# Nosocomial bacteremia in very old patients: predictors of mortality

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*ABSTRACT.* ***Background and aims:*** *Nosocomial Bacteremia (NB) is associated with high mortality in elderly patients. To determine specific prognostic factors for 7- and 30-day mortality in elderly patients with NB, we analysed the characteristics of 62 NB patients, retrospectively.* ***Methods:*** *This retrospective study concerns 62 cases of NB diagnosed within a 3-year period in a geriatric department. Bacteremia is described according to CDC definitions. Epidemiological characteristics, co-morbidities, clinical (activities of daily living (ADL) before NB) and biological findings (neutrophil count, lymphocyte count, albuminemia before NB) were collected for each patient. A systemic clinical reaction was defined by the presence of one of the following parameters: chills, hypothermia <36°C or hyperthermia >38.5°C, or shock. Types of micro-organism and source of NB were also collected. All variables were analysed for mortality at day 7 (7-day mortality) and at day 30 (30-day mortality).* ***Results:*** *The 7-day mortality rate was 21% and the 30-day rate was 45%. In multivariate analysis, 7-day mortality was only associated with the absence of systemic clinical reaction [OR 9.7 (3.7-25.7)]. Again, in multivariate analysis, 30-day mortality was associated with an ADL score <2 [OR 8.3 (4.3-16.4)] and cocci gram positive NB [OR= 3.6 (1.9-6.9)].* ***Conclusions:*** *The absence of any systemic clinical reaction as a single independent predictor for 7-day mortality suggests either a poorer immune response to nosocomial bacteremia or a delay in diagnosis. Functional status was the strongest predictor for 30-day mortality. In this population, further prospective studies need to include these factors to evaluate predictors of mortality for serious infectious diseases.*

*(Aging Clin Exp Res 2005; 17: 337-342)*



## INTRODUCTION

Nosocomial infections are more frequent in elderly patients (1). Among nosocomial infections, bacteremia is associated with high mortality in both young adults and the elderly (1-3). The most commonly accepted prognostic factors of fatal outcome are nosocomial acquisition of bacteremia, inappropriate antimicrobial therapy, age, comorbidities such as evolutive neoplasia, malnutrition, neutropenia, gram-positive bacteria, shock, and respiratory tract infection as a source of bacteremia (1, 2, 4, 5). However, few data are available specifically for old (>65 years old) and very old (>85 years old) patients (6-14). Functional status is associated with poor outcome in a number of diseases in elderly patients but has rarely been evaluated in bacteremia (6, 8, 14). To examine the impact of functional status in the outcome of bacteremia, we carried out a retrospective study concerning predictors of mortality of bacteremia in elderly patients. We considered only nosocomial bacteremia, and collected various markers (albuminemia, ADL score, temperature) before and not at the onset of bacteremia.

## METHODS

### *Hospital setting*

The study was carried out in the geriatric department of the university hospital of Grenoble, France. This department is composed of 50 acute care beds, 50 rehabilitation beds and 200 long-term care beds. Data concerning nosocomial bacteremia (CDC definition) which occurred between April 1996 and April 1999 in patients older than 65 years were collected retrospectively; the informatic system was used to select patients. In order not to miss any case of bacteremia, we checked all cases in the microbiological laboratory database.

*Key words:* Elderly, nosocomial bacteremia, outcome, prognostic factors.

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Received April 19, 2004; accepted in revised form October 14, 2004.

Aging Clin Exp Res 17: 337-342, 2005


*Definitions*

We used CDC definitions for bacteremia (15).

Bacteremia was defined as the presence of a pathogenic micro-organism in at least one blood culture within a 48-hour period beginning with the first drawing of the first blood culture. Micro-organisms which are commonly recovered from the environment or the skin (coagulase-negative *Staphylococcus*, species of *Bacillus, Corynebacterium, Propionibacterium,* and *Micrococcus*) were considered to be contaminants unless 2 different blood cultures drawn at 2 different times were positive, or one blood culture and one normally sterile site were positive for the same micro-organism.

Polymicrobial bacteremia was defined as the association of 2 or more positive blood cultures with different pathogenic micro-organisms within a 48-hour period beginning with the first drawing of the first blood culture.

Primary bacteremia was defined as the association of a sepsis syndrome (fever >38°C, rigor or shock) and one positive blood culture for pathogenic micro-organisms and 2 positive blood cultures for non-pathogenic micro-organisms without any infection of another site. All NB secondary to catheter infection were considered as primary bacteremia.

Secondary bacteremia was defined as the association of positive blood culture and the infection of another site. The latter was defined according to clinical, radiological and bacteriological findings. Skin, soft tissue, digestive, biliary and urinary tract infections were considered as the source of bacteremia if the same micro-organism was found. A bacteriological finding was not necessary for post-operative site and respiratory tract infection.

Only episodes of nosocomial bacteremia were analysed, defined as an infection not present or in incubation within 48 hours of hospital admission.

Blood cultures were performed with the standard technique. Micro-organisms were identified in the microbiology laboratory at the University Hospital of Grenoble by standard methods. Antimicrobial susceptibilities were generally ascertained by the disk diffusion technique and notified for all micro-organisms.

Antibiotic therapy was considered appropriate if the antibiotic was begun within 24 hours following the first positive blood culture drawn, if the infecting micro-organism was *in vitro* susceptible to the antibiotic used and if the drug was administered intravenously.

Functional status was measured by the Activities of Daily Living (ADL) score before the onset of bacteremia (from 3 to 30 days before bacteremia). The highest score from the date of hospital admission is reported. Each of the ADL 6 activities (bathing, dressing, toileting, walking, continence, feeding) were scored on an ordinal scale 0, 0.5 and 1 if, respectively, the patient was dependent, needed assistance, or was fully independent (16). Then, the scores were ranged from 0 to 6 according to the 6 items assessed. A score of 0 indicates total dependence and 6 total independence. Because the ADL score is not a real numeric variable and because the median score was 2, we dichotomized these scores for statistical analysis at 2.

Malnutrition was evaluated by albuminemia measured before bacteremia (from 10 to 30 days) and in the absence of inflammation: denutrition was moderate if the albumin level was 30-35 g/L, severe if 25-30g/L, and very severe if <25g/L.

*Demographic data and clinical findings*

Patient's age, gender, and ward location are reported. The following underlying diseases and conditions were reported: diabetes, stroke, cancer, COPD, dementia, immunosuppression therapy, surgery less than 1 month before, previous colonisation with methicillin-resistant *Staphylococcus aureus* (MRSA). Co-morbidities were classified in 2 categories as none, and more than one. The source of bacteremia was classified in skin and soft tissue, respiratory tract, urinary tract, digestive or biliary, peripheral venous catheter, central venous catheter, and indeterminate. If the micro-organism of the source of BI was identified, this fact was noted.

Because the absence of any systemic reaction may be a surrogate marker of the incapacity of a patient to cope with infection (7), the occurence of chills, thermic reaction (<36.5°C and >38.5°C) or shock was classified as "systemic clinical reaction" (SCR).

*Outcome*

7-day mortality was defined as the rate of death during the 7-day period after the first positive blood culture drawn, and 30-day mortality as the rate of death during the 30-day period after the first positive blood culture drawn.

*Statistical method*

All data collected were computerised in the Statistical Package for the Social Sciences (SPSS 6.1.3) program. Data on albuminemia were not available for 11 patients but all other parameters were available for all patients. Patients were classified as dead or alive at 7 days and 30 days. For bivariate analysis, qualitative variables were compared with the chi-square test of homogeneity or Fisher's exact test, as appropriate. Quantitative variables were expressed by means (± standard deviation, SD) and compared using Student's *t*-test or the Wilcoxon rank sum test, as appropriate. Odds ratios were calculated using logistic regression. Statistical significance was set at $p<0.05$. For multivariate analysis, a logistic forward stepwise model was used, including all variables which were significant at $p<0.2$ in bivariate analysis.

## RESULTS

A total of 62 cases of nosocomial bacteremia were diagnosed over a 3-year period in the Geriatric de-

Table 1 - *Chronic conditions found in 62 patients.*

| Patient characteristics | Number of cases (%) |
|---|---|
| *Comorbidities* | |
| Peripheral arterial disease | 12 (19) |
| Diabetes | 12 (19) |
| Dementia | 11 (18) |
| Evolutive neoplasia | 11 (18) |
| Surgery less than 1 month before | 7 (11) |
| Chronic obstructive bronchopneumopathy | 5 (8) |
| Corticotherapy | 4 (6) |
| Dysphagia | 2 (3) |
| Cirrhosis | 2 (3) |
| *MRSA skin colonisation* | 2 (3) |
| *Catheter* | |
| Urinary | 26 (42) |
| Venous | 16 (26) |
| Tube feeding | 6 (10) |
| *Clinical symptoms* | 54 (87) |
| *Malnutrition* | |
| Absent | 8 (15) |
| Moderate | 20 (39) |
| Severe | 16 (31) |
| Very severe | 8 (15) |

partment of the University Hospital of Grenoble. Mean age was 84 ±8 years and the sex ratio was 2 females to 1 male. Of these patients, 45% were located in acute geriatric care, 45% in rehabilitation care and 10% in long-term care. At least one chronic condition was found in 76% of patients: Table 1 lists their demographic and clinical characteristics. Clinical symptoms (chills, hypothermia, fever) were found in 87% and shock in 14.5%. Mean leucocyte count was 15 g/L ±7 and mean albuminemia 30 g/L (SD±5). Malnutrition was rarely absent and often severe (Table 1). ADL was available for all patients, and the mean score was 2.2 (SD±1.5) with a median of 2.

Two cases of bacteremia were polymicrobial. Of 64 bacteria, 61% were gram negative and 39% cocci gram positive. *Escherichia* coli accounted for 41%, *Staphylococcus aureus* for 19%, *Streptococcus sp* for 17%, *Proteus sp* for 6%, *Pseudomonas aeruginosa* for 5%, *Staphylococcus epidermidis* for 3% and other gram negative types for 9%. No resistance was found among *Streptococcus sp*; 3 *Staphylococcus aureus* out of 12 and 1 out of 2 *Staphylococcus epidermidis* were methicillin-resistant. Urinary tract infection was the most frequently identified source of NB (42%). Indeterminate and skin and soft tissue were the second and third most common sources accounting for 36% and 6% of NB respectively. Other sources were less than 5% (pneumonia, post-surgical infection, angiocholitis, endocarditis, intravascular catheter). Empirical antibiotic therapy was considered appropriate according to the definition in 74% of cases.

Mortality rates were respectively 21% and 45% at day 7 and day 30 after the first blood culture drawn. In bivariate analysis, age, gender, co-morbidities, presence of indwelling catheter, ward location, septic shock, and leucocyte count are not associated with 7-day mortality. The type of bacteria (cocci gram positive), inappropriate antimicrobial therapy, malnutrition (severe and very severe), ADL <2, albuminemia, and source of bacteremia other than the urinary tract were close to having a significant impact on mortality, and only the absence of an SCR was associated with higher mortality (Table 2). In multivariate analysis, the absence of an SCR was the only significant parameter associated with fatal outcome [Odds Ratio 9.7 (3.7-25.7)], independently of type of bacteria, inappropriate antimicrobial therapy, ADL <2, albuminemia, and source of bacteremia.

Thirty-day mortality was associated with numerous factors, as shown in Table 3. Age, gender, septic shock, leucocyte count, presence of intravascular or urinary

Table 2 - *Parameters associated with 7-day mortality (day 7).*

| | Dead (n=13) | Alive (n=49) | OR (95% CI) | *p*-value |
|---|---|---|---|---|
| Absence of systemic clinical reaction | 5 (38%) | 3 (6%) | 9.58 (1.9-48.2) | 0.009 |
| Cocci gram positive bacteremia | 8 (62%) | 17 (34%) | 3 (0.3-10.2) | 0.079 |
| Inappropriate antibiotic therapy | 6 (46%) | 10 (20%) | 3.34 (0.9-12.2) | 0.08 |
| Nutrition* | 7 (88%) | 19 (44%) | 3 (0.99-78.2) | 0.062 |
| Source of bacteremia in urinary tract | 3 (23%) | 23 (77%) | 0.2 (0.3-0.96) | 0.09 |
| ADL≤2 | 10 (77%) | 26 (53%) | 2.9 (0.7-12) | 0.12 |
| More than one co-morbidities | 2 (15%) | 13 (26.5%) | 0.5 (0.1-2.6) | 0.63 |
| Intravascular catheter | 3 (23%) | 18 (37%) | 0.6 (0.2-2.5) | 0.72 |
| Shock | 2 (15%) | 7 (14%) | 1.1 (0.2-6) | 0.73 |
| Urinary catheter | 6 (46%) | 20 (41%) | 1.2 (0.4-4.2) | 0.73 |
| Age | 83.5 | 84 | - | 0.82 |

*Severe and very severe malnutrition if albuminemia <30 g/L.

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Table 3 - *Parameters associated with 30-day mortality (day 30).*

| | Dead (n=28) | Alive (n=34) | OR (95% CI) | *p*-value |
|---|---|---|---|---|
| ADL≤2 | 23 (82%) | 13 (38%) | 7.4 (2.2-24.2) | 0.001 |
| More than one comorbidity | 27 (96%) | 20 (59%) | 18.9 (2.2-155) | 0.002 |
| Cocci gram positive bacteremia | 17 (58%) | 8 (23%) | 4.8 (1.6-14) | 0.007 |
| Source of bacteremia in urinary tract | 6 (40%) | 20 (87%) | 0.1 (0.02-0.5) | 0.007 |
| Absence of systemic clinical reaction | 7 (25%) | 1 (3%) | 11 (1.2-95) | 0.02 |
| Nutrition* | 6 (27%) | 1 (3%) | 10.5 (1.5-95) | 0.04 |
| Gender (male) | 6 (21%) | 15 (44%) | 0.3 (0.1-1.1) | 0.1 |
| Urinary catheter | 16 (57%) | 10 (29%) | 2.4 (0.8-7.1) | 0.2 |
| Inappropriate antibiotic therapy | 10 (36%) | 6 (18%) | 2.2 (0.8-8.4) | 0.2 |
| Leucocyte count (G/l)** | 13.8 | 16 | - | 0.24 |
| Age (years)** | 84.8 | 83.2 | - | 0.44 |
| Shock | 4 (14%) | 5 (15%) | 0.9 (0.2-0.8) | 0.79 |
| Ward location (acute care) | 13 (35%) | 15 (44%) | 1.09 (0.4-2.99) | 0.85 |
| Intravascular catheter | 10 (36%) | 11 (32%) | 1.2 (0.4-3.3) | 0.99 |

*Severe and very severe Malnutrition if albuminemia <30 g/L; **Student's *t*-test.

catheter, ward location, and inappropriate antibiotic therapy were not associated with fatal outcome. In multivariate analysis, only 2 variables were independently correlated with mortality: ADL score <2 [Odds Ratio 8.3 (4.3-16.4)] and cocci gram positive bacteremia [Odds Ratio 3.6 (1.9-6.9)].

## DISCUSSION

The epidemiology of nosocomial bacteremia in very old patients found in this retrospective study is comparable to previous data (6-13). The most frequent source of bacteremia is the urinary tract (6-13). The higher rate of unknown source and lower rate of respiratory tract infection are probably linked to the lack of chest radiographs available for patients located in long-term care and rehabilitation care facilities (data not shown). Indeed, the rate of pulmonary sources in studies carried out in nursing homes are less frequent (10, 11, 17) than those concerning nosocomial bacteremia (7, 8). *Escherichia coli* is the most frequent micro-organism found in blood cultures (6-10). This is different than in young adults and "young-old" patients (<75 years old) (7, 8) in whom the most frequent micro-organism is *Staphylococcus spp* (3, 5). The proportion of cocci gram positive is also comparable to previous studies in this elderly population (6-12, 14).

The 7-day mortality rate was 10-30% in patients 80 years and older (6-12, 14). We found that the absence of an SCR at the onset of bacteremia is an independent prognostic factor for 7-day mortality. The absence of fever or hypothermia has been already reported as an independent risk factor for mortality in elderly patients with bacteremia (4, 6, 12). However, our results cannot be compared with those of most other studies (6, 8, 13): hypothermia, fever, blood pressure, and chills were reported at least twice a day by nurses before the onset of bacteremia. Therefore, the absence of fever, hypothermia, chills or shock several days before positive blood cultures are correctly reported. This is different from studies including community-acquired bacteremia, in which patients without reported fever at hospital admission may have had fever before but do not know this, because they had not measured it (6, 8, 13). This may therefore represent a detection bias and lead to a decrease in the statistical significance of the absence of fever (6, 8, 13). For example, the largest study in elderly patients by Leibovici et al. found 5 independent negative predicting factors: nosocomial acquisition was the strongest one, and the absence of fever was not. However, fever was reported as a single measure and analyzed in overall bacteremia (community and nosocomial) (8).

Other known predicting factors were not found in our study. In a model of functional assessment, Delofeu et al. found 5 independent predicting factors: shock, immunodeficiency, impaired functional status (Barthel index <60), nosocomial infection, and absence of fever. In a model without functional assessment, the above authors found 2 other predicting factors: inappropriate therapy and age >65. In their view, the 2 latter factors are linked to functional status, which may be considered more important. This may also explain why inappropriate therapy was not a significant factor in our multivariate analysis. In addition, Leibovici et al. reported no impact of appropriate therapy in patient with hypothermia (4). Other explanations may be the lack of power of our study and/or the definition of appropriate antibiotic therapy used. The delay of less than 24 hours *vs* 48 hours in other studies may have decreased the number of "appropriate therapies" in our study.

The absence of SCR as a strong predicting factor may be related to a delay in diagnosis, because of the absence of cardinal symptoms suggesting an infection. It may also characterize a subgroup of patients with an impaired systemic response facing stress, in turn related to an impaired immune response, as suggested by the decreased level of cytokines (18). In this sense, patients without SCR had poor functional and nutritional status (data not shown) as previously reported (6). Delay in diagnosis is another realistic explanation. However, although atypical presentations are frequent in the elderly, geriatric caregivers and physicians are aware of this and many blood cultures are carried out for patients without fever. Also, it seems difficult to evaluate this delay; at what moment and how can we estimate the onset of bacteremia? Larger studies with correctly reported data concerning SCR and basic research concerning the function of temperature are therefore needed to confirm the present hypothesis.

Our 30-day mortality rate was 45%. Previous studies found comparative results from 35% to 50% (6, 8-10, 19). In the present study, cocci gram positive bacteremia was significantly associated with fatal outcome, independently of appropriate therapy, age, albuminemia, or source of bacteremia. This has already been reported, especially for *Staphylococcus sp* and *Enterococcus sp* (5, 9, 20, 21). In addition, a pulmonary source, which is mainly related to gram positive bacteria, is also considered as a predictor of mortality (8, 10, 14). Our data may reflect the special impact of bacteriology in a single facility, as previously reported by Mylotte et al. (14). Notably, data on cases of bacteremia had been collected in 3 different wards in the present study (acute care, rehabilitation care, and long-term care).

The second main finding of the present study is that the ADL score is the best predictor of 30-day mortality, independently of appropriate therapy, age, albuminemia, source of bacteremia, pathogens, or underlying diseases. Two studies concerning the elderly had already reported that functional capacity may be a negative prognostic factor (6, 8). However, Leibovici et al. (8) did not find it in multivariate analysis, and Delofeu et al. (6) found other more significant factors such as shock and immunodeficiency. These differences may be because the functional capacity of our patients was low (median ADL score of 2), defining a special subgroup of the elderly population for whom functional disability reveals the physiological reserves to a greater extent. Only 10% of the studied population was considered independent using the Katz index (16) compared with 39% and >50% in the studies performed by Leibovici et al. and Delofeu et al. respectively (6, 8). In addition, in the latter study, disability was linked to the immunodeficiency of the AIDS patients included in the study. Also, that population and ours are very different. A more recent study found that the independent predictors of in-hospital mortality were: pulmonary source, systolic blood pressure <90 mmHg and leukocyte count >20 g/L (14). However, although the large population described had poor mean functional status compared with our population, this was not included in their analysis.

A limitation to our findings is the absence of any severity score of underlying diseases which may interfere with functional status (22). This was because there were not enough patients with available scores to include it in our model.

## CONCLUSION

Cases of NB are associated with a high mortality rate in elderly patients. The present study emphasises the overall frailty of our elderly patients who died following NB: the absence of a systemic clinical reaction is a predictor of 7-day mortality, and both cocci gram positive bacteria in blood cultures and low functional status are predictors of 30-day mortality. These factors must be taken into account in additional prospective studies, and may help to evaluate the difficult and complex situation encountered in old patients with regard to decisions covering ethical antibiotic prescriptions.

## ACKNOWLEDGEMENTS

We wish to thank Philipp Berardi (Biochemistry and Molecular Biology Department, University of Calgary) for proofreading the manuscript.

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