Respiratory microbiome and clinical data analysis for the prediction of acute exacerbations in COPD

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Ethical review	Approved WMO
Status	Recruiting
Health condition type	Respiratory disorders NEC
Study type	Observational invasive

Summary

ID

NL-OMON51796

Source
ToetsingOnline

Brief title
REDALERT

Condition

- Respiratory disorders NEC

Synonym
chronic lung disease with persistent narrowing of the airways, Chronic Obstructive Pulmonary Disease (COPD)

Research involving
Human

Sponsors and support

Primary sponsor: Universiteit Maastricht
Source(s) of monetary or material Support: Eurostars E! 113530

Intervention

Keyword: COPD, Exacerbations, Personalized medicine, Respiratory microbiome

Outcome measures

Primary outcome

Accuracy of risk assessment for the prediction of acute exacerbations of COPD

based on microbiological and clinical analyses

Secondary outcome

- Composition of the respiratory microbiota in patients with COPD and relation

to exacerbation history and clinical parameters

- Compositional clustering of respiratory microbiota in relation to disease

phenotype

- Research changes/shifts in the respiratory microbiota in patients with COPD

in the stable phase, during exacerbation and recovery

Study description

Background summary

Chronic obstructive pulmonary disease (COPD) is characterised by progressive airflow limitation. With a global prevalence of 5-10%, COPD is one of the most common diseases of the respiratory tract and was the most prevalent chronic respiratory disease in 2017. Worldwide, more than 3 million deaths are attributed to the disease annually.

The clinical course of the disease is characterised by periods of relative clinical stability and periods of an acute worsening of symptoms (exacerbations). Exacerbations are a major reason for the loss of quality of life, and for healthcare utilization.

The vast majority of acute exacerbations are linked to acute bacterial or viral respiratory infections, which aggravate respiratory symptoms and precipitate inflammatory processes. Patients experience a worsening of symptoms like

dyspnoea, cough or mucus production that is beyond day-to-day variation and requires an adaptation of the medication.

While frequency and severity of exacerbations vary from patient to patient, patients suffering from frequent exacerbations experience a faster deterioration of lung function and higher burden of symptoms. In-hospital mortality of patients admitted to the hospital due to an acute exacerbation lies between 2.5 and 14%, with one year mortality rates following a severe (i.e. hospitalised) exacerbation of 23-43%.The prevention and early detection of exacerbations is therefore a crucial goal in the management of COPD.

In order to predict individual exacerbation risk, current tools rely solely on sociodemographic and anamnestic/clinical data. Although these approaches have gained complexity and accuracy by integrating more and more data into their calculations, they currently do not consider microbiological findings and dynamics of bacterial colonisation of the respiratory tract. However, there is growing evidence that dynamics of microbial community composition within the respiratory tract of COPD patients are associated with the development of exacerbations and their outcome.

A longitudinal analysis of the sputum microbiota of patients with COPD found that bacterial communities were relatively stable over time within most subjects, but found this stability to be lower during acute exacerbations. Moreover, the study found that microbiota profiles differed between different exacerbation phenotypes and aetiologies. Temporary changes of the sputum microbiota have also been observed in another cohort, which described four distinct clusters of microbiota composition, three of which were characterised by dysbiosis and were significantly different from a stable core microbiota. Moreover, respiratory microbiota composition was found to be distinct in patients with frequent exacerbations and associated with one-year survival following hospitalisation for an acute exacerbation of COPD. These findings suggest that monitoring changes in microbiota composition of the respiratory tract could be used to assess the individual short-term risk of acute exacerbations of COPD, and, in combination with clinical parameters be a useful tool for risk stratification in the prevention of COPD exacerbations.

Study objective

REDALERT*s goal is to combine the ISPro technology and geneXplain platform to develop an integrated solution for routine RTM analysis with:

A) novel processing methods for ISPro to accurately characterize the RTM and the relative abundance and shifts therein of microbiota
B) clinical decision-making algorithms based on the geneXplain platform to predict exacerbations from RTM samples and associated clinical patient data

Study design

The study is a prospective, longitudinal, observational two-centre study.

Patient recruitment:
Patients will be recruited and screened for eligibility among in- and outpatients at the Departments of Respiratory Medicine at University Hospital Frankfurt and Maastricht University Medical Centre. Patients can be approached both during acute as well as exacerbated disease state; however, clinical stability is a requirement for the baseline examination and commencement of data recording. Visits consists of inclusion visit, baseline examination, remote visits, half-yearly visits and exacerbation visits.

Inclusion visit:
For inclusion in the study, the patients* eligibility for participation in the study is checked by a study physician. Written informed consent is obtained before enrolment in the study.

Baseline examination (V1):
Takes place after the informed consent form is signed.
A baseline examination will be conducted before commencement of data recording and during a period of clinical stability, i.e. at least 4 weeks after the last acute exacerbation had occurred, and at least 4 weeks after the last treatment with antibiotics or systemic corticosteroids. If these conditions are fulfilled at the time of inclusion into the study, inclusion visit and baseline examination can be combined. For patients not fulfilling these criteria, the baseline examination is conducted at a later time point (when the criteria are fulfilled).

The baseline examination consists of a medical history, physical examination, and collection of biomaterials for additional analyses (a throat swab, sputum sample). Co-morbidities, current and recent medication as well as COPD-related health-care utilisation and/or medications related to exacerbations in the past 12 months will be documented. An assessment of COPD-related symptoms will be made using the COPD assessment test and the modified Medical Research Council (mMRC) dyspnoea score. As a reference prediction tool, probabilities of the occurrence of exacerbations will be calculated using the ACCEPT tool.

During the baseline visit participants will moreover be instructed how to self-collect throat swabs and sputum samples for the remote visits and prepare them for shipment. If possible, the self-collection of samples will be performed once under supervision by a member of the study staff.

Remote visits:
Remote visits (sampling only, additional sampling points to V1, V4 and

Exacerbation visits):

One week (+/- 2 days) after baseline visit (V1), one week (+/- 2 days) after visit at six months (V4), Four weeks (+/-4 days) after acute exacerbation visit (AECOPD).In order to analyse the short-term variability of the respiratory microbiota and to determine microbiota profiles after recovery from an acute exacerbation, patients are asked to self-collect a throat swab and spontaneously expectorated sputum and hand the samples in or mail them to the study centres within 5 days. If samples are to be sent by mail, participants will receive appropriate shipping material and instructions beforehand.

Full remote visit:
Two months (V2), four months (V3), eight months (V5) and ten months (V6) after baseline visit; all +/- 7 days

During structured phone interviews, patients are asked if they experienced an acute exacerbation since the last study visit. Moreover, they are asked about respiratory infections, changes in their medication, and COPD-related healthcare utilisation since the last visit, in order to identify possibly unreported/undetected exacerbations in the period since last visit. Symptom scores (CAT, mMRC) and exacerbation risk assessment using the ACCEPT tool are recorded. Patients are asked to self-collect a throat swab and spontaneously expectorated sputum and hand the samples in or mail them to the study centres within 5 days. If samples are to be sent by mail, participants will receive appropriate shipping material and instructions beforehand.

Half-yearly visit:
Six months (V4) and 12 months (V7) after baseline visit (+/- 14 days)

Patients are asked to return to the study centre for physical examinations, a regular check-in for the study procedures and handing out the remainder of the study materials. The CAT score, mMRC score and aforementioned questionnaires will be
recorded. The exacerbation risk assessment (ACCEPT tool) will be updated. Where applicable, the documentation of co-morbidities will be updated.Throat swabs and sputum samples will be collected.

Exacerbation visits:
Patients experiencing an acute exacerbation, defined as an acute worsening of respiratory symptoms resulting in additional therapy, will be asked to contact the study centre within 3 days of onset.

Patients are asked to self-collect a throat swab and sputum sample and send them to the study centre within 5 days. Respiratory symptoms, CAT and mMRC will be recorded.Four weeks after the exacerbation, patients are again asked to self-collect respiratory samples (throat swab, sputum) and send them to the study centre. If patients seek treatment for an acute exacerbation at the study

site, sampling and questionnaires can also be performed at the centre. Likewise, collection of respiratory samples can be performed on site instead of remotely, if a regular visit coincides with the sampling window for the samples collected four weeks after an acute exacerbations.

Study burden and risks

The invasive nature of this study is very mild and the risk to the subjects is very low/negligible. However, the results of this study can contribute significantly in a better/more personalized treatment for a very large patient group. The results aim to ultimately improve individual treatment of COPD, thereby improving quality of life and reducing the death rate from this disease.

Contacts

Public
Universiteit Maastricht

P. Debyelaan 25
Maastricht 6229 HX
NL
Scientific
Universiteit Maastricht

P. Debyelaan 25
Maastricht 6229 HX
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Age >= 18 years
Written informed consent
Physician-confirmed diagnosis of COPD (spirometry) (FEV1<= 80% predicted)
Smoking history: Min. 10 packyears

Exclusion criteria

Inability to understand the nature, scope, and possible consequences of the study
Life expectancy of less than 12 months
Newly diagnosed active pulmonary tuberculosis within the last 12 months
Unstable cardiopulmonary or metabolic co-morbidities
Macrolide maintenance treatment

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	27-12-2023
Enrollment:	150
Type:	Actual

Ethics review

Approved WMO

Date:	26-04-2022

Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	12-12-2024
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL79498.068.21
Other	NL9801