

Treatment of exacerbation in chronic obstructive pulmonary disease. A comparison of risk of hospitalization or death before and after guidelines has changed recommendations on antibiotics.

Background

Exacerbations of chronic obstructive pulmonary disease (COPD) contribute to high morbidity and mortality (1). An exacerbation of COPD is characterized by a worsening of shortness of breath, and an increased and more purulent expectoration. In less than half of the cases of exacerbation, a pathogenic bacterium is identified in the expectorate, that may have caused the deterioration. Most commonly found are *Haemophilus influenzae* and *Streptococcus pneumoniae*. The treatment of an exacerbation involves the use of bronchodilators, oxygen treatment, systemic corticosteroids and antibiotics. Antibiotics are initially used to treat bacterial infections early, shorten the course of disease, and prevent further deterioration of lung function. Thus, antibiotics are initiated in the hope that the rate of recurrence is reduced and the time period between exacerbations is prolonged. A longer interval between hospitalizations is important for the patient's life and for healthcare costs that increase with the severity and the number of COPD exacerbations (1). For severe exacerbations, it is shown that it is better for patients receiving broad spectrum antibiotics relative to placebo. For mild to moderate exacerbations, there are less clear trends (2-4). There is a desire to avoid the use of broad spectrum antibiotics in order to reduce the risk of selecting resistant strains. The use of amoxicillin instead of amoxicillin with clavulanic acid (amox / clav) in exacerbations in COPD has before been investigated, and the effect of the two antibiotics is found to be equivalent (5). However, it was a smaller Spanish study (n = 137), a different environment than Denmark and with a short follow-up period (10-30 days). Amoxicillin is considered to have a narrower activity spectrum than amox / clav but is expected to be effective against *Haemophilus influenzae* and *Streptococcus pneumoniae* in Denmark. Today amoxicillin is recommended as an empirical treatment of exacerbation of COPD in Denmark in mild to moderate cases.

Purpose

The purpose of this study is to systematically investigate, in a large Danish COPD population, whether the outcome of treating exacerbations in COPD is as good as before after switching from recommending a broad spectrum antibiotic (amox / clav) to recommend a more narrow spectrum antibiotics (amoxicillin). The main analysis compares the risk of hospitalization or death in the following 12 months in outpatient COPD patients who have received antibiotics for their exacerbation.

Material and method

Study design retrospective cohort study

1. Period: 1. January 2010 – 31. December 2013

2. Period: 1. January 2014 – 31. December 2016

The two periods with different guidelines will be compared with respect to primary endpoints. The first year after transition to the new guidelines is not included as it can not be expected that the guidelines were implemented from the first day.

Inclusion criteria:

- Verified COPD
- Age \geq 40 years

Exclusion criteria:

- First antibiotic treatment after inclusion in database with a different type of antibiotics than amoxicillin or amoxi / clav. Most commonly due to penicillin allergy.

Exposure-variable:

Antibiotic treatment for exacerbation with amoxicillin or amoxi / clav.

Primary endpoint:

- Time to hospitalization or death due to pneumonia or worsening of COPD within 12 months after inclusion date (1. event of registration in DrKOL after 1. January 2008)

Secondary endpoints:

- New treatment with other antibiotics within 14 days after initial treatment, indicating treatment failure.
- Hospitalization by other causes.
- Death by other causes.

Data collection:

Data is retrieved from the following registers:

- "Dansk Register for KOL": <http://www.rkkp.dk/om-rkkp/de-kliniske-kvalitetsdatabaser/kol/>
- Hospitalization, comorbidities and cause of death from "Landspatientregistret".
<http://www.esundhed.dk/sundhedsregistre/LPR/Sider/LPR.aspx>
- "Recept databasen".
<https://sundhedsdatastyrelsen.dk/da/registre-og-services/om-de-nationale-sundhedsregistre/sygedomme-laegemidler-og-behandling/laegemiddelstatistikregisteret>
- Departments of clinical microbiology in the capital region of Denmark

Statistic analysis:

The main analysis is performed on a cohort of COPD outpatients comparing the risk of hospitalization or death before and after implementation of new guidelines. Data are held up against a registry of prescribed drugs as to make sure the antibiotic treatment of an exacerbation was given according to guidelines. The analysis will be adjusted for sex, age, inhalation steroid, smoking status (active or not), FEV1 as percent of expected and Charlson comorbidity index.

Mortality and hospitalization in the two groups will be compared via Cox proportional hazard model as time-to-event.

Funding and approval

This study is fully financed and is a sub study under Copenhagen Unit for Respiratory Epidemiology.

References

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