STUDY PROTOCOL

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Infection with Streptococcus Pneumonia in patients with COPD and the incidence of MACE within the first 14 days following the infection – a multiregional epidemiological study.

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Background

There is evidence that acute infection increases the short term risk of vascular illness(1). This has been shown more specifically in patients with recent respiratory infection(2). With *Streptococcus pneumonia* being a prominent bacterial culprit in cases of bacterial pneumonia and with pneumonia also being a prevalent global infection, posing significant morbidity and mortality risk, it is important to examine if there is an association between the risk of vascular events after a pneumococcus infection(3).

A few initial studies have indicated an augmented risk of major adverse cardiac events (MACE) following pneumococcal infection (4)(5). This elevated risk of MACE is believed to be attributable to the heightened inflammatory response observed in individuals after a pneumococcal infection.

However, it remains uncertain if pneumococcal pneumonia is associated with an elevated risk of MACE. Further, if such a risk increase is actually present, it is unclear when, in the patient course, the risk is highest. This would be important to determine since prophylactic interventions could be tested in such a "high risk period".

Furthermore, it is important to investigate if the hypothesized association between pneumococcus infection and MACE is driven by AMI, strokes or other mace outcomes.

Therefore, the objective of this study, is to determine whether recent pneumococcal infection is associated with the emergence of a MACE event. Therefore, in a nationwide register-based study encompassing all patients diagnosed with pneumococcal infection, we explored whether the risk of MACE is elevated within the initial 14 days following infection compared to both pre-infection and more than 14 days post-infection periods.

Methods

Design

A nationwide register-based observational self-controlled case series design study. Data will be obtained from the following Danish registers:

1. The Danish Civil Registration System: All citizens acquire a unique personal identification number at birth in Denmark or when immigrating to Denmark. This number yields data on date of birth and sex. The personal identification number can be used to fuse information from other Danish registries.(6)(7)

2. The Danish National Patient Registry holds information on all admissions to Danish hospital since 1977 and all hospital outpatient clinic visits since 1995 [7]. The data from the Danish National Patient Registry can only be fused with information from other registries for patients with a Danish personal identification number.(8)

3. The Danish register of Cause of Death holds information on all deaths of citizens, who have died in Denmark since 1875.(9) The data from the Danish Register of Cause of Death can only be fused with information from other registries for patients with a Danish personal identification number. From this registry information was obtained in all contributing causes of death by diagnosis codes according to ICD-8 classification until 1994 and ICD-10 thereafter.(10)

4. The Danish Microbiology Database (MiBa) is a national database, that receives copies of reports from all Danish departments of clinical microbiology. It was established in 2013 and holds information from January 2010 until this date. The data from MiBa can only be fused with information from other registries for patients with a Danish personal identification number.(11)

Timeline and exposure

The risk interval, defined as 14 days from the date of laboratory confirmed pneumococcus infection or if applicable, from the date of hospital admission with pneumococcus infection, whichever occurs first. The control period is defined as an interval from up to 180 days before the pneumococcus infection, extending until end of available data excluding the period delineated as the risk interval. The date of the pneumococcus infection served as the index date for defining the exposure.

We included only patients with positive microbiological cultures and counted the exposed time from the date of culture. In cases where hospital admission preceded the positive culture by up to 5 days, we considered the date of admission as the starting point for the risk interval.

The self-controlled cases:

The cohort is formed using data from The Danish National Patient Registry and consists of all admissions to Danish hospital since 1977 and all hospital outpatient clinic visits since 1995 who fulfill the inclusion criteria:

Inclusion criteria are:

- Age > 18 years
- Laboratory verified pneumococcus infection from airway samples or blood culture.
- sample.

Exclusion criteria are:

- Cancer within 5 years and severe kidney disease (group 3 and 4)
- Patients from the western regions of Denmark, because we don't have access to microbiological data from that part of Denmark.

We will be making an interactions analysis with patients who has a former verified MACE, and if any interaction is proven, the groups will be stratified.

Outcomes

We will assess the following outcomes:

- **Primary:** All MACE within 14 days following the infection registered as lethal cardiovascular events (DG45, DI20, DI21, DI22, DI23 or DI24), cardiovascular events requiring revascularization (surgery diagnosed as KFNA00. KFNA20, KFNC10-30, KFNE00, KFNG02A, KFNG05 or KFNG05A) cardiovascular events requiring admission (hospitalization diagnosed as DG45, DI20, DI21, DI22, DI23 or DI24) and cardiovascular events requiring prescriptions of ADP receptor inhibitors or nitrates.

- **Secondary:** Severe MACE requiring admission registered as lethal cardiovascular events (DG45, DI20, DI21, DI22, DI23 or DI24), cardiovascular events requiring revascularization (surgery diagnosed as KFNA00. KFNA20, KFNC10-30, KFNE00, KFNG02A, KFNG05 or

KFNG05A) cardiovascular events requiring admission (hospitalization diagnosed as DG45, DI20, DI21, DI22, DI23 or DI24)

- Acute myocardial infarct AMI (DI210-A-B, DI211-A-B, DI213-A-C, DI214, DI219-A).
- Stroke (DG45)
- Cardiac arrhythmias (DI44, DI45, DI47, DI49, DI489, DI482, DI483, DI484, DI481, DI480, DR001, DI455A).

Statistics

The primary statistical analysis is unadjusted cox, and the secondary analysis is adjusted cox, both which will be based on the time adjusted self-controlled case series design. This sign is ideal for assessing the effect of transient exposures such as infections because each patient acts as its own control. Consequently, all confounders even if unmeasured, are natively controlled for as long as they do not vary within the observation period.(12)

The results will be presented as Hazard ratios (HR) with 95 % confidence intervals (CI), visualized by cumulative incidence plots and forest plots.

Publication of results

The results of the study will be published whether they are positive, negative, or inconclusive. Publication is planned in international peer-reviewed scientific journals. If publication in a peer-reviewed scientific journal is not possible, the results of the study will be published in report format, which will be made available via the Internet.

Ethical statement/approval

The study has been approved by the Danish Data Protection Agency. In Denmark, retrospective use of register data does not require ethical approval or patient consent.

References:

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