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Gram-negative bacteremia as a clinical marker of occult malignancy

Kirstine K. Søgaard [a,*], Dóra K. Farkas [a], Mette Søgaard [a], Henrik C. Schønheyder [b,c], Reimar W. Thomsen [a], Henrik T. Sørensen [a]

[a] *Department of Clinical Epidemiology, Aarhus University Hospital, Olof Palmes Allé 43-45, 8200 Aarhus N, Denmark*
[b] *Department of Clinical Microbiology, Aalborg University Hospital, Mølleparkvej 10, 9000 Aalborg, Denmark*
[c] *Department of Clinical Medicine, Aalborg University, Søndre Skovvej 15, 9000 Aalborg, Denmark*

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Summary *Objectives:* Gram-negative bacteremia may be a harbinger of occult cancer. We examined the risk of cancer following hospitalization with bacteremia.
Methods: Using medical databases, we conducted a nationwide population-based cohort study of all Danes with a discharge diagnosis of Gram-negative bacteremia during 1994—2013. We calculated absolute risks and standardized incidence ratios (SIRs) of cancer, comparing the observed risk to that expected in the general population.
Results: We observed 1379 cancers vs. 988 expected among 11,753 patients with Gram-negative bacteremia, corresponding to an overall SIR of 1.40 (95% confidence interval (CI): 1.32—1.47). During the first 6 months following the bacteremia diagnosis, the SIR for cancer was 3.33-fold (95% CI: 2.99—3.69) increased, corresponding to an absolute risk of 3.05%. The increased risk stemmed mainly from higher than expected occurrence of gastrointestinal cancer (3- to 13-fold higher), genitourinary cancer (4- to 10-fold higher), non-Hodgkin lymphoma (5-fold higher), non-specified metastatic cancer (5-fold higher), and breast and lung cancer (2-fold higher). The 6—12 months SIR for any cancer was 1.46 (95% CI: 1.22—1.72), and beyond 1 year of follow-up, the SIR declined to 1.13 (95% CI: 1.05—1.20).
Conclusions: Gram-negative bacteremia is a clinical marker of occult cancer.

* Corresponding author.
E-mail address: kks@clin.au.dk (K.K. Søgaard).

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Introduction

Gram-negative bacteria are a common cause of bloodstream infections in the western world.[1,2] The most frequent source of Gram-negative bacteremia is urinary tract infection, followed by gastrointestinal or pulmonary infection,[1,2] but the source remains unidentified in around 20–30% of cases.[3,4] Importantly, bacteremia may be the first sign of an unrecognized cancer. Disruption of the normal mucosal barrier caused by tumor growth, or obliteration of bile ducts or collecting ducts, can facilitate hematogenous spread of coexisting bacteria.[5,6]

Although evidence is limited, some bacteria are thought to have carcinogenic properties,[7] and colonization or infection with these bacteria possibly predict long-term increased cancer risk. Case-reports and small cohort studies have suggested a link between specific Gram-positive organisms and colorectal cancer.[8–11] The pathomechanism could be bacterial ability to attach to preneoplastic lesions in the colonic mucosa, promoting malignant progression of epithelial cells.[6] Lower urinary tract infection may be associated with an increased risk of bladder cancer.[12] The potential mechanism is inflammation-related production of nitric oxide, which promotes tumor growth and proliferation.[13] The finding of reduced cancer risk associated with antibiotic treatments after cystitis supports such a direct effect.[12]

To date, no studies have examined whether an episode of Gram-negative bacteremia is a clinical marker of occult cancer using a comparison cohort. We therefore conducted a population-based cohort study to examine absolute and relative cancer risk among patients with Gram-negative bacteremia compared with that in the general population.

Methods

Data sources and study population

This cohort study was based on the cumulative population of approximately 7 million persons in Denmark between 1994 and 2013. The Danish healthcare system provides tax-funded medical care to all Danish residents and guarantees free access to hospitals and outpatient clinics.[14] We used data from the Danish National Patient Registry (DNPR),[15] coded according to the International Classification of Diseases (ICD), Eighth Revision (during 1977–1993) and Tenth Revision (since 1994). In the DNPR, the main condition prompting a hospital admission is recorded as the primary diagnosis, whereas other conditions or diseases are recorded as secondary diagnoses.[15]

In the current study, we identified patients with a first episode of Gram-negative bacteremia between January 1, 1994 and November 30, 2013, using the ICD-10 diagnosis code "septicemia/sepsis due to other Gram-negative organism". This code has an overall positive predictive value for Gram-negative bacteremia of 86%.[4] We then restricted the cohort to patients with a primary discharge diagnosis of Gram-negative bacteremia, and excluded patients with an earlier diagnosis of this condition during the 1977–1993 period to avoid including recurrent cases.

Using ICD-8 and ICD-10 codes, we retrieved information from the DNPR starting in 1977 on comorbidities characterizing the study cohort. These included diabetes, chronic kidney disease, and chronic liver disease. We also identified patients with an inpatient or outpatient hospital contact for urologic or gastrointestinal infection within the 30 days prior to the hospitalization for Gram-negative bacteremia. As well, we extracted information on surgical or endoscopic gastrointestinal or urologic interventions, urinary catheterizations, and imaging examinations performed within 30 days before or during the hospitalization for Gram-negative bacteremia. Our motivation for documenting patients with interventions and imaging examinations was the possibility that they had other symptoms suspicious of cancer, or that the interventions themselves provoked the bacteremia. We retrieved information on secondary diagnoses (grouped as defined in the ICD-system) recorded during the same admission, to explore the prevalence of concurrent diseases or conditions indicating an underlying focus or risk factors for the bacteremic episode.

Cancer

Since 1943 all new cancer cases in Denmark have been recorded in the Danish Cancer Registry (DCR),[16] currently classified according to ICD-10 codes. We identified all incident cancers among members of the Gram-negative bacteremia cohort by linking data between the DNPR and the DCR. Patients with a previous cancer diagnosis (other than non-melanoma skin cancer) were excluded. We grouped cancers as gastrointestinal (cancers of the esophagus, stomach, small intestine, colon (including rectosigmoid colon), rectum, anus, liver, gallbladder, and pancreas), genitourinary (cancers of the kidney, renal pelvis, ureter, urinary bladder, and prostate), and other cancers.

All ICD and procedure codes used in the study are provided in the Appendix (see Supplementary data).

Statistical analysis

Patients were followed for cancer occurrence starting from the date of their first-time inpatient hospitalization with a primary discharge diagnosis of Gram-negative bacteremia until the date of death or November 30, 2013, whichever came first. We described the characteristics of Gram-negative bacteremia patients, including distributions and frequencies of gender, age categories (<40, 40–59, 60–79, and 80+ years), calendar period of bacteremia diagnosis (1994–1998, 1999–2003, 2004–2008, and 2009–2013), and the covariates discussed above. We computed median follow-up time and median age at inclusion [with interquartile range (IQR)].

Standardized incidence ratios (SIRs) were used as a measure of relative risk, comparing cancer incidence observed among patients with Gram-negative bacteremia with that expected in the entire Danish population. Expected numbers of cancer cases were estimated based on national cancer incidence rates by age (5-year age groups), sex, and calendar year (5-year periods). We computed confidence intervals (CIs) for SIRs using Byar's approximation.[17] Exact 95% CIs were used when the