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# Inhaled Corticosteroids in Patients with Chronic Obstructive Pulmonary Disease and Risk of Acquiring Streptococcus Pneumoniae Infection. A Multiregional Epidemiological study

## Introduction

Chronic obstructive pulmonary disease (COPD) is often associated with an abnormal inflammatory response of the lungs[1]. Inhaled corticosteroids (ICS) in different combinations with bronchodilators have in several randomized trials showed reduction in exacerbation risk[2-5]. However, ICS appears to have minimal or no impact on decline of lung function [6] and patients without eosinophilic inflammation may not benefit from such treatment[7]. ICS treatment is known to give increased risk of clinical pneumonia[8]. Where ICS have become first-line therapy for patients with asthma, the efficacy, safety and role of ICS in the management of patients with COPD is of a more complex nature since in some patients adverse effects may outweigh the benefits [6].

Streptococcus pneumoniae (*S. pneumoniae*) is the most common cause of community acquired pneumonia. Lower respiratory tract infections due to *S. pneumoniae* is associated with a significant morbidity and mortality worldwide, particularly among elderly, immunocompromised and patients with COPD [9, 10]. The risk for pneumonia-related mortality is almost threefold higher if pneumonia was pneumococcal [10]. Patients with chronic respiratory diseases have an increased risk of acquiring a pneumococcal pneumonia (*Rate ratio 3.7-9.8*) and an increased risk of invasive pneumococcal disease (*Rate ratio 2.5-7.7*) [9].

Previously the increased risk of pneumonia related to ICS usage has been investigated by clinical or radiological defined pneumonia. In this study we used microbial samples from the lower airways therefore conceivably a more specific method than previously. It has received very little attention and is largely unknow how ICS dosage affects the risk of specific etiologies such as *S. pneumoniae.*

This study aims to determine the risk of *S. pneumoniae* infection associated with different equivalent dosages of ICS in COPD patients adjusted for age, body mass index (BMI), gender, forced expiratory volume in 1 second (FEV1)%, use of oral corticosteroids (OCS), smoking status, and year of cohort entry.

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## Hypothesis

Use of ICS in COPD is associated with an increased risk of S. pneumonia infection in a dose-dependent manner.

## Methods

### Data sources

For this study the following registries will be used:

1. The Danish Register of Chronic Obstructive Pulmonary Disease (DrCOPD) to identify patients with COPD. DrCOPD is a nationwide register that holds individual patient data on demographics and all outpatient visits and hospital admissions due to exacerbation of COPD, in patients aged 30 years or above, at all hospital-based pulmonary clinics since 2010 [10].

2. The Danish National Patient Registry (DNPR) holds data on all hospital admissions since 1977 and all hospital outpatient visits since 1995 and will be used to characterize comorbidities in the study population [11].

3. The Danish National Database of Reimbursed Prescriptions (DNDRP) was used to identify prescribed and redeemed medication, including the exposure to ICS. The DNDRP is nationwide and includes data on all reimbursed prescriptions redeemed at Danish community and hospital-based outpatient pharmacies since 2004 [12].

4. Microbiological data from the Clinical Microbiology Departments in Eastern Denmark (Region Zealand and Capital Region), consisting of approximately 2.6 million inhabitants, will be used to identify patients with S. pneumonia.

### Study design

The study will consider all patients registered with an outpatient clinic visit from 2010 to 2017 in DrCOPD. Cohort entry will be defined as the date for the patients first outpatient clinic visit in DrCOPD. Patients with only in-hospital-registrations are excluded since these registrations do not hold information on essential patient characteristics (severity of airflow obstruction, degree of

dyspnoea, body mass index and smoking status). Patients from the western part of Denmark are not included since we cannot gain access to microbiological data from these patients.

S. pneumonia infection will be defined as any positive lower respiratory tract culture (i.e. sputum, tracheal secretion, bronchial secretion and bronchial alveolar lavage) after cohort entry.

Patients with S. pneumonia-positive lower respiratory tract sample 3 months prior to cohort entry will be excluded

**Exclusion Criteria**

Patients with malignant neoplasm (International Classification of Disease (ICD)-10 codes: C00-C97) or immunodeficiency (ICS-10 codes: D80-84, D85, D89) 5 years prior to cohort entry or prescription of disease-modifying anti-rheumatics drugs (Anatomical Therapeutic Chemical (ATC)-codes: L04AX03, L01AA01, A07EC01, L04AD01, L04AA13, L04AX01, L04AA06, P01BA02) 12 months prior to cohort entry were excluded since these conditions and drugs were suspected to be associated with the study outcome and may affect the ability to interpret the results of the study exposure.

**Follow up:**

All patients were followed from cohort entry until the first S. pneumonia -positive sample, death or 31 October 2017.

**Exposure to ICS**

Exposure to ICS are quantified as the accumulated equivalent dose using all ICS prescriptions reimbursed within 365 days prior to study entry. An accumulated dose is calculated and the different ICS types are converted into budesonide-equivalent doses, ciclesonide and fluticasone propionate being converted at ratios of 2.5:1 and 2:1, respectively. Mometasone and beclomethasone were considered equivalent to budesonide.

**Statistical analysis**

The risk of P. pneumonia associated with use of ICS will be estimated by using a Cox proportional hazard regression model.

Death will be handled as a competing risk in the model since it impedes the occurrence of S. pneumonia.

Suspected confounders and markers of disease severity (to be adjusted) age, sex, severity of airway obstruction (percentage of predicted forced expiratory volume in the first second; FEV1), body mass index (BMI), smoking status, accumulated dose of oral corticosteroids 365 days prior to cohort entry and calendar year, for entry in DrCOPD

Reference group : Non-use of inhaled corticosteroids in the entire prior year.

Patients exposed to high or moderate ICS dose will be matched 1:1 with patients exposed to low or no ICS dose based in a propensity matched population based on the same variables used in the adjusted main analysis. To address missing values for the Cox and the Propensity match, these were replaced with the most common value for the given parameter this was done to minimize attrition bias.
In patients with unknown FEV1 and BMI, measurements from the first following outpatient clinic visit will be used.

Statistical analyses will be performed using SAS statistical software.

## Ethics

The study will be submitted for approval from Danish Data Protection Agency. In Denmark, retrospective use of register data does not require ethical approval or patient consent

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