ISRCTN14487574 https://doi.org/10.1186/ISRCTN14487574

Predicting individual outcomes from a range of intravenous antibiotics for sputum-producing exacerbations of chronic lung disease, using microbial genomics and artificial intelligence

Submission date
17/12/2024

Recruitment status
Recruiting

Registration date
22/01/2025

Overall study status
Ongoing

Last Edited
22/01/2025

Condition category
Respiratory

[ ] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[ ] Results
[ ] Individual participant data
[ ] Record updated in last year

Plain English summary of protocol

Background and study aims:
Chronic airway diseases, including cystic fibrosis, chronic obstructive pulmonary disease and bronchiectasis, are characterized by recurrent pulmonary exacerbations during which patients produce thick, coloured (purulent) sputum. Exacerbations significantly worsen patient morbidity, prognosis and healthcare resources. Although treatment with antibiotics is first line (often intravenously [IV]), antibiotics frequently fail (20-50% of the time). Antibiotics are usually chosen based on the sputum bacterial culture and antibiotic sensitivity testing. Unfortunately, evidence indicates this predicts clinical response poorly, leading to trial-and-error approaches which delay effective treatment, cause progressive lung damage, and increase the risk of antimicrobial resistance in both patients and the community. Patients urgently need a point-of-care test that can predict if antibiotics are likely to be effective and which will maximise clinical response and minimise resistance. Advancements in genomic technologies have revolutionized our understanding of the lung microbiome, revealing its complexity and the concurrent presence of multiple bacterial populations. These technologies allow for detailed analysis of microbial communities, predicting their abundance, antibiotic sensitivity, and resistance profiles individually. By analysing the genetic information of these strains, along with sputum proteins and metabolites, this study aims to understand how specific antibiotics lead to successful treatment outcomes. The primary goal is to develop a new test that can more accurately predict the best antibiotic treatment for each patient, based on their sputum. This could lead to faster, more effective treatments and improve patients' quality of life.

Who can participate?
This study will observe adult patients aged 18 years old and over at the Cambridge Centre for Lung Infection (CCLI) who are receiving IV antibiotics for infection-related flare-ups of their chronic lung diseases.

What does the study involve?
This is a prospective observational study with no interventions. The study team will collect

sputum samples and detailed clinical information from these patients to analyse using genetic sequencing and artificial intelligence.

Participants will undergo:
- Research review when starting IV antibiotics and at follow-up visits (every 7 days, or when antibiotics are changed) until IV antibiotics are stopped
- Brief symptom questionnaires, and where possible, spirometry and oxygen saturation measurements during reviews
- Consent for the study to collect clinical data from their patient record

Sputum sample collection for NGS analysis and conventional microbiology
A convalescent visit more than 14 days after completing IV antibiotics
Collection of clinical outcome metadata for up to five years after enrollment
Participants may be involved multiple times if they require additional courses of IV antibiotics during the study period.

What are the possible benefits and risks of participating?
Benefits include contributing to advancing understanding of APE treatment and potentially improving future patient care. There are no significant risks to participation as this is an observational study with no interventions. The main imposition is a little time at each regular clinical visit. All information collected will be deidentified and participation will be confidential.

Where is the study run from?
The Royal Papworth Hospital NHS Foundation Trust (RPH) for patients attending the CCLI

When is the study starting and how long is it expected to run for?
April 2024 to December 2030. The study is expected to run for five years, with a target of observing at least 600 antibiotic treatment encounters.

Who is funding the study?
The study is funded by an unrestricted research programme grant from the Cystic Fibrosis Trust.

Who is the main contact?
Dr David Abelson, Fellow at Royal Papworth Hospital, david.abelson@nhs.net

Contact information

Type(s)
Public, Scientific, Principal investigator

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Integrated Research Application System (IRAS)
345064

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
CPMS 64638, Cystic Fibrosis Trust Grant Codes: THUB01, PO3129

Study information

Scientific Title
Prospective observational study to predict outcomes from a range of intravenous antibiotics for sputum-producing exacerbations of chronic lung disease, using microbial genomics and artificial intelligence

Acronym
SputaGen

Study objectives
Individual outcomes after starting IV antibiotics for an acute sputum-producing exacerbation of chronic lung disease can be predicted by a range of different IV antibiotics based on the genomics of their individual sputum microbiome and clinical information.

Ethics approval required
Ethics approval required

Ethics approval(s)
approved 23/10/2024, South West - Frenchay Research Ethics Committee (Ground Floor, Temply Quay House, 2 The Square, Bristol, BS16PN, United Kingdom; +44 (0)207 1048106; frenchay.rec@hra.nhs.uk), ref: 24/SW/0122

Study design
Prospective observational single-centre cohort study

Primary study design
Observational

Study type(s)
Diagnostic

Health condition(s) or problem(s) studied

Acute exacerbations of chronic lung disease productive of purulent sputum

Interventions

Subjective (e.g. questionnaires) and objective (e.g. time till next exacerbation) assessment of response to therapy before starting treatment and every seven days while on treatment, concurrent with sputum sampling.

Study Design:
• This is a prospective, observational, non-interventional single-centre study.
• It will be conducted at Royal Papworth Hospital NHS Foundation Trust for patients attending the Cambridge Centre for Lung Infection (CCLI) to receive intravenous antibiotics.

What Will Happen to Research Participants:
1. Enrolment:
• Eligible patients starting IV antibiotics at CCLI will be approached about participating.
• If interested, they will receive a Patient Information Sheet and have time to consider participation.
• If they agree to participate, written informed consent will be obtained.

2. Initial Data Collection:
• Participants will complete questionnaires about their symptoms and quality of life (taking 10-15 minutes).
• A sputum sample will be collected.
• Where possible, spirometry and oxygen saturation measurements will be taken.
• Clinical data will be collected from medical records.

3. Follow-up Visits:
• For outpatients: Follow-up visits will occur at each ambulatory care unit attendance (usually every 7 days while on IV antibiotics).
• For inpatients: Follow-up will occur every 7 days and when IV antibiotics are changed.
• At each follow-up:
• Brief questionnaires will be completed (taking 5-10 minutes)
• A sputum sample will be collected
• Where possible, spirometry and oxygen saturation will be measured
• Clinical data will be updated from medical records

4. Post-Treatment Follow-up:
• A final follow-up will occur more than 2 weeks after completing IV antibiotics.
• This may be in-person or by phone/video if an in-person visit is not scheduled.

The patient's active involvement in the study ceases after this follow-up visit, however, clinical outcome metadata will continue to be collected from medical records for the patient for up to 5 years from study enrolment.

If a participant requires IV antibiotics again within 5 years, they will be offered the opportunity to enrol again for the new treatment episode.

The study does not involve any interventions beyond routine clinical care. All study procedures are designed to collect data with minimal burden on participants, mostly aligning with their standard clinical care visits.

Intervention Type
Other

Phase
Not Specified

Primary outcome(s)
The generation of a mechanistic model to explain the relationship between clinical data, conventional sputum microbiology and antibiotic sensitivity results, next-generation sequencing of sputum microbial nucleic acids (DNA and RNA) and clinical outcomes, including:
1. Improvement in symptom scores measured using questionnaires including Chronic Airways Assessment Test (CAAT) and Visual Analogue Scales (VAS) measured every seven days till completion of treatment and two weeks after treatment ends
2. Time till the next exacerbation measured using patient medical notes at one timepoint
3. Changes to antimicrobial resistance, predicted using whole sputum genomics and artificial intelligence

Key secondary outcome(s))
The generation of an AI algorithm that can predict the outcome of intravenous antibiotics treatment of sputum-producing acute exacerbation of chronic lung disease. Prediction accuracy will be measured against withheld test data using standard tools from the machine learning toolbox including ROC AUC for classification and the r2 metric for regression to continuous scores.

Completion date
01/12/2030

Eligibility

Key inclusion criteria
1. Age: Subjects must be 18 years or older
2. Consent: Subjects must be able and willing to consent
3. Attending the Cambridge Centre for Lung Infection to commence a clinician-directed course of intravenous antibiotics abx for the treatment of clinically diagnosed acute pulmonary exacerbation of chronic lung disease
4. Able to produce a mucopurulent or purulent sputum sample at recruitment

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex

All

Key exclusion criteria
Patients unable to produce purulent or mucopurulent sputum at recruitment

Date of first enrolment
01/01/2025

Date of final enrolment
31/12/2030

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Royal Papworth Hospital
Papworth Road
Cambridge Biomedical Campus
Cambridge
United Kingdom
CB2 0AY

Sponsor information

Organisation
Royal Papworth Hospital NHS Foundation Trust

Funder(s)

Funder type
Charity

Funder Name
Cystic Fibrosis Trust

Alternative Name(s)
Cystic Fibrosis, cystic fibrosis (CF), CF

Funding Body Type
Private sector organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
(i) DNA and RNA sequences will be uploaded to the European Nucleotide Archive (ENA) (with core clinical metadata), accessible via the European Bioinformatics Institute, https://www.ebi.ac.uk/
(ii) Anonymised detailed clinical metadata will be made available upon request through Andres Floto, arf27@cam.ac.uk
(iii) All algorithms, and code will be made publically accessible through GitHub, www.github.com

IPD sharing plan summary
Stored in publicly available repository, Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes