April 4, 2025

Risk of infection with Staphylococcus aureus with use of inhaled corticosteroids in patients with non-cystic fibrosis bronchiectasis

Andrea Arlund Filipsen[1], Karen Hougaard Frost[1], Josefin Eklöf[1], Louise Tønnesen[1], Anna Vognsen[1], Jonas Bredtoft Boel[2], Christian Østergaard Andersen[3], Ram Benny Christian Dessau[4], Sofie Lock Johansson[5], Jens-Ulrik Jensen*[1], Pradeesh Sivapalan*[1]

[1]Section of Respiratory Medicine, Department of Medicine, Herlev and Gentofte Hospital, University of Copenhagen, Hellerup, Denmark. [2]Department of Clinical Microbiology, Herlev and Gentofte Hospital, University of Copenhagen, Herlev, Denmark. [3]Department of Clinical Microbiology, Hvidovre University Hospital, Hvidovre, Denmark. [4]Research Unit of Clinical Microbiology , Zealand University Hospital, Slagelse, Denmark. [5] Section of Respiratory Medicine, Department of Medicine, Odense Universitetshospital, University of Southern Denmark, Odense, Denmark.

*Contributed equally

INTRODUCTION

Inhaled corticosteroids (ICS) are commonly prescribed for managing bronchiectasis (BE), asthma, and chronic obstructive pulmonary disease (COPD) due to their efficacy in alleviating symptoms. However, there is little evidence supporting their effect on exacerbations and lung function parameters (1,2). Moreover, ICS use is associated with side effects such as oral candidiasis, dysphonia, and an increased risk of pneumonia in patients with COPD (3,4). In addition to these concerns, the airway microbiome plays a crucial role in disease progression in BE, and the most commonly isolated bacteria from airway secretions in patients with BE include *H. influenzae, P. aeruginosa, M. catarrhalis, S. pneumoniae,* and *S. aureus* (*SA*) (5). Studies have shown that BE patients infected with *SA* often have worse outcomes, including more frequent exacerbations. However, the role of ICS in this association remains unclear. While it is well-documented that ICS use increases the risk of infections in COPD patients (2), there is limited evidence linking ICS use to an increased prevalence of *SA* or other pathogens in BE. Given the shared disruptions in airway defense mechanisms between COPD and BE, it is plausible that a similar risk exists. This study aims to determine the association between ICS use and risk of *SA* infection in non-cystic fibrosis BE.

OBJECTIVE

To clarify the association between use of inhaled corticosteroids in patient with bronchiectasis and risk of *SA*, and to determine if there is a dose-dependent increase in the risk of infection with this bacterium with increased dose of ICS.

HYPOTHESIS

Use of ICS in bronchiectasis patients is associated with an increased risk of *SA* infection in a dose-dependent manner.

METHODS

Data sources

1. 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 define the cohort as well as characterize comorbidities in the study population(6).

2. The Danish National Database of Reimbursed Prescriptions (DNDRP) will be 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 1995(7).

3. Microbiological data from the Clinical Microbiology Departments in Eastern Denmark (Region Zealand and Capital Region), consisting of approximately 2.7 million inhabitants, will be used to identify patients with a lower respiratory tract culture with *SA*. Registered data from 1st of January, 2001 to 1st of January, 2020 was used in the study.

4. The Danish Civil Registration System (CRS) includes individual information on the unique personal identification number, name, sex, date of birth and vital status.

Study population: The study will consider all patients with diagnosis of bronchiectasis from 1st of January, 2001 to 31st of December, 2018.

Inclusion criteria: Cohort entry will be defined as date of bronchiectasis diagnosis (International Classification of Disease (ICD)-10 codes: J47). Patients from the western part of Denmark will not be included since we do not have access to microbiological data from these patients. Lower airway infection with *SA* will be defined as any lower respiratory tract culture (i.e.,

sputum, tracheal secretion, bronchial secretion and bronchial alveolar lavage) positive of *SA* identified after patients' entry into cohort.

Exclusion Criteria:

- Patients with cystic fibrosis (ICD-10 codes: E84, Q33).
- Patients in whom *SA* has been cultured from lower respiratory tract samples within 12 months prior to cohort entry.
- Malignant neoplasm (ICD-10 codes: C00-C97) or immunodeficiency (ICD-10 codes: D80-84, D85, D89) 5 years prior to cohort entry.
- 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.

Outcome: *SA* was defined as any positive lower respiratory tract culture (i.e., sputum, tracheal secretion, bronchial secretion and bronchial alveolar lavage) after cohort entry.

Follow up: All patients will be followed from cohort entry until the first *SA*-positive culture, death, 365 days after inclusion or to the end of study period (31st December 2018).

ICS type	**Equivalence conversion ratio**
Beclomethasone	1:1
Momethasone	1:1
Beclomethasone HFA	1:2
Fluticasone propionate	1:2
Ciclesonide	1:2.5
Fluticasone furoate	1:10

Table 1: Budesonide equipotent doses for inhaled corticosteroids. HFA: hydrofluoroalkane.

Exposure to ICS: All prescriptions for ICS, alone or in fixed-dose combination inhalers, redeemed within 365 days prior to cohort entry will be identified. All doses of ICS will be converted to budesonide-equivalent doses. Budesonide equivalence conversion ratios for all ICS

are displayed in Table 1, as previously done by Heerfordt et al. (8). Patients receiving ICS were divided into three groups based on mean daily dose: Low (<400 ug/day), moderate (400-1,000 ug/day) and high (>1,000 ug/day)(9). Non-users of ICS during the entire study period will serve as the reference category. For the sensitivity analysis, use of ICS will be assessed as a time-dependent variable.

Statistical analysis: The risk of a lower airway infection with *SA* 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 *SA*. Suspected confounders and markers of disease severity include age, Charlson Comorbidity Index (CCI), sex, concomitant COPD/asthma (ICD-10 DJ449, DJ459) and accumulated dose of oral corticosteroids (OCS) 365 days prior to cohort entry, and calendar year for entry into the cohort. These will all be adjusted for in the model. Statistical analyses will be performed using R Statistical Software. To assess the association between use of ICS in patients with BE and risk of *SA* in a dose dependent manner, while adjusting for CCI, sex, and OCS dose, we aim to achieve a sample size of at least 7000 patients. This allows us to detect a significant hazard ratio of 1.3 between patients with low/nonuse and moderate/high use of ICS.

- *Significance level (α):* 0.05 (two-tailed test)
- *Power (1−β):* 0.80
- *Variance inflation factor*: 1.40 (R^2 = 0.28).
- *Proportion of population expected to experience an event:* 0.11
- *Proportion of sample with moderate/high dose compared to reference level:* 0.27

For sensitivity analysis, a propensity score weighted Cox proportional hazard regression model will be used. As a further sensitivity analysis, a Cox proportional hazard regression where the outcome is *SA* cultured a second time will be performed. Subgroup analyses for age, sex, COPD/asthma and antibiotic use 12 months prior to cohort entry will be performed.

Timetable and workspace: The study commences in February 2025, with analyses and manuscript preparation to take place by spring 2025. The manuscript will be submitted in June 2025 to a peer reviewed journal. The project will be written at Herlev and Gentofte Hospital at Copenhagen Respiratory Research.

ETHICS

For this study, the authors were granted access to data in nationwide registries in accordance with current Danish laws (Data Protection Agency: P-2020-1223). According to these laws, informed consent is not required for registry-based studies. The linkage between registries was done by using unique personal identification numbers, which allows an exact linkage on patient level and ensures complete follow-up.

REFERENCES

1. Choi H, McShane PJ, Aliberti S, Chalmers JD. Bronchiectasis management in adults: state of the art and future directions. Vol. 63, The European respiratory journal. 2024.
2. Kapur N, Petsky HL, Bell S, Kolbe J, Chang AB. Inhaled corticosteroids for bronchiectasis. Vol. 2018, Cochrane Database of Systematic Reviews. John Wiley and Sons Ltd; 2018.
3. Wang CY, Lai CC, Yang WC, Lin CC, Chen L, Wang HC, et al. The association between inhaled corticosteroid and pneumonia in COPD patients: The improvement of patients' life quality with COPD in Taiwan (IMPACT) study. International Journal of COPD. 2016 Nov 8;11(1):2775–83.
4. Roland NJ, Bhalla RK, Earis J, Roland N, Bhalla R. The Local Side Effects of Inhaled Corticosteroids* Current Understanding and Review of the Literature [Internet]. Available from: www.chestjournal.orgCHEST/126/1/JULY,2004
5. Chalmers JD, Chang AB, Chotirmall SH, Dhar R, McShane PJ. Bronchiectasis. Nat Rev Dis Primers. 2018 Dec 1;4(1).
6. Lynge E, Sandegaard JL, Rebolj M. The Danish national patient register. Scand J Public Health. 2011 Jul;39(7):30–3.
7. Schmidt M, Schmidt SAJ, Adelborg K, Sundbøll J, Laugesen K, Ehrenstein V, et al. The Danish health care system and epidemiological research: From health care contacts to database records. Vol. 11, Clinical Epidemiology. Dove Medical Press Ltd; 2019. p. 563–91.
8. Heerfordt CK, Rønn C, Harboe ZB, Ingebrigtsen TS, Jordan AS, Wilcke JT, et al. Inhalation devices and inhaled corticosteroids particle size influence on severe pneumonia in patients with chronic obstructive pulmonary disease: A nationwide cohort study. BMJ Open Respir Res. 2023 Sep 28;10(1).
9. Asthma: diagnosis, monitoring and chronic asthma management (BTS, NICE, SIGN) [Internet]. 2024. Available from: www.nice.org.uk/guidance/ng245