Use of Inhaled Corticosteroids in Patients with Chronic Obstructive Pulmonary Disease and risk of acquiring *Haemophilus influenzae* infection

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**Introduction**

Inhaled corticosteroids seem to decrease the risk of acute COPD exacerbations in patients with some degree of eosinophilic inflammation [1-3]. However, administration of ICS is also associated with a higher risk of pneumonia in COPD patients [4] because corticosteroids dampen immune responses, which results in reduced autoimmune-mediated inflammation but also increases the susceptibility to respiratory infections such as pneumonia [5-7].

Non-typeable *Haemophilus influenzae* (NTHi) is a Gram-negative coccobacillus that commonly resides in the human airways [8]. NTHi can be found in the lower respiratory tract of 30% - 50% of COPD patients [9] and is one of the most common bacterial causes of acute exacerbation of COPD (AECOPD) [10].

A previous study showed that the inflammatory response to NTHi infection is suppressed by Budenoside, but the intracellular infection of alveolar epithelial cells and lung tissue with *Haemophilus* is also inhibited. The study focuses on cellular level but does not comment on the overall risk of infection and especially when it is associated with COPD, and neither establishes a dose-response relationship between ICS use and risk of infection[11].

To the best of our knowledge, no previous studies have clarified the risk of *Haemophilus Influenzae* infection with use of different dosages of inhaled corticosteroid in COPD patients.

**Objective:**

To clarify the association between use of inhaled corticosteroids and risk of *Haemophilus influenzae*, and whether or not there is a dose-dependent increase in the risk of infection with this bacterium.

**Hypothesis**

Use of ICS in COPD patients with severe-very severe disease is associated with an increased risk of *H. influenzae* 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 [12].

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 characterise comorbidities in the study population [13].

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 [14].

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 H. influenza.

Study population

The study will consider all patients registered with an outpatient clinic visit from 2010 to 2017 in DrCOPD.

Inclusion criteria

Cohort entry will be defined as the date for the patients first outpatient clinic visit in DrCOPD. Patients with only in-hospital-registrations will not be included 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 were not included since we could not gain access to microbiological data from these patients.

Haemophilus influenzae 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 H. influenza-positive lower respiratory tract sample 12 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 Haemophilus influenzae-positive sample, death or to the end of selected study period.

Exposure to ICS
All prescriptions for ICS, alone or in combination inhaler, redeemed 365 days prior to cohort entry will be identified. All doses of ICS will be converted to budesonide-equivalent doses: Beclomethasone and mometasone will be considered equivalent to budesonide. Fluticasone will be considered twice as potent as budesonide.

Dose-response will be assessed by dividing ICS exposure into tertiles (low, moderate and high dose) based on the accumulated dose in the year prior to cohort entry. Non-use during the entire period will be used as reference category.

**Statistical analysis**

The risk of *H. influenzae* 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 *H. influenzae*.

**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, antibiotics use and accumulated dose of oral corticosteroids 365 days prior to cohort entry and calendar year for entry in DrCOPD. (Exposure to oral corticosteroids will be divided into low and high dose categories based on the median cumulative dose.)

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

Interactions between accumulated exposure of oral corticosteroids 365 days prior to cohort entry as well as type of ICS will be tested.

Patients exposed to high or moderate ICS dose will be matched 1:1 with patients exposed to low or no ICS dose based on the same variables used in the adjusted main analysis.

In patients with unknown FEV₁ and BMI, measurements from the first following outpatient clinic visit will be used.

Patients with unknown smoking status will be classified as non-active smokers (most common among the patients with known status).

We will also do an analysis where we will ask to have *H. influenzae* cultured minimum 2 times.

**Statistical analyses will be performed using SAS Studio.**

**TIMETABLE**

The study commences January 2020 and analyses will take place in the spring of 2020. The manuscript will be submitted early in the autumn of 2020.

**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.
REFERENCES


