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Chronic heart failure and risk of hospitalization with pneumonia: A population-based study

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ABSTRACT

Background: Chronic heart failure may increase risk of pneumonia due to alveoli flooding and reduced microbial clearance. We examined whether chronic heart failure is a risk factor for pneumonia-related hospitalization.

Methods: In this large population-based case–control study we identified adult patients with a first-time primary or secondary discharge diagnosis of viral or bacterial pneumonia between 1994 and 2008, using health care databases in Northern Denmark. For each case, ten sex- and age-matched population controls were selected from Denmark's Civil Registration System. We used conditional logistic regression to compute relative risk (RR) for pneumonia-related hospitalization among persons with and without pre-existing heart failure, overall and stratified by medical treatment. We controlled for a wide range of comorbidities, socioeconomic markers and immunosuppressive treatment.

Results: The study included 67,162 patients with a pneumonia-related hospitalization and 671,620 population controls. The adjusted OR for pneumonia-related hospitalization among persons with previous heart failure was 1.81 (95% confidence interval (CI): 1.76–1.86) compared with other individuals. The adjusted pneumonia RR was lower for heart failure patients treated with thiazides only (adjusted OR = 1.56, 95% CI: 1.46–1.67), as compared with patients whose treatment included loop-diuretics and digoxin as a marker of increased severity (adjusted OR = 1.95, 95% CI: 1.85–2.06) or both loop-diuretics and spironolactone (adjusted OR = 2.02, 95% CI: 1.90–2.15). The population-attributable risk of pneumonia hospitalizations caused by heart failure in our population was 6.2%.

Conclusions: Patients with chronic heart failure, in particular those using loop diuretics, have markedly increased risk of hospitalization with pneumonia.

1. Introduction

Hospitalizations with pneumonia have increased by up to 50% in Western populations during the past 15 years [1–3], and pneumonia is a leading cause of death [4–6]. The prevalence of many chronic diseases has increased because of lifestyle factors, population aging, and longer disease survival [7]. This increase is expected to contribute to a further rise in pneumonia hospitalizations, both in the Western world [8] and in developing countries [9].

Chronic heart failure may be a major risk factor for hospitalization with pneumonia, yet population-based studies on this association are few [10–15]. Persons with heart failure may have increased susceptibility to severe pneumonia for several reasons [8]. Alveoli flooding may interfere with normal physiological mechanisms operating in the alveolar lining fluid at the interphase between air and the lung tissue (including effective opsonins and macrophages), thus hampering microbial clearance and increasing the risk of bacterial infection [16]. Also, pneumonia may induce or worsen heart failure and cardiogenic pulmonary edema as cardiac output fails to meet the needs during infection, increasing the risk of being hospitalized with pneumonia [1].

A few cohort and case–control studies have included heart failure on a list of predictors for pneumonia, with widely varying relative risk estimates between 1.5 and 3.8 [11–13,17]. Studies on the effect of the severity of heart failure on the risk of pneumonia are, to our knowledge, absent. Bearing in mind that pre-existing heart failure increases risk of death following pneumonia by 30–50% [8,18,19], it is important to investigate heart failure as risk factor for pneumonia and to clarify which patients are at particularly increased risk. We undertook a large population-based case–control study to assess these associations.

2. Materials and methods

We conducted this study in the Danish counties of North Jutland and Aarhus, with a mixed rural and urban population of approximately 1.15 million people. The Danish National Health service provides tax-supported health care for all residents, including free access to primary care and hospitals, and reimbursement of a portion of the

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cost of most prescription drugs [20]. Civil registration numbers, unique identifiers assigned to each Danish citizen, which encode birth date and sex, allow accurate linkage among registries.

2.1. Identification of patients hospitalized with pneumonia

Hospital registries in Aarhus and North Jutland counties contain information on all hospitalizations since 1977 and on all outpatient visits since 1995. Data include dates of admission and discharge and up to 20 discharge diagnoses coded by physicians according to the International Classification of Diseases (10th revision (ICD-10) during the study period and 8th revision (ICD-8) before 1994). We identified all hospitalized in-patients aged 15 years or older who had lived in the counties at least 12 months before admission and who had one of the following first-time primary (first-listed) or secondary discharge diagnoses recorded between 1997 and 2005: viral or bacterial pneumonia (J12.x–J18.x), legionellosis (A481.x), or ornithosis (A709.x) [1]. We thus aimed to include both community-acquired pneumonia (CAP) and hospital-acquired pneumonia (HAP) episodes, since chronic heart failure may increase the risk for both.

2.2. Selection of population controls

The Central Population Registry, which is updated daily, contains electronic records of all changes in vital status, including change of address, date of emigration, and date of death, for the entire Danish population since 1968. On the date of each patient's first pneumonia-related hospital admission (the index date), we selected 10 controls from the Central Population Registry, matched by age (same year of birth), sex, and residence (the same county). We employed the risk set sampling technique [21], i.e., eligible controls had to be alive and at risk of a first hospitalization with pneumonia as recorded in their hospitalization history on the date the corresponding case was admitted.

2.3. Data on heart failure

For both cases and controls, we identified persons with pre-existing heart failure from the counties' hospital registries, as previously explained [8]. Heart failure was defined as a previous hospital registry diagnosis or outpatient diagnosis of congestive heart failure; pulmonary edema with mention of heart failure; left ventricular failure; unspecified heart failure; cardiomyopathy; or hypertensive heart disease with congestive heart failure (with or without hypertensive renal disease or renal failure). We considered diagnoses recorded within five years preceding (but not including) the date of hospitalization for pneumonia (see Appendix A for specific ICD codes). We further disaggregated patients with heart failure into five subcategories of heart failure-related conditions: 1) cardiomyopathy (with or without any of the following diagnoses); 2) heart valve disease (with or without any of the other diagnoses except cardiomyopathy); 3) myocardial infarction (with or without atrial fibrillation); 4) atrial fibrillation only; and 5) none of the above diagnoses.

Databases containing information on prescriptions for all reimbursed drugs dispensed from pharmacies in the counties [22] permitted us to classify the heart failure patients according to preadmission medication use. We used the intensity of medical treatment as a surrogate measure of increasing heart failure severity. According to Danish, European and North American treatment guidelines in force at the time of our study [23,24], thiazides should be preferentially prescribed for mild heart failure only, whereas loop-diuretics should be used in all other cases. Digoxin could be used in patients with severe left ventricular dysfunction already treated with other heart failure drugs, whereas spironolactone is preferentially prescribed to the most severe subset of patients. Based on these considerations and observed prevalence of preadmission medication use, we classified treatment as follows: 1) thiazide-based regimens without loop-diuretics; 2) loop-diuretic-based regimens excluding digoxin and spironolactone; 3) loop-diuretic-based regimens including digoxin but not spironolactone; 4) loop-diuretic-based regimens including spironolactone; 5) other heart failure medications not including any diuretics (at least one prescription for slow-acting nitrates, ACE inhibitors, angiotensin reuptake blockers, or oral anticoagulants); and 6) none of the above heart failure medications [see Appendix A for specific ATC codes].

2.4. Data on potential confounding factors

We obtained data on comorbidity and other covariates from the hospital and prescription databases. For each case and control subject, we collected data on 19 different major disease categories (except heart failure) as included in the Charlson comorbidity index [25]. Disease categories include major risk factors for pneumonia such as chronic obstructive pulmonary disease, previous cardiovascular and cerebrovascular diseases, diabetes, cancer, and HIV/AIDS. We assessed the presence of these conditions based on the complete hospital discharge history before the pneumonia hospitalization [26]. We then defined three comorbidity levels as low (Charlson score of 0), medium (1–2), and high (3+). We also collected hospital registry data on previous alcoholism-related disorders (yes/no) not included in the Charlson index. We furthermore retrieved data on prescriptions for immunosuppressive drugs, including corticosteroids prescribed within one year, and systemic antibiotics prescribed within 6 months prior to the hospitalization with pneumonia. The Central Population Registry provided data on marital status (married, never married, divorced or widowed, marital status unknown), persons living with small children attending day care centers (younger than 6 years of age, yes/no), and degree of urbanization (residence in a rural area with a population of 0–10,000, in a provincial town with a population of 10,000–100,000, or in a city with more than 100,000 inhabitants).

2.5. Statistical analysis

We used conditional logistic regression to compute crude and adjusted odds ratios (OR) as a measure of the incidence rate ratio for pneumonia-related hospitalization among persons with and without heart failure, with associated 95% confidence intervals (CI). In subsequent models, heart failure exposure was further subcategorized according to the preadmission heart failure medications, and heart failure-related conditions. In all models, we adjusted for the potential confounding effect of comorbidities, history of alcoholism-related conditions, pre-admission use of antibiotics or immunosuppressant, marital status, household presence of small children attending day care centers, and degree of urbanization. The population-attributable pneumonia risk from heart failure was calculated as $P \times (OR - 1) / ([P \times (OR - 1)] + 1)$, where $P =$ prevalence of heart failure in controls.

All analyses were conducted using the SAS software. The Danish Data Protection Agency approved the study (record no. 2009-41-3866).

3. Results

3.1. Descriptive data

We identified 67,162 patients with a first incident pneumonia-related hospitalization and 671,620 population controls (Table 1). The study population was 53% male and 47% female, with a median age of 73 (interquartile range 60 to 81) years. A total of 12,339 pneumonia cases (18.4%) and 53,989 controls (8.0%) had a previous diagnosis of heart failure. Compared with their age-matched population controls, pneumonia cases were much more likely to have a history of any hospital-diagnosed comorbidity (61% vs. 34%), in particular chronic pulmonary disease, cancer and vascular diseases. Cases were also much more likely to have recently used immunosuppressants including corticosteroids or antibiotics, and were more likely to be unmarried (Table 1).