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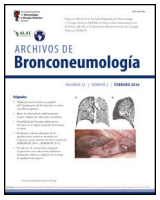

Scientific Letters

Time-based Register and Analysis of COPD Endpoints (TRACE) Project: Methodology and Workflow

Registro y análisis en el tiempo de resultados clínicos en EPOC (Proyecto TRACE): metodología y procedimiento

Dear Editor,

Over the last few decades, several observational prospective cohorts have added to our understanding of the clinical presentation and the progression of chronic obstructive pulmonary disease (COPD). Although the different studies available have provided valuable information on specific aspects of the disease over a fixed period of time,[1,2] its direct implications for daily clinical practice have been less profound than expected partly due to the use of specific advanced diagnostic tools, which are not always routinely available in clinical practice. Accordingly, it would be desirable to conduct a prospective observational cohort study evaluating the tools normally available to the clinician in their daily clinical practice.

The *Time-based Register and Analysis of COPD Endpoints* (TRACE) cohort (clinicaltrials.gov NCT03485690) is a single-center, prospective cohort study aimed at evaluating COPD patients prospectively using tools normally used in the clinic. The study starts from the hypothesis that is possible to identify different patient types with different clinical behavior who show a different response to treatment by using common clinical tools available at all health centers attending patients with respiratory diseases. The protocol has been approved by the Local Ethical Health Authorities (Portal de Ética de la Investigación Biomédica de Andalucía, approval actas 08/2015 and 07/2017). Due to the observational and non-interventional nature of the study, an informed consent was waived. The ethical committee was notified of this circumstance and approved the procedure clearly recorded in the protocol.

The objective of the study is to accomplish three specific aims: (1) to describe the variation over time of different clinical variables and the results of the complementary tests routinely used in the clinic, (2) to define the different behavior patterns of the disease, and (3) to evaluate the impact of different therapeutic approaches on this behavior in the different patient types in terms of lung function improvement, perception of symptoms and exacerbation frequency. The primary endpoint is survival. The secondary endpoints include dyspnea, measured by modified Medical Research Council scale, the number of moderate or severe exacerbations, forced expiratory volume in one second (FEV_1) annual decline, forced expiratory flow at 25–75% of expiration, peak expiratory flow, peripheral blood eosinophils count, serum alpha1-antitrypsin, total IgE, bronchial colonization, and inhaled and oral COPD-related medication use.

The study population is composed solely of COPD patients recruited from specialized COPD-dedicated outpatient clinics in a tertiary university hospital. Estimated sample size was 1440 cases. Adult patients with a diagnosis of COPD according to current guidelines[3] receiving routine follow-up in our dedicated COPD outpatient clinic have been selected for inclusion. The protocol does not pre-specify any exclusion criteria, except for the complete reversibility of lung function testing during follow-up. The inclusion of patients was piloted study since 2012, a procedure that was completed in 2015.

After identification of cases, the patients are followed up at yearly visits *sine die* until they die or are lost to follow-up. The study is guided by a Steering Committee, consisting of six academic respiratory physicians who attend patients regularly. All the subjects receive their prescribed medication and therapeutic interventions throughout the study with any changes in medication being ordered by the physician in charge, according to the patient's clinical status. During the yearly visits, clinical, functional, radiological and analytical information is recorded using a standardized questionnaire.

All the clinical variables were obtained from the patient and included: socio-demographics (gender, age), tobacco history, comorbidities, clinical presentation during the previous year in a stable state (including dyspnea evaluation, cough and sputum production, color of the sputum if present, wheezing and symptoms suggestive of asthma), exacerbations and hospitalization in the previous year, current pharmacological and non-pharmacological treatment. Complementary tests, included, at least, chest radiology, pre- and post-bronchodilator spirometry and analytical results (blood eosinophils, alpha1-antitrypsin, total IgE). With this information, the patients are initially categorized according to the different versions of the Global Initiative of Obstructive Lung Disease (GOLD) document[3] and the Spanish national guidelines for COPD (GesEPOC),[4] and the classification is adapted to the successive updates of these documents during the follow-up, whenever possible.

Asthma-like symptoms are also recorded, including the presence of rhinitis, variability of respiratory symptoms during the year and worsening of respiratory symptoms when exposed to non-specific triggers. The comorbidities are recorded following different comorbidity composite scores, including the Charlson comorbidity index,[5] the COPD specific comorbidity test (COTE),[6] the COMorbidities in Chronic Obstructive Lung Disease (COMCOLD) index,[7] and the Functional Comorbidity Index.[8]

Exacerbations are recorded at each yearly clinical visit. For the present study, an exacerbation is defined as any increase in perceived respiratory symptoms which requires additional medication to control them. To consider two exacerbations as different episodes, a time lapse between episodes of at least 4 weeks from the end of the exacerbation or 6 weeks from the beginning is required.[9] The information provided by the patient regarding exacerbation frequency is matched with the information in the clinical record. Emergency ward visits and hospital admissions due to exacerbations are also noted.

Non-pharmacological treatments over the previous year are noted at every visit, including the persistence of active smoking, daily exercise, and influenza and pneumococcal vaccinations. Oral and inhaled pharmacological therapies for COPD are also noted,

as is the use of home-based therapies, including home mechanical ventilation, long-term oxygen therapy and nebulizers.

Spirometries are performed so far with a Masterlab Pneumatic Tachograph (Erich Jaeger GHBH, Würzburg, Germany). The spirometer is calibrated daily, and the results adjusted by the atmospheric conditions. Patients are instructed to withhold their inhaler medication on the day of the test, in order to record pre- and post-bronchodilator spirometry. If this is not the case, then the spirometry is considered post-bronchodilator. The bronchodilator test is performed after the administration of 400 μg of salbutamol via a pressured metered dose inhaler with a chamber. The spirometry is performed according to current standards assessing the quality of the results. Parameters recorded in absolute values and percentage predicted values are forced vistal capacity (FVC), FEV_1, FEV_1/FVC ratio, peak expiratory flow, and forced expiratory flow between 25% and 75% of the FVC. The main limitation is in relation to the non-use of advanced diagnostic techniques beyond those recommended for clinical practice.

TRACE is a prospective cohort study is an opportunity to identify specific patients who have a specific response to various treatments using tools available to any clinician. Their results may provide new information on how to make a more personalized medicine in real clinical practice.

Final declarations

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Conflicts of interest

JLLC has received honoraria during the last 3 years for lecturing, scientific advice, participation in clinical studies or writing for publications for (alphabetical order): AstraZeneca, Boehringer Ingelheim, Chiesi, CSL Behring, Esteve, Ferrer, Gebro, GlaxoSmithKline, Grifols, Menarini, Novartis, Rovi, and Teva.

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Infección pulmonar por *Lophomonas blattarum*

Lung Infection Caused by Lophomonas blattarum

Estimado Director:

Presentamos una serie de 6 casos, 4 mujeres y 2 varones, con una mediana de 57 años, todos con comorbilidades que condicionaban un estado de inmunosupresión. Ingresaron con síntomas respiratorios y una radiografía de tórax con infiltrados pulmonares compatibles con neumonía bacteriana, se les inició tratamientos antibióticos empíricos, sin obtener respuesta, con deterioro progresivo junto con cultivos negativos.

Caso 1: Paciente femenina de 18 años, derivada del área urbana con diagnóstico de empiema pleural izquierdo. Presentó una tomografía simple de tórax en la cual se observó un secuestro pulmonar infectado en lóbulo inferior izquierdo. Se le realizó una lobectomía inferior izquierda por toracotomía lateral, sin complicaciones, en el examen de la pieza quirúrgica se encontró una infección por *Lophomonas blattarum* (fig. 1), por lo que se inició tratamiento con metronidazol. La paciente presentó un postoperatorio favorable y se le dio el alta médica al quinto día, con resolución completa de su cuadro respiratorio.

Caso 2: Paciente masculino de 52 años, procedente del área rural con antecedente de insuficiencia renal crónica, que ingresó con insuficiencia respiratoria aguda grave, se le hizo un hemograma y radiografía de tórax, que fueron compatibles con neumonía adquirida en la comunidad (NAC), por lo que recibió tratamiento antibiótico empírico y oxigenoterapia, sin mejoría. Ante la falta de respuesta se decidió broncoscopia con toma de muestras. El estudio directo mostró parásitos flagelados y se inició metronidazol intravenoso con gran mejoría. El paciente completó 20 días de tratamiento domiciliario, con resolución completa del cuadro.

Caso 3: Paciente masculino de 55 años, procedente del área urbana, con antecedente de tuberculosis pulmonar en tratamiento con isoniazida y rifampicina, ingresó por un cuadro de insuficiencia respiratoria grave que requirió intubación orotraqueal. Por la alta sospecha de sobreinfección se inició antibioterapia empírica, sin mejoría. Ante la falta de respuesta se procedió a una broncoscopia y se observó al examen directo de la muestra protozoos flagelados