed as sensitivity, specificity, predictive values, and likelihood ratios reported with 95% confidence intervals where appropriate. Receiver operating characteristic (ROC) analysis will be performed. Statistical modelling will also be performed to explore the effect of combining tests on diagnostic accuracy in order to identify the most accurate diagnostic strategy.

The study is designed to be able to find a difference in area under the curve (AUC) from 0.7 to 0.8 between two tests, which requires 200 verified CAP cases and 200 controls (power 0.8, alpha 0.05, AUC below 0 hypothesis 0.7) and 150 verified pyelonephritis cases and 150 controls (power 0.8, alpha 0.05, AUC below 0-hypothesis 0.6) (42).

Objective 3 - Diagnostic accuracy of POC-UFC on diagnosing and excluding bacteriuria

This diagnostic accuracy study will include all participants. Index test is the POC-UFC and reference standard is the urine culture. The primary outcome is bacteriuria, defined as significant growth of any bacteria. A urine culture will be considered positive with a cut-off of > 1000 CFU/ml for uropathogens and >10.000 CFU/ml for others.

A secondary diagnostic test will be performed, where the reference standard is the expert panel assessment. The outcome is urinary tract infection. The test positive of the index test is bacteuria combined with leukocytes.

The index test results will not be available for the performers of the reference standard test. The reference standard results will be available after the index test has been performed.

A demographic characteristic of the study populations will be presented. Cross-tabulation of the index test result by the reference standard results will be made including missing results, and used to determine diagnostic accuracy expressed as sensitivity, specificity, predictive values, and likelihood ratios reported with 95% confidence intervals where appropriate. Receiver operating characteristic (ROC) analysis will also be performed.

Urine culture shows significant growth of uropathogenic bacterium in approximately 50% of people with suspected APN(25). Asymptomatic bacteriuria accounts for about 20% in the elderly population, depending on gender and age (43), which among 1000 inpatients suspected of infection, of which 15% have APN, gives a sensitivity of 50% (95% CI: 42-58 %) and a negative predictive value of 90% (95% CI: 77-83%). With the expectation of identifying at least 150 cases of APN among our study population, an improvement in sensitivity to 70% (95% CI: 62-77%) and negative predictive value to 95% (95% CI: 93 -96%) could be found with 95% security.

Objective 4 – Addition of POC-PCR analysis of sputum to the diagnostic set-up for CAP on antibiotic prescribing

This RCT will include all participants in track A, who had a sputum sample collected. Intervention group: sputum samples analysed by POC-PCR. Control group: routine microbiology analysis. It is a superiority randomized trial. Primary outcome is targeted versus non-targeted antibiotic treatment prescribed at four hours after admission. Targeted treatment is defined as narrow spectrum antibiotics directed against CAP, antibiotics directed against a detected respiratory pathogen or no antibiotics (e.g. in the absence of a bacterial pathogen and/or presence of a viral pathogen) (appendix VII). Non-targeted treatment is defined as broad spectrum antibiotics not directed against a specific pathogen or antibiotics not directed against CAP. The analyses will follow the intention-to-treat principal and a hierarchical mixed effect logistic model will be utilized to analyze the primary outcome to accommodate the hierarchical structure of the random effect, which manifest according to different personnel collecting the samples and geographical variation.

Secondary outcomes are length of stay, 30 days mortality, in-hospital mortality, admission to intensive care unit, readmission to hospital within 30 days from day of discharge, and antibiotic treatment at 48 hours of admission. A reliability analysis for POC-PCR and routine culturing will be performed as secondary analysis calculating the Intra-class correlation coefficient

To achieve a power of 82% for the main analysis, 200 patients with suspected CAP must be included. To accommodate the bias presented by Gail et al (44) the generalized mixed effect models will be adjusted for strong predictors. If the sample size is not sufficient for a generalized mixed effect models the corresponding univariate analysis will be conducted.

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Objective 5 - Diagnostic accuracy of POC-US and ULDCT on diagnosing CAP

This diagnostic accuracy study will include all participants in track A, who had the HRCT performed. Index test is the POC-US, ULDCT, and chest x-ray. The reference standard is HRCT. The primary outcome is inflammatory changes in the lungs compatible with CAP.

The index test results will not be available for the performers of the reference standard test. The reference standard results will be available after the index test has been performed.

A demographic characteristic of the study populations will be presented. Cross-tabulation of the index tests result by the reference standard results will be made including missing results, and used to determine diagnostic accuracy expressed as sensitivity, specificity, predictive values, and likelihood ratios reported with 95% confidence intervals where appropriate. Receiver operating characteristic (ROC) analysis will also be performed.

It is assumed that the reference standard will find 98% of the patients and index test 90%. With a power of 80%, at least 132 patients with verified CAP should be included (one-sided McNemar test).

Objective 6 - Diagnostic accuracy of CEUS on diagnosing APN

This diagnostic accuracy study will include all participants in track B, who had both the CEUS and MRI performed. Index test is the CEUS and reference standard is MRI. The primary outcome is the presence of renal inflammatory changes compatible with APN. The reference standard will be described by an expert radiologist, who before describing will be informed of some standardized clinical and paraclinical parameters (e.g. fever, CRP, flank pain, and relevant comorbidity), but will be blinded to the results of the other imaging investigations. The CEUS will be conducted and described by a consultant radiologist. The scans will be post process evaluated in the software VueBox. Each kidney is divided into an upper, middle and lower part for each, and these regions are compared in the evaluation of diagnostic agreement.

The index test results will not be available for reference standard performer and describer. The reference standard results will not be available for the index test performers.

A demographic characteristic of the study populations will be presented, and the time interval of the two scans will be reported. Cross-tabulation of the index test result by the reference standard results will be made including missing results, and used to determine diagnostic accuracy expressed as sensitivity, specificity, predictive values, and likelihood ratios reported with 95% confidence intervals where appropriate. Receiver operating characteristic (ROC) analysis will also be performed.

It is assumed that the reference standard finds 98% of patients and index test 90%. With a power of 80%, at least 132 patients must be included (one-sided McNemar test).

Objective 7 - Diagnostic accuracy of POC-US in diagnosing hydronephrosis in patients suspected of APN

This diagnostic accuracy study will include all participants in track B, who had both the POC-US and MRI successfully conducted. Index test is the POC-US and reference standard is MRI. The primary outcome is the presence of hydronephrosis. The reference standard is described by an expert radiologist. The POC-US will be evaluated by the executive study assistants.

The index test results will not be available for reference standard evaluator. The reference standard results will not be available for the index test performers.

A demographic characteristic of the study populations will be presented, and the time interval of the two scans will be reported. Cross-tabulation of the index test result by the reference standard results will be made including

missing results, and used to determine diagnostic accuracy expressed as sensitivity, specificity, predictive values, and likelihood ratios reported with 95% confidence intervals where appropriate. Receiver operating characteristic (ROC) analysis will also be performed.

It is assumed that the reference standard finds 98% of patients and index test 90%. With a power of 80%, at least 132 patients must be included (one-sided McNemar test).

Applicable to all sub-studies

Annually, 5.7% of patients admitted to an ED are diagnosed with CAP and 2.4% with APNs (data from the ED at Hospital Sønderjylland). Taking into account exclusion criteria, weekends/holidays/missing data, and experience in patient recruitment, it is estimated that at least 1000 patients admitted with suspected infection must be included in the study, of which at least 200 patients will be diagnosed with pneumonia and at least 150 patients with APN.

No interim analysis will be made. Non-participant analysis is performed. For missing data multiple imputation is used. Any drop out during the study and the reason will be reported. It is anticipated that once the patients has consented, the drop-out rate will be minimal.

Ethics and dissemination

The project was approved by the Regional Committees on Health Research Ethics for Southern Denmark (S-20200188), registered by the Danish Data Protection Agency (no. 20/60508) and by clinicaltrials.gov (NCT: 04661085, 04681963, 04667195, 04652167, 04686318, 04686292, 04651712, 04645030, and 04651244). Registration date was November-December 2020. Signed informed consent will be obtained from all participants after information of the project has been given both in writing and orally.

Participation in track A will contain additional imaging. Patients under the age of 40 are therefore excluded from the CT due to the extra risk of developing cancer from the radiation. A local hospital physicist has helped with the following calculations: A typical HRCT gives a radiation dose of approximately 2.2 mSv which corresponds to a cancer risk of 1:9100. An X-ray gives a radiation dose of approximately 0.06 mSv which corresponds to a cancer risk of 1:333330. An ULDCT gives a radiation dose of approximately 0.1 mSv which corresponds to a cancer risk of 1:200000. Participation in track A gives each participant approximately 2.26 mSv (ULDCT and HRCT) which corresponds to a cancer risk of 1:8850(45-48). The examination time of ULDCT and HRCT is approximately 10 minutes.

Use of US contrast in rare cases cause allergic reactions; less than 1/10.000 exponents require medical treatment due to allergic reaction (49). The examination time of advanced US is approximately 20 minutes.

MRI does not provide any radiation dose to the patients and is without intravenous contrast. The examination time is approximately 45 minutes, which is aligned with normal MRI examination time.

Overall, risks related to participation in the study is considered minimal, and furthermore, chances are that the additional diagnostic imaging will inform the clinician in a favorable way before the onset of patient treatment.

The treating staff informs the patients about relevant test results. All medical records including laboratory and imaging can be assessed by the patient via the Danish public healthcare web portal (www.sundhed.dk)

Protocol amendments

Important protocol modifications like changes in eligibility criteria or outcome will be communicated to the relevant parties, i.e. sponsor, trial registry, and scientific ethical committee, and explicit described in future publications.

Dissemination policy

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The results of the study will be presented in English peer-reviewed recognized scientific journals. The results of the project will also be disseminated through participation in academic and other conferences, as well as through the printed and electronic press. The author panel will include the steering committee, project assistants, and local coordinators in accordance with the Vancouver criteria. No professional writers will be used. Positive, negative and inconclusive results will be published. Diagnostic accuracy studies will follow the guidelines for reporting diagnostic accuracy studies (STARD) (50), cross sectional studies will follow the guidelines for strengthening the reporting of observational studies in epidemiology (STROBE) (51), and randomized studies will follow the consolidated standards of reporting trials (CONSORT) (52).

Access to data

Only the members of the steering committee and project assistants will have access to the final trial dataset. Other researches may be granted access to the anonymized data for analysis on reasonable request to the corresponding authors.

Discussion

COVID-19 and the consequent societal lockdown might affect trial recruitment and patient distribution. This might lead to an extended recruitment period, as patients suspected of an infectious not related to COVID-19 may be admitted to other departments than the ED, so the ED will be able to handle the many COVID-19 patients. The lockdown may also reduce the number of infections in the society, so fewer patient will visit the hospital, and the distribution of the infections might differ since e.g. the airborne transmitted infections will be reduced. This challenge will especially sub-study 1 be aware of when presenting the results.

After completion of the study, a novel diagnostic algorithm will be developed. Subsequently, the plan is to test the algorithm in a national setting including at least eight EDs. The results can be implemented in daily work and routines. The study will also be able to characterize the patients, who are diagnosed at the ED with an infection of unknown origin and prescribed broad-spectrum antibiotics.

The study is only generalisable to settings where appropriately trained staff and equipment can perform POC-US, and well-resourced settings where a rapid POC-PCR and POC-UFC service is available.

The results of the study will have both national and international interest, as the challenges are common and the solutions can easily be applied in hospitals with a similar technological context. Securing rapid and reliable diagnosis of two of the most common infections diagnosed in the ED, will encourage the reduction of broad-spectrum antibiotics and thereby the development of multi-resistant bacteria.

Declarations

Abbreviations: acute pyelonephritis (APN), Anatomical therapeutic chemical (ATC), area under the curve (AUC), community-acquired pneumonia (CAP), cluster of differentiation 4 (CD4), contrast enhanced ultrasound (CEUS), Coronavirus Disease 2019 (COVID-19), C-reactive protein (CRP), emergency department (ED), human immunodeficiency virus (HIV), high-resolution dose computed tomography (HRCT), magnetic resonance imaging (MRI), Objective Structured Assessment of US Skills (OASUS), polymerase-chain-reaction (PCR), serum procalcitonin (PCT), Point-of-care (POC), receiver operating characteristic (ROC), Soluble urokinase plasminogen activator receptor (suPAR), urine flow cytometry (UFC), ultralow dose computed tomography (ULDCT), and ultrasound (US).

Protocol version: January 25th 2021, version 1.0

Ethics approval: The project was approved by the Regional Committees on Health Research Ethics for Southern Denmark (S-20200188), registered by the Danish Data Protection Agency (20/60508) and by clinicaltrials.gov (NCT:

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04661085, 04681963, 04667195, 04652167, 04686318, 04686292, 04651712, 04645030, and 04651244). Each patient provided written informed consent.

Data sharing statement: Due to Danish laws on personal data, data cannot be shared publicly. To request these data, please contact the corresponding author for more information.

Competing interests: The authors declare that they have no competing interests

Patient and Public Involvement: The patients or public were not involved in the development of the research question or the study design.

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Authors´ contributions: HS, OG, FSR, ERBP, CØ, CBL, TAS, SP, MBC, and CBM conceptualized and all authors designed the study and data collection in detail. HS, AH, MHL, MBC, and CBM reviewed the literature. AH, MHL, MBC, and MAH will recruit participants, and HS, OG, FSR, ERBP, CØ, CBL, TAS, SP, MBC, and CBM will supervise data collection and analysis. HS, AH, MHL, MBC, MAH, and CBM will carry out statistical analysis and write the first manuscripts, which will be critically reviewed by all authors, who will finally approve the manuscripts before submission.
HS and CBM are responsible for the overall content as guarantors. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Steering committee: Composed of representatives from the involved type of departments: emergency, microbiology, biochemistry, and radiology. The role of the committee is to develop the scientific framework of the study, make final decisions on major issues during the data collection and data management period. The committee is responsible for all financial issues. Members of the steering committee are HS, OG, FSR, ERBP, and CBM.

Roles and responsibilities: University Hospital of Southern Denmark is the legal sponsor. CBM is the study chief investigator (Christian.Backer.Mogensen@rsyd.dk), and HSA is the principal investigator.

Participating departments: All departments are located in Denmark
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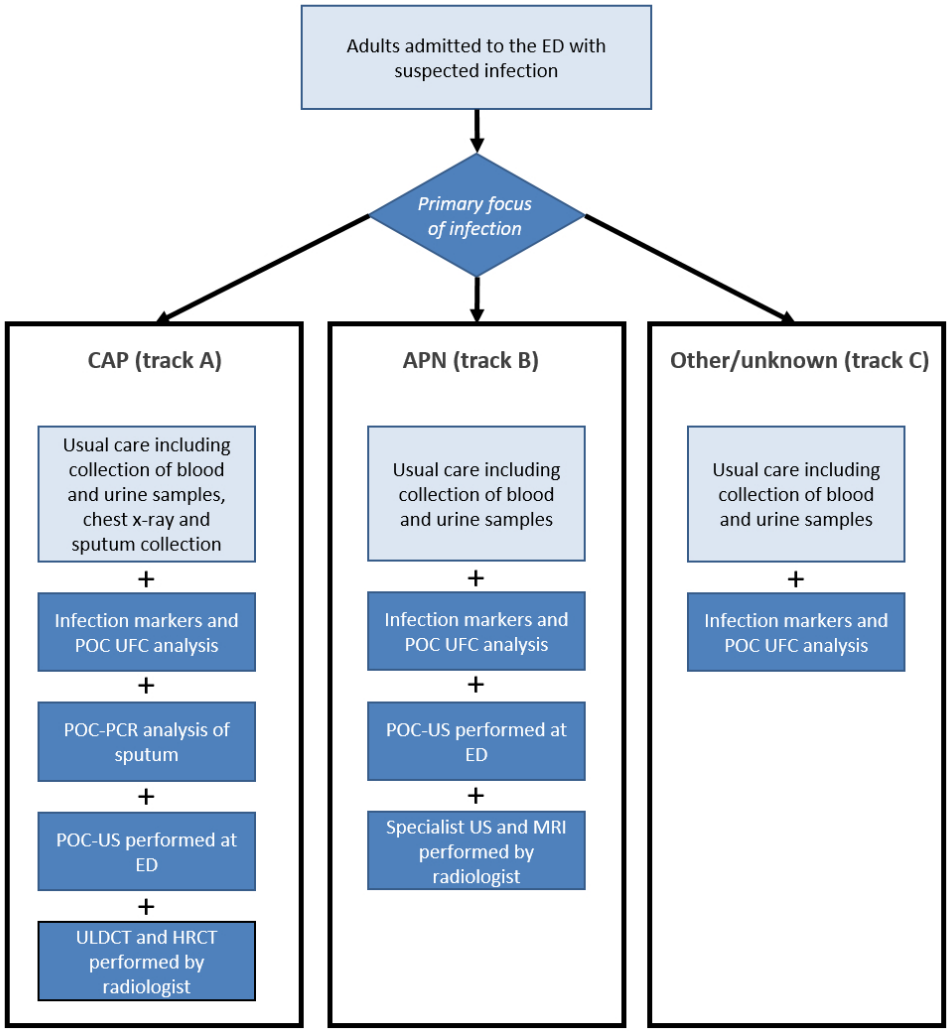


Figure 1 Design of patient flow and diagnostic tracks

170x182mm (150 x 150 DPI)

Appendix

I. Informed consent materials
II. Biological specimens
III. Schedule of enrollment, interventions, and assessments
IV. Targets in POC-PCR
V. Recommended action list
VI. Template for reference standard
VII. Algorithm for antibiotic prescription

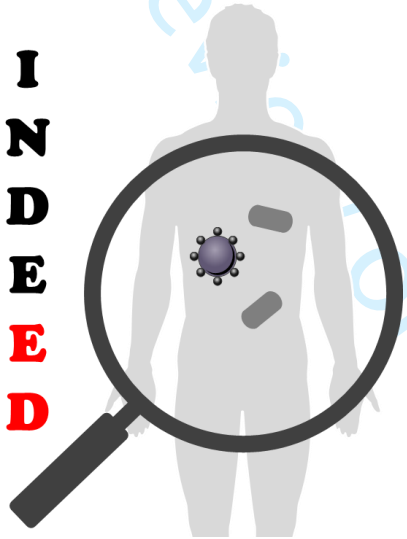
Appendix I - Informed consent materials

Informed consent materials given to the participants has been developed in three versions – track A, B, and C, respectively. The written consent form can be found at the end of appendix I. It is all in Danish.

Participant information - Track A

Deltagerinformation om deltagelse i videnskabeligt forskningsprojekt for personer, der indlægges akut med mistanke om lungebetændelse

Forbedret diagnostik af akutte infektioner



Infectious Diagnostics in Emergency Departments (INDEED study)

Et samarbejdsprojekt på tværs af specialer på Sygehus Sønderjylland, Sygehus Lillebælt og Odense Universitetshospital med udgangspunkt i Akutafdelingerne

Vi vil spørge, om du vil deltage i et videnskabeligt projekt?

Projektet handler om at blive bedre til at diagnosticere lungebetændelse på Akutafdelingen, så en målrettet behandling kan igangsættes så hurtigt som muligt.

Før du beslutter, om du vil deltage i projektet, skal du fuldt ud forstå, hvad projektet går ud på, og hvorfor vi gennemfører det. Vi vil derfor bede dig om at læse denne deltagerinformation grundigt.

Hvis du beslutter dig for at deltage, vil vi bede dig om at underskrive en samtykkeerklæring. Husk, at du har ret til at rådføre dig hos familie, venner eller bekendte. Du har også ret til betænkningstid før du underskriver, men da der er tale om en akut infektion, som kræver hurtig behandling, beder vi om, at du beslutter dig inden for 30 minutter.

Det er frivilligt at deltage i projektet. Du kan når som helst og uden at give en grund trække dit samtykke tilbage. Hvis du trækker dit samtykke om deltagelse i projektet tilbage, vil det ikke få konsekvenser for din videre behandling.

Projektets mål

De redskaber og undersøgelser, der eksisterer i dag til at diagnosticere lungebetændelse, har mange begrænsninger. Det udfordrer lægen i at stille en sikker diagnose inden for kort tid og igangsætte en målrettet behandling. Det kan få konsekvenser for den enkelte persons indlæggelsesforløb. Hvis man behandler med antibiotika som dækker flere bakterier end nødvendigt vil det også bidrage til udviklingen af bakterier, som er modstandsdygtige over for mange antibiotika.

Projektet har derfor til formål at finde bedre redskaber, som kan hjælpe lægen til at stille en sikker diagnose inden for få timer for personer, indlagt akut med mistanke om lungebetændelse.

Det undersøger projektet

Projektet vil undersøge

- hvilke symptomer, tegn og forhold, der kendetegner lungebetændelse og sygdomsgraden
- hvilke markører for infektion i blodet, der bedst kan identificere en lungebetændelse og sygdomsgraden
- om en ny metode til at måle bakterier i urinen er nyttig
- om en ny metode til at identificere bakterier i sekret fra lungerne er nyttigt
- om ultralydsundersøgelse og CT-skanning med meget lav strålingsrisiko kan bruges til at diagnosticere lungebetændelse

Plan for projektet

Projektet foregår på Fælles Akutmodtagelsen i Aabenraa, Sygehus Sønderjylland, på Akutafdelingen i Kolding, Sygehus Lillebælt, og på Fælle Akut Modtagelsen i Odense, Odense Universitetshospital. Fra

februar 2021 til vinteren 2021/22 vil 500 voksne personer, som indlægges akut med mistanke om lungebetændelse på de tre akutafdelinger, blive inviteret til at deltage.

Personalet vil i forbindelse med din indlæggelse opsøge og informere dig om projektet, og tilbyde deltagelse i projektet. Da det er vigtigt at en akut infektion bliver behandlet hurtigt, vil vi bede dig om at tilkendegive din beslutning inden for en halv time.

Det indebærer deltagelse i projektet for dig

Deltagelse i projektet betyder, at du vil modtage den normale behandling, afdelingen tilbyder, og derudover få foretaget ekstra undersøgelser.

Vi vil stille dig nogle spørgsmål omkring dine symptomer, tidligere og aktuelle sygdomme, og hvordan du har det. Vi beder i den forbindelse adgang til din patientjournal, for at følge op på eventuelle tidligere indlæggelser, den aktuelle indlæggelse, og eventuelle indlæggelser inden for den næste måned efter du er udskrevet.

Vi vil tage 14mL ekstra blod svarende til 2 ekstra rør, når du alligevel får taget blodprøve, og hjælpe dig med at aflevere en urinprøve.

Af det sekret fra lungerne, som der bliver taget ifølge normal behandling, vil vi tage en lille del fra nogle af projektpersonerne, og undersøge det med en ny metode.

Det blod, urin og sekret fra lungerne, der indhentes til projektet, vil blive destrueret, når projektet er afsluttet.

Hvis du vælger at deltage, skal du have taget to ekstra skanninger af lungerne. 1) Ultralydsskanning som foretages på akutafdelingen og tager 5 min. 2) En CT-skanning som består af en skanning med meget lav strålingsrisiko, og en højopløselig CT-skanning, som er den mest præcise skanning, der benyttes på lungerne i dag. CT-skanningen vil i alt tage 10 min.

Dit samtykke vil give den forsøgsansvarlige, sponsor og dennes repræsentant direkte adgang til relevante helbredsoplysninger i journalen for at kunne gennemføre, overvåge og kontrollere projektet. I projektet vil behandlingen af personoplysninger følge databeskyttelsesloven og databeskyttelsesforordningen. Efter indsamling af de ønskede informationer vil dine persondata blive fjernet fra vores registreringssystem, og dit personnummer vil blive erstattet af en kode (pseudo-anonymisering).

Bivirkninger, risici, komplikationer og ulemper

Der er ingen eller kun få kendte risici eller bivirkninger ved at deltage i projektet. Alle prøvetagningsmetoder er velkendte og almindeligt anvendte procedurer, som vi har stor erfaring med og kendskab til. Der kan dog være risici ved undersøgelserne, som vi endnu ikke kender. Vi beder dig derfor om at fortælle, hvis du oplever problemer i forbindelse med prøvetagning og undersøgelser. Hvis vi opdager bivirkninger, som vi ikke allerede har fortalt dig om, vil du naturligvis blive orienteret med det samme, og du vil skulle tage stilling til, om du ønsker at fortsætte med prøvetagning og undersøgelser.

De ekstra blodprøver til projektet tages i forbindelse med de blodprøver, der alligevel tages ved indlæggelse. Risici og bivirkninger ved at få taget en blodprøver kan være ubehageligt, lette smerter og/eller blå mærker, og i nogle tilfælde besvimelse. I sjældne tilfælde kan der opstå en mindre blodansamling eller betændelse ved indstiksstedet.

Urinprøven kan som regel afleveres i et bæger, opsamlet ved toiletbesøg. Er du kateterbærer eller på grund af sygdom ikke selv kan lade vandet, kan det blive nødvendigt at hjælpe vandladningen på vej med et kateter, som er et tyndt plastikrør til indførsel i blæren via urinrøret. Denne procedure kan give let ubehag og eventuelt kortvarig mindre blødning fra slimhinderne.

Skanningerne er ikke forbundet med smerte, men du kan eventuelt opleve ubehag ved flytningen til CT-skanneren. Væsentligste risiko i forbindelse med deltagelse i projektet er den ekstra stråledosis som CT-skanningen medfører. Den ekstra stråledosis, du udsættes for, udgør i alt lidt mindre end den baggrundsstråling, som du normalt udsættes for i løbet af et år. Strålingen fra skanningen medfører en let øget risiko for udvikling kræft på ca. 0,01-0,1% og svarer til, at den samlede livstidsrisiko for kræft stiger fra 25% til 25,1%. Denne risiko vurderes dog betydningsløs i forhold til de risici, der i øvrigt er ved din aktuelle indlæggelse.

Dine prøvesvar

Ønsker du svar på de almindelige blod- og urinundersøgeler, kan du se det på www.sundhed.dk. Svar på de ekstra blod- og urinundersøgelser i projektet vil ikke fremkomme her, da vi ikke kender betydningen af resultaterne endnu. Har svarene et alarmerende resultat, vil den behandlende læge få besked og vil vurdere, om det har betydning for din behandling. Resultatet af den ekstra undersøgelse af sekret fra lungerne, som der vil kunne blive lavet i projektet, vil lægen, der behandler dig, blive orienteret om.

Skanningsresultaterne vil være synlige for lægerne, der behandler dig, og indgå i deres vurdering og behandling. Hvis vi skulle opdage noget, der kunne give os mistanke om andre sygdomme (f.eks. kræft), vil vi via din læge kontakte dig og tilbyde yderligere udredning. Bidrager skanningerne ikke med viden, der ændrer på din behandling eller diagnose, hører du ikke nærmere til skanningsresultatet.

Nytte ved projektet

Projektet er vigtigt for at vi fremadrettet kan gøre indlæggelsesforløbet for personer, der indlægges akut med mistanke om lungebetændelse, bedre. Projektet vil have en afgørende betydning for praksis på akutafdelingerne, og formentligt hvilken type antibiotika lægen ordinerer. Et mere målrettet antibiotikaforbrug vil bidrage til reduktion af bakterier, der er modstandsdygtige over for antibiotika, og dermed sikre at infektioner i fremtiden også kan behandles med antibiotika.

For dig personligt, vil deltagelse ikke umiddelbart have en betydning for dit behandlingsforløb. Hvis der skulle ske at være nogle særlige komplikationer til din aktuelle sygdom relateret til lungerne, vil vi dog med de ekstra scanninger formentlig hurtigere erkende dette.

Udelukkelse fra undersøgelse

Du vil udgå af dele af projektet, hvis nogle af undersøgelserne mislykkes af fx tekniske grunde eller hvis din behandlende læge vurderer, at det er for risikabelt for dig at deltage.

Adgang til projektets resultater

Projektets samlede resultater vil blive offentliggjort 2024 i videnskabelige tidsskrifter samt på sygehusenes hjemmesider. Resultater med relevans for beslutningstagere i sundhedsvæsenet vil blive offentliggjort i danske medier og tidsskrifter. Det sikres, at ingen deltagere kan genkendes i det, som offentliggøres. Har du interesse i at vide mere om projektets resultater, kan du efter offentliggørelse opsøge dem via http://www.sygehussonderjylland.dk/wm521282.

Vi håber, at du med denne information har fået tilstrækkeligt indblik i, hvad det vil sige at deltage i projektet, og at du føler dig rustet til at tage beslutningen om din eventuelle deltagelse. Hvis du vil vide mere, er du meget velkommen til at kontakte os. Information om dine rettigheder er vedlagt denne deltagerinformation sidst i dokumentet (Bilag 1).

Hvis du beslutter dig for at deltage i projektet, vil vi bede dig om at underskrive samtykkeerklæringen. Du kan vælge om du vil give samtykke til hele projektet eller kun dele af projektet. Det er frivilligt at deltage i projektet, og du kan når som helst og uden at give en grund trække dit samtykke tilbage. Det vil ikke få konsekvenser for den videre behandling.

Yderligere oplysninger kan fås ved henvendelse til

Professor og overlæge Christian Backer Mogensen
Fælles Akutmodtagelsen, Sygehus Sønderjylland
Kresten Philipsens Vej 15 - 6200 Aabenraa
Christian.Backer.Mogensen@rsyd.dk
Tlf: 79971123

Initiativtagere til projektet

Projektet er primært udarbejdet i samarbejde mellem Akutafdeling, Biokemisk Afdeling og Mikrobiologisk Afdeling, og Radiologisk Afdeling på Sygehus Sønderjylland, Sygehus Lillebælt og Odense Universitets Hospital. Projektet er forankret på Sygehus Sønderjylland og Institut for Regional Sundhedsforskning på Syddansk Universitet, som er ansøgnings- og bevillingsansvarlige.

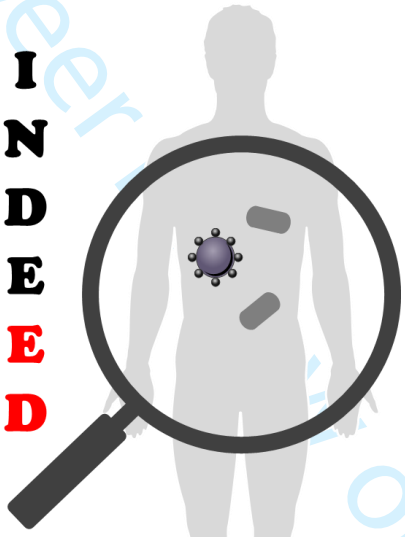
Økonomisk støtte til projektet

Projektet har fået økonomisk støttet i form af ph.d. stipendiater fra Syddansk Universitet (1.650.000kr), ph.d.-stipendiater fra Sygehus Sønderjylland (4.800.000kr) samt støtte til drift fra Region Syddanmark (500.000kr). Forsøgsansvarlige har ingen økonomisk tilknytning til støttegivere eller andre interessenter i forsøget. Der vil ikke være en økonomisk kompensation til patienter, der deltager i projektet.

Participant information - Track B

Deltagerinformation om deltagelse i videnskabeligt forskningsprojekt for personer, der indlægges akut med mistanke om nyrebækkenbetændelse

Forbedret diagnostik af akutte infektioner



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Vi vil spørge, om du vil deltage i et videnskabeligt projekt?

Projektet handler om at blive bedre til at diagnosticere akut nyrebækkenbetændelse på Akutafdelingen, så en målrettet behandling kan igangsættes så hurtigt som muligt.

Før du beslutter, om du vil deltage i projektet, skal du fuldt ud forstå, hvad projektet går ud på, og hvorfor vi gennemfører det. Vi vil derfor bede dig om at læse denne deltagerinformation grundigt.

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Det er frivilligt at deltage i projektet. Du kan når som helst og uden at give en grund trække dit samtykke tilbage. Hvis du trækker dit samtykke om deltagelse i projektet tilbage, vil det ikke få konsekvenser for din videre behandling.

Projektets mål

De redskaber og undersøgelser, der eksisterer i dag til at diagnosticere nyrebækkenbetændelse, har mange begrænsninger. Det udfordrer lægen i at stille en sikker diagnose inden for kort tid og igangsætte en målrettet behandling. Det kan få konsekvenser for den enkelte persons indlæggelsesforløb. Hvis man behandler med antibiotika som dækker flere bakterier end nødvendigt vil det også bidrage til udviklingen af bakterier, som er modstandsdygtige over for mange antibiotika.

Projektet har derfor til formål at finde bedre redskaber, som kan hjælpe lægen til at stille en sikker diagnose inden for få timer for personer, indlagt akut med mistanke om akut nyrebækkenbetændelse.

Det undersøger projektet

Projektet vil undersøge

- hvilke symptomer, tegn og forhold, der kendetegner nyrebækkenbetændelse og sygdomsgraden
- hvilke markører for infektion i blodet, der bedst kan identificere en nyrebækkenbetændelse og sygdomsgraden
- om en ny metode til at måle bakterier i urinen er nyttig
- om ultralydsundersøgelse med og uden kontrastvæske kan bidrage til at diagnosticere nyrebækkenbetændelse

Plan for projektet

Projektet foregår på Fælles Akutmodtagelsen i Aabenraa, Sygehus Sønderjylland, på Akutafdelingen i Kolding, Sygehus Lillebælt, og på Fælle Akut Modtagelsen i Odense, Odense Universitetshospital. Fra februar 2021 til vinteren 2021/22 vil 300 voksne personer, som indlægges akut med mistanke om nyrebækkenbetændelse på de tre akutafdelinger, blive inviteret til at deltage.

Personalet vil i forbindelse med din indlæggelse opsøge og informere dig om projektet, og tilbyde deltagelse i projektet. Da det er vigtigt at en akut infektion bliver behandlet hurtigt, vil vi bede dig om at tilkendegive din beslutning inden for en halv time.

Det indebærer deltagelse i projektet for dig

Deltagelse i projektet betyder, at du vil modtage den normale behandling, afdelingen tilbyder, og derudover få foretaget ekstra undersøgelser.

Vi vil stille dig nogle spørgsmål omkring dine symptomer, tidligere og aktuelle sygdomme, og hvordan du har det. Vi beder i den forbindelse adgang til din patientjournal, for at følge op på eventuelle tidligere indlæggelser, den aktuelle indlæggelse, og eventuelle indlæggelser inden for den næste måned efter du er udskrevet.

Vi vil tage 14mL ekstra blod svarende til 2 ekstra rør, når du alligevel får taget blodprøve, og hjælpe dig med at aflevere en urinprøve.

Det blod og urin, der indhentes til projektet, vil blive destrueret, når projektet er afsluttet.

Vi vil tilbyde dig tre ekstra skanninger af nyrerne. 1) Ultralydsskanning som foretages på akutafdelingen og tager 5 min. 2) Ultralydsskanning, hvor der sprøjtes kontrastvæske ind i dine blodåre, og som foretages af en røntgenlæge. Skanningen tager 20 min. 3) MR-skanning af røntgenlægen, og som tager 45 min. Det tilstræbes, at skanningerne foretages i forbindelse med din indlæggelse. Hvis du udskrives før, kan det være nødvendigt, at du møder op til skanningerne dagen efter.

Dit samtykke vil give den forsøgsansvarlige, sponsor og denne repræsentant direkte adgang til relevante helbredsoplysninger i journalen for at kunne gennemføre, overvåge og kontrollere projektet. I projektet vil behandlingen af personoplysninger følge databeskyttelsesloven og databeskyttelsesforordningen. Efter indsamling af de ønskede informationer vil dine persondata blive fjernet fra vores registreringssystem, og dit personnummer vil blive erstattet af en kode (pseudo-anonymisering).

Bivirkninger, risici, komplikationer og ulemper

Der er ingen eller kun få kendte risici eller bivirkninger ved at deltage i projektet. Alle prøvetagningsmetoder er velkendte og almindeligt anvendte procedurer, som vi har stor erfaring med og kendskab til. Der kan dog være risici ved undersøgelserne, som vi endnu ikke kender. Vi beder dig derfor om at fortælle, hvis du oplever problemer i forbindelse med prøvetagning og undersøgelser. Hvis vi opdager bivirkninger, som vi ikke allerede har fortalt dig om, vil du naturligvis blive orienteret med det samme, og du vil skulle tage stilling til, om du ønsker at fortsætte med prøvetagning og undersøgelser.

De ekstra blodprøver til projektet tages i forbindelse med de blodprøver, der alligevel tages ved indlæggelse. Risici og bivirkninger ved at få taget en blodprøver kan være ubehageligt, lette smerter og/eller blå mærker, og i nogle tilfælde besvimelse. I sjældne tilfælde kan der opstå en mindre blodansamling eller betændelse ved indstiksstedet.

Urinprøven kan som regel afleveres i et bæger, opsamlet ved toiletbesøg. Er du kateterbærer eller på grund af sygdom ikke selv kan lade vandet, kan det blive nødvendigt at hjælpe vandladningen på vej med et

kateter, som er et tyndt plastikrør til indførsel i blæren via urinrøret. Denne procedure kan give let ubehag og eventuelt kortvarig mindre blødning fra slimhinderne.

Det kontraststof, der bruges til ultralydsskanningen, består overvejende af små luftbobler. Det er ikke farligt for kroppen. Der kan opstå milde, kortvarige bivirkninger som fx hovedpine, svimmelhed, ændret smags- og lugtesans. Dette ses hos 0,5-5 %. I meget sjældne tilfælde kan man udvikle en allergisk reaktion, når stoffet sprøjtes ind i blodårerne. Disse alvorlige reaktioner er beskrevet hos mindre end 1/16.500. Du vil derfor blive observeret i 20 minutter efter skanningen, for at se om der skulle opstå bivirkninger eller allergisk reaktion.

MR-skanningen kan godt føles som lang tid. Skanningen er larmende og du har derfor høreværn på. Der er *ingen* strålebelastning eller andre påvirkninger af kroppen forbundet med en MR-skanning.

Dine prøvesvar

Ønsker du svar på de almindelige blod- og urinundersøgeler, kan du se det på www.sundhed.dk. Svar på de ekstra blod- og urinundersøgelser i projektet vil ikke fremkomme her, da vi ikke kender betydningen af resultaterne endnu. Har svarene et alarmerende resultat, vil den behandlende læge få besked og vil vurdere, om det har betydning for din behandling.

Skanningsresultaterne vil være synlige for lægerne, der behandler dig, og indgå i deres vurdering og behandling. Hvis vi skulle opdage noget, der kunne give os mistanke om andre sygdomme (f.eks. kræft), vil vi via din læge kontakte dig og tilbyde yderligere udredning. Bidrager skanningerne ikke med viden, der ændrer på din behandling eller diagnose, hører du ikke nærmere til skanningsresultatet.

Nytte ved projektet

Projektet er vigtigt for at vi fremadrettet kan gøre indlæggelsesforløbet for personer, der indlægges akut med mistanke om nyrebækkenbetændelse, bedre. Projektet vil have en afgørende betydning for praksis på akutafdelingerne, og formentligt hvilken type antibiotika lægen ordinerer. Et mere målrettet antibiotikaforbrug vil bidrage til reduktion af bakterier, der er modstandsdygtige over for antibiotika, og dermed sikre at infektioner i fremtiden også kan behandles med antibiotika.

For dig personligt, vil deltagelse ikke umiddelbart have en betydning for dit behandlingsforløb. Hvis der skulle ske at være nogle særlige komplikationer til din aktuelle sygdom relateret til nyrerne, vil vi dog med de ekstra skanninger formentlig hurtigere erkende dette.

Udelukkelse fra undersøgelse

Du vil udgå af dele af projektet, hvis nogle af undersøgelserne mislykkes af fx tekniske grunde eller hvis din behandlende læge vurderer, at det er for risikabelt for dig at deltage.

Adgang til projektets resultater

Projektets samlede resultater vil blive offentliggjort 2024 i videnskabelige tidsskrifter samt på sygehusenes hjemmesider. Resultater med relevans for beslutningstagere i sundhedsvæsenet vil blive offentliggjort i danske medier og tidsskrifter. Det sikres, at ingen deltagere kan genkendes i det, som offentliggøres. Har du interesse i at vide mere om projektets resultater, kan du efter offentliggørelse opsøge dem via http://www.sygehussonderjylland.dk/wm521282.

Vi håber, at du med denne information har fået tilstrækkeligt indblik i, hvad det vil sige at deltage i projektet, og at du føler dig rustet til at tage beslutningen om din eventuelle deltagelse. Hvis du vil vide mere, er du meget velkommen til at kontakte os. Information om dine rettigheder er vedlagt denne deltagerinformation sidst i dokumentet (Bilag 1).

Hvis du beslutter dig for at deltage i projektet, vil vi bede dig om at underskrive samtykkeerklæringen. Du kan vælge om du vil give samtykke til hele projektet eller kun dele af projektet. Det er frivilligt at deltage i projektet, og du kan når som helst og uden at give en grund trække dit samtykke tilbage. Det vil ikke få konsekvenser for den videre behandling.

Yderligere oplysninger kan fås ved henvendelse til

Professor og overlæge Christian Backer Mogensen
Fælles Akutmodtagelsen, Sygehus Sønderjylland
Kresten Philipsens Vej 15 - 6200 Aabenraa
Christian.Backer.Mogensen@rsyd.dk
Tlf: 79971123

Initiativtagere til projektet

Projektet er primært udarbejdet i samarbejde mellem Akutafdeling, Biokemisk Afdeling og Mikrobiologisk Afdeling, og Radiologisk Afdeling på Sygehus Sønderjylland, Sygehus Lillebælt og Odense Universitets Hospital. Projektet er forankret på Sygehus Sønderjylland og Institut for Regional Sundhedsforskning på Syddansk Universitet, som er ansøgnings- og bevillingsansvarlige.

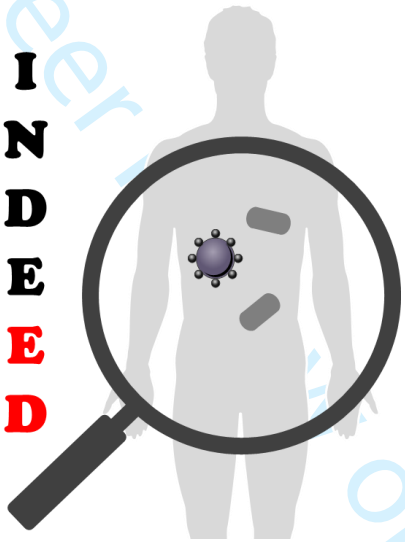
Økonomisk støtte til projektet

Projektet har fået økonomisk støttet i form af ph.d. stipendiater fra Syddansk Universitet (1.650.000kr), ph.d.-stipendiater fra Sygehus Sønderjylland (4.800.000kr) samt støtte til drift fra Region Syddanmark (500.000kr). Forsøgsansvarlige har ingen økonomisk tilknytning til støttegivere eller andre interessenter i forsøget. Der vil ikke være en økonomisk kompensation til patienter, der deltager i projektet.

Participant information - Track C

Deltagerinformation om deltagelse i videnskabeligt forskningsprojekt for personer, der indlægges akut med mistanke om infektion

Forbedret diagnostik af akutte infektioner



Infectious Diagnostics in Emergency Departments (INDEED study)

Et samarbejdsprojekt på tværs af specialer på Sygehus Sønderjylland, Sygehus Lillebælt og Odense Universitetshospital med udgangspunkt i Akutafdelingerne

Vi vil spørge, om du vil deltage i et videnskabeligt projekt?

Projektet handler om at blive bedre til at diagnosticere akutte infektioner på Akutafdelingen, så en målrettet behandling kan igangsættes så hurtigt som muligt.

Før du beslutter, om du vil deltage i projektet, skal du fuldt ud forstå, hvad projektet går ud på, og hvorfor vi gennemfører det. Vi vil derfor bede dig om at læse denne deltagerinformation grundigt.

Hvis du beslutter dig for at deltage, vil vi bede dig om at underskrive en samtykkeerklæring. Husk, at du har ret til at rådføre dig hos familie, venner eller bekendte. Du har også ret til betænkningstid før du underskriver, men da der er tale om en akut infektion, som kræver hurtig behandling, beder vi om, at du beslutter dig inden for 30 minutter.

Det er frivilligt at deltage i projektet. Du kan når som helst og uden at give en grund trække dit samtykke tilbage. Hvis du trækker dit samtykke om deltagelse i projektet tilbage, vil det ikke få konsekvenser for din videre behandling.

Projektets mål

De redskaber og undersøgelser, der eksisterer i dag til at finde ud af, hvilken type infektion, der er skyld i indlæggelsen på Akutmodtagelsen, har mange begrænsninger. Det udfordrer lægen i at stille en sikker diagnose inden for kort tid og igangsætte en målrettet behandling. Det kan få konsekvenser for den enkelte persons indlæggelsesforløb Hvis man behandler med antibiotika som dækker flere bakterier end nødvendigt vil det også bidrage til udviklingen af bakterier, som er modstandsdygtige over for mange antibiotika.

Projektet har derfor til formål at finde bedre redskaber, som kan hjælpe lægen til at stille en sikker diagnose inden for få timer for personer, indlagt akut med mistanke om infektion.

Det undersøger projektet

Projektet vil undersøge

- hvilke symptomer, tegn og forhold, der kendetegner de forskellige typer af infektioner og sygdomsgraden
- hvilke markører for infektion i blodet, der bedst kan angive typen af infektion og sygdomsgraden
- om en ny metode til at måle bakterier i urinen er nyttig

Plan for projektet

Projektet foregår på Fælles Akutmodtagelsen i Aabenraa, Sygehus Sønderjylland, på Akutafdelingen i Kolding, Sygehus Lillebælt, og på Fælle Akut Modtagelsen i Odense, Odense Universitetshospital. Fra februar 2021 til vinteren 2021/22 vil 1000 voksne personer, som indlægges akut med mistanke om infektion på de tre akutafdelinger, blive inviteret til at deltage.

Personalet vil i forbindelse med din indlæggelse opsøge og informere dig om projektet, og tilbyde deltagelse i projektet. Da det er vigtigt at en akut infektion bliver behandlet hurtigt, vil vi bede dig om at tilkendegive din beslutning inden for en halv time.

Det indebærer deltagelse i projektet for dig

Deltagelse i projektet betyder, at du vil modtage den normale behandling, afdelingen tilbyder, og derudover få foretaget ekstra undersøgelser.

Vi vil stille dig nogle spørgsmål omkring dine symptomer, tidligere og aktuelle sygdomme, og hvordan du har det. Vi beder i den forbindelse adgang til din patientjournal, for at følge op på eventuelle tidligere indlæggelser, den aktuelle indlæggelse, og eventuelle indlæggelser inden for den næste måned efter du er udskrevet.

Vi vil tage 14mL ekstra blod svarende til 2 ekstra rør, når du alligevel får taget blodprøve, og hjælpe dig med at aflevere en urinprøve.

Det blod og urin, der indhentes til projektet, vil blive destrueret, når projektet er afsluttet.

Dit samtykke vil give den forsøgsansvarlige, sponsor og denne repræsentant direkte adgang til relevante helbredsoplysninger i journalen for at kunne gennemføre, overvåge og kontrollere projektet. I projektet vil behandlingen af personoplysninger følge databeskyttelsesloven og databeskyttelsesforordningen. Efter indsamling af de ønskede informationer vil dine persondata blive fjernet fra vores registreringssystem, og dit personnummer vil blive erstattet af en kode (pseudo-anonymisering).

Bivirkninger, risici, komplikationer og ulemper

Der er ingen eller kun få kendte risici eller bivirkninger ved at deltage i projektet. Alle prøvetagningsmetoder er velkendte og almindeligt anvendte procedurer, som vi har stor erfaring med og kendskab til. Der kan dog være risici ved undersøgelserne, som vi endnu ikke kender. Vi beder dig derfor om at fortælle, hvis du oplever problemer i forbindelse med prøvetagning og undersøgelser. Hvis vi opdager bivirkninger, som vi ikke allerede har fortalt dig om, vil du naturligvis blive orienteret med det samme, og du vil skulle tage stilling til, om du ønsker at fortsætte med prøvetagning og undersøgelser.

De ekstra blodprøver til projektet tages i forbindelse med de blodprøver, der alligevel tages ved indlæggelse. Risici og bivirkninger ved at få taget en blodprøver kan være ubehageligt, lette smerter og/eller blå mærker, og i nogle tilfælde besvimelse. I sjældne tilfælde kan der opstå en mindre blodansamling eller betændelse ved indstiksstedet.

Urinprøven kan som regel afleveres i et bæger, opsamlet ved toiletbesøg. Er du kateterbærer eller på grund af sygdom ikke selv kan lade vandet, kan det blive nødvendigt at hjælpe vandladningen på vej med et kateter, som er et tyndt plastikrør til indførsel i blæren via urinrøret. Denne procedure kan give let ubehag og eventuelt kortvarig mindre blødning fra slimhinderne.

Dine prøvesvar

Ønsker du svar på de almindelige blod- og urinundersøgeler, kan du se det på www.sundhed.dk. Svar på de ekstra blod- og urinundersøgelser i projektet vil ikke fremkomme her, da vi ikke kender betydningen af resultaterne endnu. Har svarene et alarmerende resultat, vil den behandlende læge få besked og vil vurdere, om det har betydning for din behandling.

Nytte ved projektet

Projektet er vigtigt for at vi fremadrettet kan gøre indlæggelsesforløbet for personer, der indlægges akut med mistanke om infektion, bedre. Projektet vil have en afgørende betydning for praksis på akutafdelingerne, og formentligt hvilken type antibiotika lægen ordinerer. Et mere målrettet antibiotikaforbrug vil bidrage til reduktion af bakterier, der er modstandsdygtige over for antibiotika, og dermed sikre at infektioner i fremtiden også kan behandles med antibiotika.

For dig personligt, vil deltagelse ikke have en betydning for dit behandlingsforløb, da resultaterne af undersøgelserne først vil blive evalueret når projektet er afsluttet på akutafdelingen.

Udelukkelse fra undersøgelse

Du vil udgå af dele af projektet, hvis nogle af undersøgelserne mislykkes af fx tekniske grunde

Adgang til projektets resultater

Projektets samlede resultater vil blive offentliggjort 2024 i videnskabelige tidsskrifter samt på sygehusenes hjemmesider. Resultater med relevans for beslutningstagere i sundhedsvæsenet vil blive offentliggjort i danske medier og tidsskrifter. Det sikres, at ingen deltagere kan genkendes i det, som offentliggøres. Har du interesse i at vide mere om projektets resultater, kan du efter offentliggørelse opsøge dem via http://www.sygehussonderjylland.dk/wm521282.

Vi håber, at du med denne information har fået tilstrækkeligt indblik i, hvad det vil sige at deltage i projektet, og at du føler dig rustet til at tage beslutningen om din eventuelle deltagelse. Hvis du vil vide mere, er du meget velkommen til at kontakte os. Information om dine rettigheder er vedlagt denne deltagerinformation sidst i dokumentet (Bilag 1).

Hvis du beslutter dig for at deltage i projektet, vil vi bede dig om at underskrive samtykkeerklæringen. Du kan vælge om du vil give samtykke til hele projektet eller kun dele af projektet. Det er frivilligt at deltage i projektet, og du kan når som helst og uden at give en grund trække dit samtykke tilbage. Det vil ikke få konsekvenser for den videre behandling.

Yderligere oplysninger kan fås ved henvendelse til

Professor og overlæge Christian Backer Mogensen
Fælles Akutmodtagelsen, Sygehus Sønderjylland
Kresten Philipsens Vej 15 - 6200 Aabenraa
Christian.Backer.Mogensen@rsyd.dk
Tlf: 79971123

Initiativtagere til projektet

Projektet er primært udarbejdet i samarbejde mellem Akutafdeling, Biokemisk Afdeling og Mikrobiologisk Afdeling, og Radiologisk Afdeling på Sygehus Sønderjylland, Sygehus Lillebælt og Odense Universitets Hospital. Projektet er forankret på Sygehus Sønderjylland og Institut for Regional Sundhedsforskning på Syddansk Universitet, som er ansøgnings- og bevillingsansvarlige.

Økonomisk støtte til projektet

Projektet har fået økonomisk støttet i form af ph.d. stipendiater fra Syddansk Universitet (1.650.000kr), ph.d.-stipendiater fra Sygehus Sønderjylland (4.800.000kr) samt støtte til drift fra Region Syddanmark (500.000kr). Forsøgsansvarlige har ingen økonomisk tilknytning til støttegivere eller andre interessenter i forsøget. Der vil ikke være en økonomisk kompensation til patienter, der deltager i projektet.

Bilag 1: Forsøgspersoners rettigheder i et sundhedsvidenskabeligt forskningsprojekt

Som deltager i et sundhedsvidenskabeligt forskningsprojekt skal du vide, at:

- din deltagelse i forskningsprojektet er helt frivillig og kun kan ske efter, at du har fået både skriftlig og mundtlig information om forskningsprojektet og underskrevet samtykkeerklæringen.
- du til enhver tid mundtligt, skriftligt eller ved anden klar tilkendegivelse kan trække dit samtykke til deltagelse tilbage og udtræde af forskningsprojektet. Såfremt du trækker dit samtykke tilbage påvirker dette ikke din ret til nuværende eller fremtidig behandling eller andre rettigheder, som du måtte have.
- du har ret til at tage et familiemedlem, en ven eller en bekendt med til informationssamtalen.
- du har ret til betænkningstid, før du underskriver samtykkeerklæringen.
- oplysninger om dine helbredsforhold, øvrige rent private forhold og andre fortrolige oplysninger om dig, som fremkommer i forbindelse med forskningsprojektet, er omfattet af tavshedspligt. behandling af oplysninger om dig, herunder oplysninger i dine blodprøver og væv, sker efter reglerne i databeskyttelsesforordningen, databeskyttelsesloven samt sundhedsloven. Den dataansvarlige i forsøget skal orientere dig nærmere om dine rettigheder efter databeskyttelsesreglerne.
- der er mulighed for at få aktindsigt i forsøgsprotokoller efter offentlighedslovens bestemmelser. Det vil sige, at du kan få adgang til at se alle papirer vedrørende forsøgets tilrettelæggelse, bortset fra de dele, som indeholder forretningshemmeligheder eller fortrolige oplysninger om andre.
- der er mulighed for at klage og få erstatning efter reglerne i lov om klage- og erstatningsadgang inden for sundhedsvæsenet. Hvis der under forsøget skulle opstå en skade kan du henvende dig til Patienterstatningen, se nærmere på www.patienterstatningen.dk.

Dette tillæg er udarbejdet af det Videnskabsetiske komitésystem og kan vedhæftes den skriftlige information om det sundhedsvidenskabelige forskningsprojekt. Spørgsmål til et konkret projekt skal rettes til projektets forsøgsansvarlige. Generelle spørgsmål til forsøgspersoners rettigheder kan rettes til den komité, som har godkendt projektet.

Revideret 21. september 2019

Written consent form – track A, B, and C

Informeret samtykke til at deltage i et sundhedsvidenskabeligt projekt

Forbedret diagnostik af akutte infektioner

- Infectious Diseases in Emergency Departments (INDEED study)

Erklæring fra forsøgspersonen:
Jeg har fået skriftlig og mundtlig information, og jeg ved nok om formål, metode, fordele og ulemper til at sige ja til at deltage.

Jeg ved, at det er frivilligt at deltage, og jeg altid kan trække mit samtykke tilbage uden at miste mine nuværende eller fremtidige rettigheder til behandling.

Jeg giver hermed samtykke til at deltage i projektet og har fået en kopi af dette samtykkeark samt en kopi af den skriftlige information om projektet til eget brug.

Forsøgspersonens navn: _____

Forsøgspersonens Cpr-nummer: _____

Dato: _____ Underskrift: _____

Hvis der kommer nye væsentlige helbredsoplysninger frem om dig i forskningsprojektet vil du blive informeret. Vil du **frabede** dig information om nye væsentlige helbredsoplysninger, som kommer frem i forskningsprojektet, bedes du markere her: _____ (sæt x)

Erklæring fra den, der afgiver information:

Jeg erklærer, at forsøgspersonen har modtaget mundtlig og skriftlig information om forsøget.

Efter min overbevisning er der givet tilstrækkelig information til, at der kan træffes beslutning om deltagelse i forsøget.

Navnet på den, der har afgivet information:

Dato: _____ Underskrift:_____

Appendix II - Biological specimens

In this study, blood will be collected for analysis of serum procalcitonin (PCT) and Serum soluble urokinase plasminogen activator receptor (suPAR) and for a research biobank to store blood until analysis is feasible.

	Blood for analysis of PCT and suPAR	**Blood for research biobank**
Collection	The blood will be collected in an EDTA plasma tube.	Biobank blood is only collected for patient in track A and includes one tube of EDTA plasma and one tube of LiHeparin plasma.
Storage	At two of the sites, the analysis will be performed within is tested within two hours from the collection of the blood sample. At the third site, samples will be stored locally in a -80 °C freezer. The samples are pseudonymized with a code to protect the identity of the participants. All samples and code lists are stored safely and separately to prevent unauthorized access.	All samples will be stored locally in a -80 °C freezer. The samples are pseudonymized with a code to protect the identity of the participants. All samples and code lists are stored safely and separately to prevent unauthorized access.
Sample analysis	*Serum procalcitonin (PCT)* Serum PCT concentration is quantified with an automated sandwich immunoassay "ECLIA" (Elecsys®, BRAHMS PCT-analyses) on Cobas e801. Calibration is performed after Cobas e pack has been registered in the instrument and is standardized to the BRAHMS PCT LIA assay. The correlation of Elecsys BRAHMS PCT analyses has been compared to BRAHMS PCT LIA and to BRAHMS PCT sensitive KRYPTOR with similar results of r=0.981 and r=0.988 respectively. Quality control is performed after each calibration and regularly following the standard procedure. The manufacture states a lower limit of detection 0.02 µg/L up to 100 µg/L. The functional assay sensitivity is identified at ≤ 0.06 ng/mL. In this study a range from 0.06 µg/L to 100 µg/L will be measured. Normal healthy individuals have a PCT concentration < 0.1 µg/L. All plasma samples are screened for potential interfering substances like bilirubin, hemoglobin and lipids and no	Molecular analysis for future use in ancillary studies will take place after all samples have been collected.

	results will be included with significant interference. There is no hook-effect in PCT concentrations measured up to 1000 µg/L. The precision of PCT assay is expected to be <3% CV or similar. This is estimated from the internal quality controls using PC PCT1 (lot.419495) and PC PCT2 (lot.419497) at target PCT levels 0.49 and 9.44 ng/L showing a precision of 2.67 % CV and 2.63 % CV, respectively.	
	Serum soluble urokinase plasminogen activator receptor (suPAR) Serum suPAR is measured using suPARnostic© Tubilatex assay reagents (validated on Cobas© c111) protocol for Cobas© c702 and c502 applying the Multi-Pack cassettes (Roche Diagnostics, Mannheim, Germany) (42). Calibration is performed at least once a month or in connection to a new batch of TurbiLatex reagents, after calibration a quality control is performed. Measure range of the suPARnostic© Tubilatex assay is 1.8 µg/L to 16.0 µg/L on Cobas© c502 analyzer. The assay's limit of blank, limit of detection and limit of quantification are 1.0 µg/L, 1.2 µg/L and 1.2 µg/L respectively. Expected values for patients attending ED's range from 3-6 µg/L and can reach double digits in patients with severe disease related to poor prognosis. High concentration of SuPAR above 20 µg/L may be false positive results related with interference used by high concentration of hemoglobin, lipids or bilirubin. There is no identified interference in concentrations of bilirubin >350 µmol/L, triglycerides > 3.3g/L, hemoglobin > 1.4 g/L or rheumatoid factor > 440 IU/mL. The highest concentration of suPAR is tested at 47.5 µg/L without hook-effect and the linearity is from 1.8 µg/L to 26.6 µg/L. The mean value of precision of the test is 3.4 µg/L, 7.1 µg/L, 10.2 µg/L for low, middle and high concentrations of SuPAR respectively. The accuracy of suPARnostic© Tubilatex is compared with suPARnostic© ELISA with similar results < 15 % of difference. The precision of suPAR assay is expected to be < 5% CV or similar. This is estimated from external quality assessment material, HK 19 (Product code 2226 DK, Lot. No.	

	201808) analyzed repeatedly during five different days on c502 and c702 and the mean content of suPAR determined by turbidimetry was 2.15 mg/ L and 2.03 mg/L (CV% 4.56 and 5.52) for the Cobas c502 and c702 instruments, respectively.	
Evaluation	The results will be saved in a study database and not be visible for the physician in the medical journal.	The results will be saved in a study database. The expiry date of the research biobank is expected to be October 2022. After expiry date, the remaining material in the research bank will be destroyed.
Location	Samples will be located at Bloodsamples, Biochemistry and Immunology, University Hospital of Southern Denmark, Aabenraa, Denmark	Samples will be located at: - Bloodsamples, Biochemistry and Immunology, University Hospital of Southern Denmark, Aabenraa, Denmark - Biochemistry and Immunology, University Hospital of Southern Denmark, Kolding, Denmark - Clinical Biochemistry and Pharmacology, Odense University Hospital, Odense, Denmark

Appendix III - Schedule of enrollment, interventions and assessments

	STUDY PERIOD										
	RECRUITMENT	ALLOCATION	POST-ALLOCATION							CLOSE-OUT	
TIMEPOINT (h=hours, d=days)	**-½h**	**0h**	<1h	<4h	<24h	<48h	<5d	<7d	<14d	30d	90d
ENROLMENT											
Eligibility screeen	x										
Informed consent	x										
Physician assessment	x										
Allocation		x									
INTERVENTIONS – all tracks											
Collection of blood sample			x								
• PCT analysis									x		
• suPAR analysis									x		
Collection of urine sample				x							

• POC-UFC analysis				x							
INTERVENTIONS – track A											
Collection of sputum sample			x								
• POC-PCR analysis and presented to the treating physician				x							
POC-US					x						
ULDCT and HRCT					x						
INTERVENTIONS – track B											
CEUS					x						
POC-US					x						
MRI					x						
ASSESSMENTS											
Collection of patient characteristic (patient interview and look up in medical record)				x							
CRP results				x							
Dipstick result				x							
Urine routine culturing result								x			

Sputum routine culturing and PCR result								x			
Antibiotic prescription				x		x	x				
Expert panel reference standard								x			
Length of stay											x
Mortality											x
Admission to ICU and readmission											x

Appendix IV - Targets in POC-PCR

The BIOFIRE® FILMARRAY® Pneumonia plus Panel is testing for 27 of the most common pathogens involved in Lower respiratory tract infections and 7 genetic markers of antibiotic resistance.

Bacteria (semi quantitative)	Antibiotic Resistance Genes
Acinetobacter calcoaceticus-baumannii complex *Enterobacter cloacae* *Escherichia coli* *Haemophilus influenzae* *Klebsiella aerogenes* *Klebsiella oxytoca* *Klebsiella pneumoniae group* *Moraxella catarrhalis* *Proteus spp.* *Pseudomonas aeruginosa* *Serratia marcescens* *Staphylococcus aureus* *Streptococcus agalactiae* *Streptococcus pneumoniae* *Streptococcus pyogenes*	**ESBL** CTX-M **Carbapenemases** KPC NDM Oxa48-like VIM IMP **Methicilin Resistance** mecA/mecC and MREJ

Atypical Bacteria (Qualitative)	Viruses
Legionella pneumophila *Mycoplasma pneumoniae* *Chlamydia pneumoniae*	Influenza A Influenza B Adenovirus Coronavirus Parainfluenza virus Respiratory Syncytial virus Human Rhinovirus/Enterovirus Human Metapneumovirus Middle East Respiratory Syndrome Coronavirus (MERS-CoV)

Appendix V – recommended action list

Guidance of results from POC-PCR

FilmArray® Pneumonia Panel plus

This guidance is developed to the INDEED-study (Infectious diseases in Emergency Department).

Emergency department physicians from Hospital Sønderjylland in Aabenraa, Hospital Lillebælt in Kolding, and Odense University Hospital in Odense, will receive this action card along with the results from sputum sample analyses.

In case of doubt in the interpretation of the results, the physician is encouraged to contact the local clinical microbiologist.

Agens	Association with CAP[#]	Remarks	Antibiotics	
			First choice	Penicillin allergy
*Streptococcus pneumoniae**	Frequent and likely pathogen	Part of the normal microbiota in upper respiratory tract. May be contamination with pharyngeal microbiota.	Benzylpenicillin 1.2g (2 mill.IE) x4 i.v. *or* Phenoxymethylpenicillin 0.6g (1 mill.IE) x4 oral	Cefuroxime 1.5g x 3 i.v. *or* Roxithromycin 300mg x1 oral
*Haemophilus influenza**	Frequent and likely pathogen		Ampicillin 2g x4 i.v. *or* Benzylpenicillin 1.2g (2 mill. IE) x4 i.v. *or* Piv-ampicillin 1g x3 oral *or* Amoxicillin 1g x3 oral	Cefuroxime 1.5g x 3 i.v. *or* Doxycycline 100mg x2 first 24 hours oral followed by 100mg x1 oral
*Streptococcus pyogenes**	Probable, but rare pathogen	Part of the normal microbiota in upper respiratory tract. These pathogens relatively often represent contamination with pharyngeal microbiota. Infection caused by *Streptococcus pyogenes* or *Staphylococcus aureus* will usually results in severe pneumonia.	Benzylpenicillin 1.2g (2 mill. IE) x4 i.v.	Cefuroxime 1.5g x3 i.v.
*Streptococcus agalactiae**	Rare pathogen in adults		Benzylpenicillin 1.2g (2 mill. IE) x4 i.v.	Cefuroxime 1.5g x3 i.v.
*Staphylococcus aureus**	Probable, but rare pathogen		Cloxacillin 1g x4 i.v.	Cefuroxime 1.5g x3 i.v.
*Moraxella catarrhalis**	Probable pathogen		Piperacillin-tazobactam 4/0.5g x3 i.v. *or* amoxicillin-clavulanic acid 500/125mg x3 oral	Cefuroxime 1.5g x3 i.v. *or* Roxithromycin 300mg x1 oral *or* Azithromycin 500mg x1 oral
Legionella pneumophila *Mycoplasma pneumonia*	Likely causative pathogen	Is not a part of the normal respiratory microbiota.	Azithromycin 500mg x1 i.v./oral	
Chlamydia pneumoniae	Probable causative pathogen	Is not a part of the normal respiratory microbiota Will usually cause mild infections. In case of severe infection, other pathogens/super-infection should be considered.	Azithromycin 500mg x1 i.v./oral	

Agens	Association with CAP[#]	Remarks	Antibiotics
*Pseudomonas aeruginosa**	Very rare causative pathogens	These findings usually represents colonization.	These findings should typically not lead to adjustment of empirical antimicrobial treatment.
*Acinetobacter calcoaceticus-baumannii complex**			
*Enterobacter cloacae**			
*Escherichia coli**			
*Klebsiella (Enterobacter) aerogenes**			
*Klebsiella oxytoca**			
*Klebsiella pneumoniae group**			
*Proteus spp.**			
*Serratia marcescens**			
Influenza A Influenza B	Frequent pathogens	Is not a part of the normal respiratory microbiota Bacterial superinfection can occur.	Consider whether the patient's pneumonia symptoms can be explained by viral infection, and whether antibiotic treatment is necessary / indicated.
Parainfluenza virus Respiratory Syncytial Adenovirus Coronavirus *(does not include SARS-CoV-2)* Human Rhinovirus/Enterovirus Human Metapneumovirus	Probable pathogens	Usually causes mild infections. In case of severe infection, other pathogens / superinfection should be considered. May be an accidental finding due to previous /recent / asymptomatic infection.	
Not detected *(POC-PCR(FilmArray) is negative)*	A negative result does not rule out pneumonia, but means that CAP caused by the most common pathogens is less likely. Consider whether the pneumonia diagnosis is correct and consider investigation for rare causes of pneumonia (e.g. tubeculosis or *Chlamydia psittaci*).		

#CAP: Community-Acquired Pneumonia

*: Concentration (copies/mL) is reported in the POC-PCR (FilmArray) result

Most bacterial causative pathogens of CAP are also part of the normal respiratory microbiota or may colonize the upper respiratory tract, and the clinical relevance of these findings must always be assessed carefully.

For the bacterial agents marked with "*", a concentration (copies/mL) is reported in the POC-PCR (FilmArray) result. There is a reasonable correlation between copies/mL and the culture-based measure "CFU/mL", however, "copies/mL" is typically a factor of 10-100 higher than the corresponding "CFU/mL".

The limits of significance are not well established and depend probably on the agent, the quality of the sample and the clinical context - and must therefore be used with caution. The Infectious Diseases Society of America and the American Society of Microbiology[1] propose the following culture-based limits for hospital-acquired pneumonia:

Culture-based measure	POC-PCR (FilmArray) concentration	Interpretation (caution)
$< 10^4$ CFU/mL	≈ $< 10^5$ copies/mL	Indicates mixture with normal flora
$10^4 – 10^5$ CFU/mL	≈ 10^5-10^6 copies/mL	Gray zone
$> 10^5$ CFU/mL	≈ $>10^6$ copies/mL	Indicates real findings

Developed by microbiologist Flemming Rosenvinge, Department of Clinical Microbiology, Odense University Hospital in Odense, and microbiologist Claus Østergaard, Department of Clinical Microbiology, Hospital Lillebælt in Kolding, Denmark

Version 1.1 – February 7th 2021

[1] *Miller, J. M., Binnicker, M. J., Campbell, S., et al. A Guide to Utilization of the Microbiology Laboratory for Diagnosis of Infectious Diseases: 2018 Update by the Infectious Diseases Society of America and the American Society for Microbiology. Clinical Infectious Diseases, 67(6), e1–e94. https://doi.org/10.1093/cid/ciy381*

Appendix VI - Template for expert panel reference standard

The template for the expert panel reference standard is illustrated in the table:

<table>
<tr><th>Main question</th><th>Sub-question</th></tr>
<tr><td rowspan="2">Does the patient has an infection?
❑ Yes ❑ No</td><td>If yes, what was the focus of infection?
❑ Respiratory ❑ Urinary tract ❑ Other</td></tr>
<tr><td>If yes, was the focus of infection identified within 48 hours?
❑ Yes ❑ No</td></tr>
<tr><td colspan="2">If focus is respiratory infection</td></tr>
<tr><td colspan="2">What type of respiratory infection was the patient primarily hospitalized with?
❑ Covid-19 pneumonia
❑ CAP
❑ COPD – exacerbation
❑ Aspiration pneumonia
❑ Other – please specify (by using a list of ICD-10 diagnosis): _____</td></tr>
<tr><td colspan="2">If focus is urinary tract infection (UTI)</td></tr>
<tr><td>What type of UTI was the patient primarily hospitalized with?
❑ UTI without systemic effects (cystitis)
❑ UTI with systemic effects (pyelonephritis/urosepsis)</td><td>If UTI with systemic effects, please specify
❑ Pyolonephritis (local symptoms + fever + increased CRP)
❑ Urosepsis (UTI + 2 qSOFA or relevant bacteremia)
❑ Cannot be further specified
❑ Other – please specify (by using a list of ICD-10 diagnosis): _____</td></tr>
<tr><td colspan="2">If focus of infection is other than respiratory and urinary tract infection</td></tr>
<tr><td colspan="2">What type of infection was the patient primarily hospitalized with?
❑ Unknown focus ❑ Soft tissue abscess
❑ Erysipelas ❑ Cholecystitis
❑ Tonsillitis ❑ Diverticulitis
❑ Gastroenteritis ❑ Pancreatitis
❑ Endocarditis ❑ Appendicitis
❑ Meningitis
❑ Other – please specify (by using a list of ICD-10 diagnosis): _____</td></tr>
</table>

Appendix VII - Algorithm for antibiotic treatment

The algorithm specify if the antibiotic treatment is targeted or non-targeted. Targeted treatment is defined as narrow spectrum antibiotics directed against CAP, antibiotics directed against a detected respiratory pathogen or no antibiotics (e.g. in the absence of a bacterial pathogen and/or presence of a viral pathogen. Non-targeted treatment is defined as broad spectrum antibiotics not directed against a specific pathogen or antibiotics not directed against CAP.

Narrow spectrum antibiotics (NS) is defined in table 1. Targeted treatment (TT) for the different types of agens is defined in table 2. Treatment with other antibiotics (not listed as NS or TT in table 1 and 2) is classified non-targeted treatment (NT).

Table 1 Narrow spectrum antibiotis

Antibiotic treatment – narrow spectrum	
No penicillin allergy	Reported penicillin allergy
Benzylpenicillin Phenoxymethylpenicillin	Benzylpenicillin Phenoxymethylpenicillin Clindamycin Macrolide Cefuroxime

Table 2 Targeted treatment

	Antibiotic treatment - targeted	
Agens	No penicillin allergy	Reported penicillin allergy
Streptococcus pneumonia, pyogenes, or agalactiae	Benzylpenicillin Phenoxymethylpenicillin	Benzylpenicillin Phenoxymethylpenicillin Clindamycin Macrolide Cefuroxime
H. influenzae	Benzylpenicillin Ampicillin Piv-ampicillin Amoxicillin Amoxicillin-clavulanate Piperacillin/Tazobactam Cefuroxime Doxycycline Ciprofloxacin	Benzylpenicillin Ampicillin Piv-ampicillin Amoxicillin Amoxicillin-clavulanate Piperacillin/Tazobactam Cefuroxime Doxycycline Ciprofloxacin
Moraxella catarrhalis	Amoxicillin-clavulanate Piperacillin/Tazobactam Cefuroxime or Macrolide	Amoxicillin-clavulanate Piperacillin/ Tazobactam Cefuroxime Macrolide
Staphylococcus aureus	Cloxacillin	Benzylpenicillin

	Dicloxacillin	Phenoxymethyl-penicillin Macrolid Cefuroxime Cloxacillin Dicloxacillin Clindamycin Macrolide Cefuroxime
Legionella pneumophila	Macrolide Ciprofloxacin Moxifloxacin Doxycycline Tetracycline	Macrolide Ciprofloxacin Moxifloxacin Doxycycline Tetracycline
Mycoplasma pneumoniae or Chlamydia pneumoniae	Macrolide Moxifloxacin Doxycycline Tetracycline	Macrolide Moxifloxacin Doxycycline Tetracycline

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

Completed SPIRIT checklist

Section/item	ItemNo	Description	Page in protocol
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	3
Protocol version	3	Date and version identifier	17
Funding	4	Sources and types of financial, material, and other support	17
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	17
	5b	Name and contact information for the trial sponsor	3+18
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	18
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	18
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	6-7
	6b	Explanation for choice of comparators	6-7
Objectives	7	Specific objectives or hypotheses	7-8

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	8
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8-9
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9-11
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	15
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	12
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7-8
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	12-15
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	9+appendix III
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	12-15
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	12
Methods: Assignment of interventions (for controlled trials)			
Allocation:			

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	10
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	10
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	10
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	10
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	-
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	12-15
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	-
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	12-15
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	12-15
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	12-15
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	12-15

Methods: Monitoring

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	11-12
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	15
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	12
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	12

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	15-16
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	16
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	9
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	-
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	15-16
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	17
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	16
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	-

Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	16
	31b	Authorship eligibility guidelines and any intended use of professional writers	16
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	16
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Appendix I
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Appendix II