Risk Factors for Septicemia-Associated Mortality in Older Adults

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Synopsis

Septicemia is the 10th leading cause of death among older adults in the United States; its mortality rate has steadily increased over the past decades. Little is known about factors which predispose to septicemia mortality in the elderly.

The authors investigated risk factors for septicemia-associated mortality in 10,269 older adults as part of a longitudinal study of three communities (East Boston, MA; New Haven, CT; and Iowa and Washington Counties, IA). During 6 years of followup, 177 persons (3.2 per 1,000 person-years) had septicemia ICD9 038 (International Classification of Diseases, ninth revision) reported on their death certificate.

In a multivariate proportional-hazards model, septicemia mortality was significantly ($P<0.05$) and independently associated with age, male sex, history of diabetes, history of cancer requiring hospitalization, smoking one pack of cigarettes per day or more, not drinking alcohol in the year prior to baseline, disability in activities of daily living, cognitive impairment, and missing cognitive testing score. These factors might be useful in developing an at-risk population for testing septicemia treatment or prevention strategies in a community setting. Further investigation is needed to explain underlying mechanisms of increased risk of subsequent septicemia.

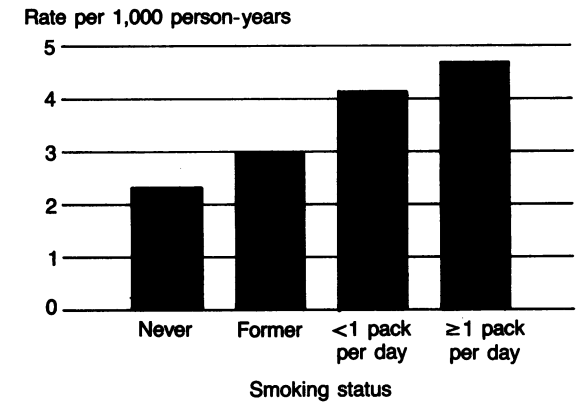
SEPTICEMIA IS the 13th leading cause of death in the United States and the second leading infectious cause of death. Among persons ages 65 or more years, septicemia was the 10th leading cause of death and accounted for more than 16,000 deaths (81 percent of all septicemia deaths) in 1988 (*1*). Continuing an increasing trend observed for at least five decades, the septicemia mortality rate doubled during the 1980s, to an age-adjusted rate of 4.6 per 100,000 (*1,2*).

The hospitalization rate for septicemia also doubled during the 1980s, increasing to the point that 425,000 hospitalizations mentioned the diagnosis in a single year (*3*), including more than 100,000 among older Medicare beneficiaries (*4*). In 1988, septicemia ranked 18th on a list of leading hospital discharge diagnoses among older Medicare beneficiaries and ranked 8th among those ages 85 years and older (*4*). The mortality rate for patients hospitalized with septicemia is approximately 25 percent (*3*). Between $5 and $10 billion are spent annually for treatment and the associated costs of septicemia (*5*).

The etiology of septicemia is commonly associated with the risks of high technology medicine. The increasing case rates have been attributed to the increasing number of immunocompromised individuals at risk for the illness, greater use of invasive procedures and medical devices, and a higher index of suspicion accompanied by greater recognition through diagnostic tests (*2*). Although much attention has been focused on hospital-acquired septicemia cases, population-based studies suggest that, in fact, the majority of cases are community-acquired (*6,7*). Moreover, the continued importance of mortality in the elderly attributed to infections, including septicemia, may reflect its role as a "terminal illness" among elders with chronic disease (*8*).

Population-based studies of septicemia have

Septicemia-associated mortality rate per 1,000 person-years according to smoking status at baseline



Note: Rates were age-adjusted.

rarely been conducted (*9*). Consequently, community-based risk factors for septicemia are not well described, with the exception of advancing age, black race, and male sex (*1–4,10*). Studies of pneumococcal bacteremia in Charleston, SC, (*6,11*) confirmed these demographic associations and suggested that the increasing bacteremia rates between 1974 and 1986 were largely confined to the very young and the oldest old. Clinical studies have identified other risk factors for pneumococcal septicemia mortality, including prior splenectomy, alcoholism, and other chronic diseases such as cancer (*12–14*). Further, the virulence of the infectious organism may be reflected in increased case-fatality rates for nosocomial bloodstream infections (*15*).

We investigated risk factors for septicemia-associated mortality in older adults living in the community, focusing on the role of health habits and chronic conditions including disease, functional disability, and cognitive impairment. By using baseline risk factors, we could examine the relation of chronic conditions with septicemia as a terminal event. The Established Populations for the Epidemiologic Studies of the Elderly (EPESE) provide an opportunity to examine prospectively collected data from three communities.

Materials and Methods

The data come from three EPESE communities which are part of a collaborative longitudinal study of older men and women, initiated and funded by the Epidemiology, Demography and Biometry Program of the National Institute on Aging. Descriptions of the populations studied and the methods employed have been previously published (*16–19*). Briefly, between 1981 and 1983, more than 10,000 noninstitutionalized participants ages 65 or more years were enrolled in East Boston, MA; Iowa and Washington Counties, IA; and New Haven, CT. Initial interviews were completed with 80–84 percent of eligible community residents using population surveys in East Boston and rural Iowa and a stratified random sample (housing type, sex) in New Haven. Trained interviewers conducted the household baseline surveys and six annual followup interviews.

The followup ascertained major outcomes, including vital status, which first came from interviews with proxies and was augmented by use of the National Death Index. We requested copies of death certificates, and a single nosologist coded their information using the ninth revision of the International Classification of Diseases (ICD9) (*20*). Cases of septicemia (ICD9 038) were identified from the underlying, immediate, and contributing cause of death fields on the death certificate. This reflects the total occurrence of septicemia at the time of death (*10*).

In this study, we chose potential risk factors based on both their availability in the baseline survey and hypothesized connections with septicemia-related mortality in older adults. During the initial interview, information on age, sex, race, chronic conditions diagnosed by a health care provider, health habits, and disability measures were obtained. Smoking status was classified as current smoker, former smoker, or never smoker. Number of cigarettes smoked per day by current smokers was grouped as less than 20 or 20 or more to examine intensity of smoking.

A lifetime history of each of five conditions (heart attack, stroke, cancer, diabetes mellitus, and hip fracture) was coded as present if the participant reported that a health care provider said that the diagnosis was definite. Diagnosis of cancer accompanied by hospitalization was examined as a marker of more severe disease. Use of medications for congestive heart failure (CHF) was examined since participants had not been questioned regarding the condition; it was considered positive if the participant reported taking both a digitalis preparation and a diuretic agent during the preceding 2 weeks.

Body-mass index was computed as weight (kilogram [kg]) divided by the square of height (meter [m]) from self-reported data and divided into quartiles. Alcohol consumption in the previous year was assessed by combining questions pertaining to intake of beer, wine, and liquor. If the participant

Table 1. Septicemia mortality rates according to age and sex, Established Populations for the Epidemiologic Studies of the Elderly, 1981–88

Sex and age group (years)	Number of deaths		Number of person-years	Mortality rate[1,2]	
	Underlying	All mentions		Underlying	All mentions
Men:					
65–74	7	25	10,658	0.7	2.3
75–84	5	35	7,794	0.6	4.5
85 and older	4	23	1,987	2.0	11.6
Total	16	83	20,439	0.77	3.9
Women:					
65–74	7	15	15,343	0.5	1.0
75–84	15	44	14,225	1.1	3.1
85 and older	12	35	4,620	2.6	7.6
Total	34	94	34,188	0.84	2.2

[1] Rate per 1,000 person-years. [2] Rate for total is age-adjusted.

was unable to climb a flight of stairs, perform heavy housework, or walk a half-mile without help, disability was considered present (*21*). Limitations in six activities of daily living (ADLs—walking, bathing, dressing, eating, transferring from bed to chair, and using the toilet) were coded as the sum (0, 1, or 2 or more) of those that the individual was unable to perform or required help from another person (*22,23*).

Cognitive function was evaluated with the Short Portable Mental Status Questionnaire (SPMSQ) (*24,25*) and classified as follows: no impairment (0–2 errors, scored as 0), mild-moderate impairment (3–4 errors, scored as 1), and severe impairment (5 or more errors scored as 2). The SPMSQ was not asked of proxy respondents.

The final sample included initial interviewees with up to 6 years of followup, excluding those without both a followup interview and a known date of death. This sample comprised 10,269 participants: 3,809 in East Boston, 3,663 in Iowa, and 2,797 in New Haven.

Statistical Methods

Septicemia mortality incidence rates (per 1,000 person-years) were examined according to age and sex, directly age-adjusted to the standard population of the three sites combined (*26*). Cox proportional-hazards regression models were used to calculate the relative risk (RR) for the measures of interest (separate models for sociodemographic factors, chronic diseases, health behaviors and body-mass index, and functional status measures) adjusted for age and sex. The final model computed overall estimates of RR using those variables from the initial models which were significant ($P<0.1$). Analyses were stratified by community using the blocking option of SAS PROC PHGLM (*27*).

'Death rates from septicemia increased with age. The male-female ratio was approximately 1 for septicemia as underlying disease but greater than 1 for all septicemia mentions. The septicemia-associated death rate (per 1,000 person-years) ranged from 2.3 in never smokers to 4.6 in heavy smokers.'

Results

During 6 years of followup, 177 persons (83 men and 94 women) had septicemia reported on their death certificate, representing 5 percent of all deaths. Fifty (28 percent) participants, 16 men and 34 women, died with septicemia as the underlying cause; in 92 percent, the organism was not specified. Septicemia-associated deaths due to other underlying causes occurred in all major disease categories, including 29 circulatory system, 23 cancer, and 21 pneumonia-influenza. Sites of infection noted on the death certificate of those with septicemia included the lung and the urinary and gastrointestinal tracts and others.

Death rates from septicemia increased with age (table 1). The male-female ratio was approximately 1 for septicemia as underlying disease but greater than 1 for all septicemia mentions. The septicemia-associated death rate (per 1,000 person-years) ranged from 2.3 in never smokers to 4.6 in heavy smokers (see figure).

Table 2. Relation of chronic disease, health behavior, and disability risk factors to septicemia mortality, Established Populations for the Epidemiologic Studies of the Elderly, 1981–88

Category	Relative risk[1]	95 percent CI[2]
	Sociodemographic Model[3]	
Age (10-year difference)	2.0	1.6, 2.4
Sex, male	1.6	1.2, 2.2
Race, black	1.2	0.8, 1.9
	Chronic Diseases Model[4]	
History of:		
Diabetes	2.2	1.5, 3.1
Cancer with hospitalization	1.5	1.0, 2.3
Hip fracture	1.8	1.0, 3.2
Stroke	1.7	1.0, 2.8
Heart attack	1.0	0.6, 1.5
Congestive heart failure medication use	1.4	0.9, 2.2
	Health Behaviors and Body-Mass Index Model[4]	
Smoking status (number of cigarettes per day):		
Never (reference group)	1.0	...
Former	0.8	0.4, 1.6
Current (less than 20)	0.9	0.3, 2.7
Current (20 or more)	2.1	1.0, 4.4
Alcohol consumption in previous year: yes	0.4	0.2, 0.7
Body-mass index:		
Lowest quartile (reference group)	1.0	...
Second quartile	0.5	0.2, 1.1
Third quartile	0.6	0.3, 1.3
Highest quartile	0.6	0.3, 1.3
	Physical and Cognitive Function Model[4]	
Ability to climb stairs, walk one-half mile, and do heavy housework: disability	1.4	1.0, 2.0
Activities of daily living: disability[5]	1.5	1.1, 2.0
Cognitive function:		
Impairment[6]	1.6	1.3, 2.0
SPMSQ missing	2.0	1.2, 3.6

[1] Relative risks computed from Cox regression models based on septicemia-associated deaths of 177 persons.
[2] CI = confidence interval.
[3] Relative risks adjusted for main effects shown and education.
[4] Relative risks adjusted for main effects shown plus age and sex.
[5] Coded as the number of limitations: 0 = 0, 1 = 1, 2 = 2 or more. Relative risk shown for 1 limitation.
[6] Coded as the number of errors on Short Portable Mental Status Questionnaire (SPMSQ): 0 = no impairment, 1 = mild-moderate impairment, 2 = severe impairment. Relative risk shown for mild-moderate impairment.

Age and male sex were associated with septicemia-related mortality (table 2). Race and educational attainment were not associated with mortality from septicemia in this largely white cohort (less than 6 percent black and less than 1 percent other racial groups). We initially examined separate models including history of chronic diseases, health behaviors, body-mass index, and functional status measures (table 2) and developed a final model using variables from the initial models significant at the $P<0.1$ level.

In the final model, septicemia mortality was significantly ($P<0.05$) and independently associated with age, history of diabetes, history of cancer requiring hospitalization, current heavy smoking (20 cigarettes or more per day), not drinking alcohol in the year prior to baseline, disability in activities of daily living, cognitive impairment, and missing SPMSQ score (table 3). The RRs related to disability in this final model were quite similar to those in the initial analysis (table 2). Three factors were significantly ($P<0.05$) associated with septicemia mortality in single sites, but not in the final model: hip fracture (Iowa), stroke (New Haven), and inability to walk a half-mile, climb stairs, or do heavy housework without help (East Boston). All other variables significantly associated in the sites exhibited consistent relationships in the final model (data not shown).

To confirm the results, we limited the analysis to cases in which septicemia was the underlying cause of death in another multivariate Cox proportional-hazards model, using the same dependent variables as in the final model. The results were consistent with the analyses reported previously, and statistically significant for the following variables: diabetes, cognitive impairment, and missing SPMSQ score (data not shown).

We examined the reported site of death and any evidence of a nursing home stay after baseline to assess the role of institutional setting in septicemia mortality. Of the 177 participants who died with septicemia, 154 (87 percent) died in a hospital, and 18 (10 percent) in a nursing home; among all other deaths, 61 percent died in a hospital, and 21 percent in a nursing home. Seventy-three septicemia-related deaths (41 percent) had evidence of a nursing home stay, compared with 34 percent among all other deaths.

Discussion

Septicemia occurred quite frequently at the time of death in this longitudinal study of elders in three communities. The age-adjusted septicemia mortality rate (underlying cause of death) was 82 per 100,000 in this study, higher than the rate of 54 nationally in 1988 (*1*). Five percent of death certificates in the study mentioned septicemia, which exceeds the 3 percent reported nationally (*10*). This percentage enhanced the statistical power of the study and allowed us to analyze a number of potential risk factors, although it may limit the generalizability of our results. Cognitive impairment, heavy smoking, and diabetes mellitus were the strongest risk factors

for septicemia mortality established in this analysis, based on high RR and consistency in the analyses. While men appeared to have greater septicemia death rates, the results were not consistent with the analysis of underlying cause of death. There was low statistical power to find a relation between race and septicemia because only 6 percent of the cohort were African Americans (*19*).

Several other limitations also deserve consideration. The physician nearly always reported septicemia without specifying the organism on the death certificate. Underreporting of septicemia on the death certificate is very likely. We could not determine whether the infection was acquired in the community or in an institution. The septicemia case-fatality rate is lower for community-acquired infections than for the hospital-acquired (*5*), and it is possible that risk factors could differ depending on where the infections was acquired. Self-reported diagnoses such as diabetes may have some imprecision, but we believe this was rare and would have only a small effect on our conclusions.

The prospective nature of this study allowed for the examination of a variety of medical, functional, and behavioral risk factors that would put persons at risk for septicemia mortality well in advance of its occurrence. This study is exploratory in nature, and we examined a number of plausible risk factors. The associations between baseline factors and subsequent septicemia mortality suggest causality, but we recommend confirmation prior to such an interpretation.

The outcome measure, septicemia at the time of death, combines two related but distinct occurrences: bloodstream infection and death. Thus, the correlations we observed could have resulted from an association of the risk factors with either an initial infection, progression to bacteremia, or the case fatality of the infection. More detailed studies are required to delineate the causal pathways.

This is the first report describing an association between smoking and septicemia mortality. However, this finding may reflect the absence of large population studies of older smokers, because most septicemia deaths occur in that age group. Former smokers had the same risk as nonsmokers for septicemia mortality, and the data suggest a possible increase in risk with heavier smoking among current smokers. Smoking has been associated with deaths due to pneumonia (*19*) and all causes (*17*) as well as development of respiratory infections (*28*) and pressure sores (*29*). Smoking alters cell-mediated immune function and antibody levels

Table 3. Final model of relation of chronic disease, health behavior, and disability risk factors to septicemia mortality, Established Populations for the Epidemiologic Studies of the Elderly, 1981–88

Category	Relative risk[1]	95 percent CI[2]
Age (10-year difference)	1.8	1.4,2.3
Sex, male	1.9	1.3,2.6
History of:		
Diabetes	2.0	1.4,2.9
Cancer with hospitalization	1.6	1.1,2.5
Hip fracture	1.5	0.9,2.7
Stroke	1.3	0.8,2.2
Smoking status (number of cigarettes per day):		
Never smoker (reference group)	1.0	...
Former smoker	1.0	0.7,1.5
Current smoker (less than 20)	1.6	0.9,2.8
Current smoker (20 or more)	2.2	1.3,3.6
Alcohol consumption in previous year: yes	0.6	0.4,0.8
Ability to climb stairs, walk one-half mile and do heavy housework: disability	1.2	0.9,1.7
Activities of daily living: disability[3]	1.4	1.0,1.9
Cognitive function:		
Impairment[4]	1.6	1.3,2.0
SPMSQ missing	2.3	1.3,4.0

[1] Relative risks computed from Cox regression models including all main effects shown based on septicemia-associated deaths of 177 persons.
[2] CI = confidence interval.
[3] Coded as the number of limitations: 0 = 0, 1 = 1, 2 = 2 or more. Relative risk shown for one limitation.
[4] Coded as the number of errors on Short Portable Mental Status Questionnaire (SPMSQ): 0 = no impairment, 1 = mild-moderate impairment, 2 = severe impairment. Relative risk shown for mild-moderate impairment.

'We examined the reported site of death and any evidence of a nursing home stay after baseline to assess the role of institutional setting in septicemia mortality. Of the 177 participants who died with septicemia, 154 (87 percent) died in a hospital, and 18 (10 percent) in a nursing home; among all other deaths, 61 percent died in a hospital, and 21 percent in a nursing home.'

(*28*), which may plausibly explain our results. It would be important to know if older adults could decrease their risk of bloodstream infection by stopping smoking.

Severe cognitive impairment, inability to complete the cognitive screening test, and two or more ADL limitations were associated with a twofold or

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greater risk of septicemia mortality. The consequences of severe physical disability or cognitive impairment include inability to care for oneself, depression of consciousness, and admission to a nursing home, any of which may predispose to septicemia. For example, cognitive impairment from Alzheimer's disease might eventually depress consciousness enough to affect the gag reflex and lead to aspiration and lung infection. Altered mental status may facilitate development of decubitus ulcers and subsequently bloodstream infections. Inability to care for oneself may result in nutritional or immunologic deficits, or both, which can impair resistance to infection (*8*). Finally, physical and cognitive impairment frequently lead to admission to a nursing home (*18*), where the risk of institutionally acquired infection may increase substantially.

To our knowledge, this is the first report associating diabetes with septicemia mortality in a population-based study. A recent report on the mortality of diabetics (*30*) did not find any relationship with septicemia mortality. Although the mechanism is not clear, diabetics frequently develop skin infections and neuropathic foot ulcers, and immunologic abnormalities have been reported which could increase the risk of bloodstream infections.

We found that those who had consumed alcohol in the previous year were at lower risk for septicemia mortality than those who had not consumed alcohol. While some clinical reports associated alcoholism with septicemia (*14*), others have reported no relation with case-fatality rates (*12,13*). Among the elderly, nondrinkers include both never drinkers and persons who have quit drinking. Early selective mortality among heavy drinkers (*31*) may subsequently lower mortality among the nondrinkers and explain these results, although we cannot exclude the possibility that participants may have misreported their consumption.

In this study, the hypothesized risk factors were determined well in advance to predict septicemia as a terminal event. This procedure is quite different from studies that have evaluated more immediate factors that preceded the determination of bloodstream infection, frequently in hospitalized patients (*32*). Immediate predictors of bacteremia include fever, shaking chills, rapidly or ultimately fatal disease, major comorbidity, signs of peritonitis, a sign of infection in the abdomen, and intravenous drug abuse (*32*). The hygienic and appropriate use of intravascular catheters and invasive devices is also quite important. Predictors of mortality in hospital-acquired bacteremia include age and severity of underlying disease (*15*).

The goal of this research is to identify risk factors predictive of septicemia mortality well in advance of its occurrence. Given the increasing importance of septicemia-associated mortality as well as the emergence of new strategies that might be used to treat or prevent sepsis (*33*), the factors identified in this analysis might be useful in developing or testing such strategies in a community setting. The underlying mechanisms that could explain how smoking, diabetes, and alterations of physical and cognitive functioning increase the risk of subsequent septicemia require further investigation.

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