Atypical Presentation of Bacteremia in Older Patients Is a Risk Factor for Death

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1 **Atypical presentation of bacteremia in older patients**

2 **is a risk factor for death**

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Abstract

Background: The absence of fever in bacteremia in older patients is known to delay diagnosis. Our objective was to determine whether atypical presentation was associated to mortality due to bacteremia in older patients and factors associated with this atypical presentation.

Methods: We conducted an observational prospective study in two French university hospitals in 2016-2017 including patients aged ≥ 75 years with bacteremia. Atypical presentation was defined as the absence of a temperature $\geq 38.3^{\circ}\text{C}$ or $< 36^{\circ}\text{C}$, chills or hypotension. Mortality and dependence for Activities of Daily Living (ADL) were recorded at 1 week (D7) and 3 months (D90).

Results: Among the 151 patients (mean age 85.4 ± 5.8 years) enrolled, atypical presentation prevalence was 21.2%. D7 and D90 mortality rates were 7.9% and 40.0%, respectively. . Atypical presentation was independently associated with D7 (odds ratio (OR) 4.46, 95% confidence interval (CI) 1.04–19.24) and D90 mortality (OR 3.76, 95% CI 1.30–10.92) after controlling for other prognostic factors. Diabetic patients and those infected with *Staphylococcus aureus* were more likely to have atypical signs of infection. ADL score decreased from 3.6 ± 2.0 before bacteremia to 2.8 ± 2.1 at D90 ($p < 0.001$).

Conclusion: Older patients with bacteremia have poor vital and functional prognoses in the short and long terms. The absence of typical signs of infection is associated with mortality. Blood culture should be considered for older, especially diabetic patients with acute unexplained clinical manifestations.

1 Introduction

2 The population of older people has increased in recent decades; the proportion of people
3 aged >60 years is expected to reach 30% in Europe and North America in 2050 (1). Older
4 people are more prone to develop infections (2,3), with a 13-fold higher risk relative to
5 younger people (3). Bacteremia is defined by the presence of a microorganism in blood
6 culture. It accounts for 7% of infections occurring in older individuals (4) and has death rates
7 of 11–30% after 1 week (5-11) and up to 45% after 1 month (12). Long-term outcomes
8 associated with bacteremia in older patients, such as functional and/or cognitive decline, the
9 rate of institutionalization and quality of life, remain poorly documented (5).

10 The clinical presentation of infection may differ between older and younger people (13).

11 Fever is absent in up to 30% of older people (7,8,10,14), and this absence is associated with
12 a poorer outcome (8,10,15). Signs of infection can also be hidden by more obvious
13 symptoms of decompensated comorbidity, which can delay diagnosis and the initiation of
14 antimicrobial treatment, thereby worsening the prognosis. In our practice, bacteremia
15 presentation in older patients is heterogeneous: some older patients present similarly to
16 younger ones, with chills and fever or hypothermia (9,14,16), whereas others present only
17 fatigue or delirium. Such heterogeneity is well known in geriatrics, where presentations
18 range from healthy aging (1) with few chronic pathologies and independence in all activities
19 of daily living to bedridden status and total dependence (17).

20 We hypothesized that atypical presentation of bacteremia, i.e., the absence of fever, chills
21 and signs of severe infection, would be a risk factor for death due to the resulting delay in
22 diagnosis.

23 The main objective of this prospective study was to determine whether atypical presentation
24 of bacteremia was an independent risk factor for mortality in patients aged over 75. The

- 1 secondary objectives were to describe risk factors associated with atypical presentation and
- 2 to describe patients' functional status over time (before bacteremia and up to 1 and 3
- 3 months afterwards).
- 4

1 **Material and Methods**

2 ***Population and setting***

3 This observational prospective study was conducted in two university hospitals: in Bordeaux
4 (Centre Hospitalo-Universitaire) and Paris (Groupe hospitalier Pitié-Salpêtrière-Charles-Foix)
5 between April 2016 and April 2017. All consecutive patients aged ≥ 75 years who were
6 hospitalized in the geriatric department (Bordeaux and Paris), internal medicine, infectious
7 diseases or emergency departments or intensive care unit (ICU) (Bordeaux) with positive
8 blood culture were enrolled. These medical wards recruit non-selected patients from home
9 or nursing-homes directly or *via* emergency departments. Blood cultures considered false-
10 positive (i.e. presence of a contaminant) were excluded. If one patient had several
11 bacteremia episodes, he was enrolled only at the first episode.

12 ***Definitions***

13 Bacteremia was defined according to the Centers for Disease Control criteria (18) as 1/ the
14 presence of a recognized pathogenic bacteria in one or more blood samples, or 2/ the
15 presence of a contaminant (*Corynebacterium* spp., *Bacillus* spp. excluding *Bacillus anthracis*,
16 *Propionibacterium* spp., coagulase-negative staphylococci, viridians group streptococci,
17 *Aerococcus* spp. or *Micrococcus* spp.) cultured from two or more blood cultures drawn on
18 separate occasions associated with clinical signs of infection.

19 Bacteremia was considered to be “nosocomial” when occurring 48 h after hospital
20 admission, “healthcare-associated” when it was acquired after contact with healthcare
21 services (18,19). Otherwise, bacteremia was considered to be “community acquired.”
22 Fever (temperature $\geq 38.3^{\circ}\text{C}$), hypothermia (temperature $< 36^{\circ}\text{C}$), chills and hypotension
23 (systolic blood pressure $< 90\text{mmHg}$) were considered to be typical clinical signs of bacteremia.
24 If one of these signs was present at the time of blood collection, bacteremia clinical

1 presentation was considered “typical”. The clinical presentation of bacteremia was
2 considered “atypical” when none of these signs was present.
3 The source of bacteremia was established when a primary site of infection was identified
4 because of obvious local clinical signs of infection or because of isolation of the same
5 bacteria at this site by microbiological sampling. Secondary localizations were also collected.
6 A bacteremia episode was considered “severe” when it led to ICU admission, organ failure or
7 septic shock (20).
8 Basal temperature has been described to be lower in older patients (21). To detect patients
9 with a significant increase of temperature (at least 1,1°C as recommended by Infectious
10 Diseases Society of America (IDSA)) during bacteremia episode even if they were considered
11 afebrile, we compared temperature at the time of blood collection to their baseline
12 temperature measured in the morning once the infectious episode had resolved or before
13 when available. Antimicrobial treatment was considered appropriate when bacteria was
14 susceptible to *in vitro* testing and if treatment was started before bacterial susceptibility was
15 known by the physician.

16 **Data collection**

17 Data were obtained from medical records and interviews with patients, relatives and/or
18 general practitioners. Patients received a written explanation of the study protocol. The
19 study protocol was approved by the Committee for the Protection of Persons (DC 2016/55),
20 the French National Agency Regulating Data Protection (n° 1935307 v 0) and the Ethics
21 Committee of Bordeaux University Hospital (n°CE-GP-2018/16).
22 All clinical signs were noted at the time of blood collection. The presence of geriatric
23 syndromes (delirium, falling, acute urine retention or incontinence and decreased general
24 condition/functional decline) was also recorded at that time.

1 Data on patients' demographic characteristics and reasons for admission to hospital were
2 collected. Comorbidities were assessed using the Charlson Comorbidity Index (CCI) (22) and
3 the number of medications prescribed.

4 Activities of daily living (23) and Instrumental Activities of Daily Living (24) scores were used
5 to evaluate the functional status of patients 3 months before (retrospective), during and 3
6 months after admission to hospital. These items were scored numerically, with higher
7 numbers representing better functioning.

8 Factors that could impact clinical presentation, i.e., non-steroidal anti-inflammatory drug,
9 steroid or antibiotic prescription, and use of beta blockers within 7 days before bacteremia
10 onset, were also recorded.

11 In addition, microbiological data (pathogens isolated from blood cultures, susceptibility
12 patterns) and data on antimicrobial treatment (appropriateness, interval between symptom
13 onset and treatment initiation) were collected. Patients' vital status, living place and
14 functional status were evaluated at D7, 1 month (D30) and 3 months (D90), by telephone
15 after discharge.

16 ***Statistical analyses***

17 Demographic, clinical and bacteriological characteristics were described at baseline and
18 compared according to clinical presentation. Categorical variables were presented as
19 percentages and frequencies and compared by χ^2 or Fisher's exact test, as appropriate.

20 Continuous variables were presented as the mean $\pm$ standard deviation and compared by
21 the Student t test or Mann–Whitney U test, as appropriate. In order to determine whether
22 atypical presentation was associated to D7- and D90-mortality, we carried out a binary
23 logistic regression controlling for other prognostic factors. A binary logistic regression model
24 was also used to identify variables associated with atypical presentation. Clinical and

1 biological variables with p values <0.20 in univariate analyses and variables suspected of
2 being confounding factors were then entered into a multivariate logistic regression model. A
3 backward selection method was used to obtain a model in which all variables had p
4 values<0.05. Activities of Daily Living scores before and after (at D30 and D90) bacteremia
5 were compared by one-way analysis of variance. Kaplan–Meier curves and log-rank tests
6 were realized to compare survival over time according to the bacteremia clinical
7 presentation.

8 Based on previous reports, the expected D30 mortality rate in this older population was
9 ~20% (25,26). We hypothesized that the “atypical group” mortality rate would be twice as
10 high as that in the “typical group.” Hence, sample size determination using an α risk of 0.05
11 and a power of 95% established that enrollment of at least 127 patients was needed.

12 P values<0.05 were considered to be significant. Statistical analyses were performed using
13 SPSS 24.0 software.

14

Results

Population baseline characteristics

Over the study period, 151 consecutive patients with bacteremia were enrolled. The mean age was 85.4 ± 5.8 years and 47.0% of patients were female. All but six surviving patients were followed until D90. Demographic, clinical, biological and microbiological characteristics are described in Tables 1 and 2. Briefly, before being admitted to hospital, 122 (80.8%) patients lived at home (69.7% with domestic help). This population was dependent (Activities of Daily Living score 3.8 ± 2.0 , Instrumental Activities of Daily Living score 2.4 ± 2.6) and affected by multiple illnesses (mean CCI score 3.9 ± 2.7 , polypharmacy (≥ 5 medications/patient) in 109 (72.2%) patients). This population was heterogeneous since 41.7% ($n=63$) had Activities of Daily Living ≥ 5 and 29.8% ($n=45$) were ≤ 2 . When the blood samples were drawn, 119 (78.8%) patients presented with typical signs of bacteremia and were defined as the “typical group”; thirty-two (21.2%) patients who showed none of these signs were defined as the “atypical group”. When patients had no typical sign of infection, it was interesting to note that blood culture were collected because of high levels of C-reactive protein (CRP) or leukocytosis. Fifty-nine (39.1%) bacteremia were community-acquired. Urinary tract infections were prevalent ($n=73$, 48.3%). Blood cultures identified 163 pathogens and 22 (13.5%) multidrug-resistant bacteria (Table 2). In accordance with urinary and digestive sources of infection, the majority ($n=106$, 65.0%) of bacteria identified were Gram negative, mostly *Escherichia coli* ($n=66$, 40.5%).

Mortality and morbidity of bacteremia in older patients

The cumulative D7, D30 and D90 mortality rates in this study were 7.9%, 22.0% and 40.0%, respectively. The etiologies of death are shown in Figure 1. The main causes of mortality were bacteremia at D7 ($n=9$, 75.0%), the occurrence of a new infection at D30 ($n=33$, 47.6 %)

and the worsening of an underlying chronic disease at D90 (n=11, 45.8%).

An atypical clinical profile was associated significantly and independently with death at D7 and D90 in the multivariate analyses [odds ratio (OR) 4.46, 95% confidence interval (CI) 1.04–19.24-and OR 3.76, 95% CI 1.30–10.92, respectively] after adjusting for potential prognostic factors (as age, sex, body mass index, Charlson score, severity, appropriateness of antimicrobial treatment, time between symptoms and start of antimicrobial treatment, nosocomial infection, chronic heart failure, urinary tract origin, bacteria responsible for bacteremia) (supplementary data).

Despite their atypical presentation 71.9% (n=23) patients received appropriate empiric antimicrobial treatment compared to 79% (n=94) in the typical group (p=0.39). Nevertheless, the interval between symptoms which had led to blood collection and the start of antimicrobial treatment tended to be longer for atypical patients (30.4 vs. 18.2 h, p=0.06).

Figure 2 shows patient survival over time (Kaplan-Meier curves) according to the clinical presentation when blood samples were collected.

Fifty-three (35.1%) bacteremia episodes were considered to be severe. Bacteremia induced a decline in functional status that lasted for >3 months (Figure 3). Among survivors, 19 (25.0%) patients were admitted to rehabilitation services and nine (11.8%) were admitted to nursing homes. Mean hospital stay was long (17.9 ± 14.9 days).

Description of patients according to clinical presentation and predictive factors for atypical presentation of bacteremia

The most frequent typical sign of bacteremia was fever (n=98, 65.3%). Other typical signs identified were chills (n=44, 29.1%), hypotension (n=28, 18.5%) and hypothermia (n=6, 4.0%). Patients with atypical presentation were not more prone to present delirium, functional decline, falls or comorbidity exacerbations than patients with typical signs. But,

1 they presented more secondary infectious localizations than patients in the typical group.
2 Neither the Charlson score nor Activities of Daily Living or Instrumental Activities of Daily
3 living scores differed significantly between groups. The comparison of patients according to
4 clinical presentation (typical vs. atypical) is presented in Table 3. In the multivariate analyses,
5 predictive factors for atypical clinical manifestations were *S. aureus* infection and diabetes.
6

Discussion and Conclusion

This prospective study of 151 bacteremia episodes confirmed our hypothesis that atypical presentation of bacteremia (accounting for 20% of enrolled patients) is a risk factor for early and late mortality in older patients. We confirmed that bacteremia in older patients has a poor long-term prognosis, with functional decline even 3 months later. Diabetic patients and those infected with *S. aureus* were more prone to having atypical signs of bacteremia.

The bacteremia mortality rates in our study (8% at D7, 22% at D30 and 40% at D90) differed from those described previously; for example, Yahav *et al.* (5) reported higher D7-mortality rates (14–22%) in a review on more than 3000 episodes of bloodstream infections in older patients. The discrepancies can be explained by the inclusion of patients with more severe infection and inappropriate empirical antimicrobial treatment (25,27), as well as an increased number of cases of pulmonary origin and bacteremia of unknown origin, which are known to be associated with worse prognoses (28). Lee *et al.* (9) described a 26% D90 mortality rate in 69 patients aged over 85 hospitalized for community-acquired bacteremia only, which is known to be associated with a better prognosis than nosocomial bacteremia. Leibovici *et al.* (27) described in 1993 an 80% D90 mortality rate in 338 patients aged over 80 hospitalized with community-acquired or nosocomial bacteremia, but 25% of enrolled patients had malignancies, which could explain in part this increased late mortality rate since antineoplastic treatments at that time were less efficient.

Our study is among the first to demonstrate that atypical clinical manifestation of bacteremia is a risk factor for early and long-term mortality. Using the same definition of “atypical” except for fever, which was defined as temperature $>38.5^{\circ}\text{C}$, Gavazzi *et al.* (12) obtained similar results, but only for nosocomial bacteremia and only at D7. The trend toward an increased delay in the initiation of antimicrobial treatment in the “atypical”

1 group, which is a well-known mortality risk factor, could, in part, explain this increased early
2 mortality (10, 29-31). However antibiotic initiation delay was not a risk factor for mortality in
3 multivariate analyses in the present study. One difficulty concerns the definition of the
4 “beginning” of a bacteremia episode, especially in the atypical group. Hence, data on any
5 delay of antibiotic initiation should be considered with caution. Patients in the atypical group
6 presented more secondary infectious localizations, assuming that their atypical presentation
7 increased delay to diagnosis. The presence of local clinical signs of infection indicating the
8 potential source of bacteremia was not included in the definition of typical or atypical
9 presentation of bacteremia since their presence did not suggest the diagnosis of an
10 associated bacteremia. But those signs could have influenced delay to diagnosis and led to
11 initiation of antibiotics earlier and modify prognosis. Nevertheless, in our study, percentage
12 of patients with local signs of infection at time of blood collection was similar in atypical and
13 typical group. Hence this should have not impacted outcome in the two groups.

14 The higher mortality rate in the atypical group cannot be attributed to a greater severity of
15 infection, as severe bacteremia was equally prevalent in the two groups. We can assume
16 that the atypical group bears an intrinsic severity that is not linked directly to the severity of
17 bacteremia, but is perhaps linked to the immunological status of the patients, as suggested
18 by Gavazzi *et al.* (12); the absence of fever may be the consequence of an impaired systemic
19 immune response to infection. Nevertheless, we did not find reduced levels of CRP or
20 leukocytosis in the atypical group. Additional studies are needed to analyze immunological
21 biomarkers, such as lymphocytes, using immunophenotyping, protein electrophoresis and
22 immunoglobulin dosage at baseline to determine whether immunological abnormalities are
23 linked to the “atypical” presentation of bacteremia. This “atypical” group could also be more
24 sensitive to post-sepsis immunosuppression, leading to greater mortality from new

1 infections (32).

2 Functional status and comorbidity scores were not associated with atypical presentation of

3 bacteremia in our study, but we did observe an association with diabetes. Other researchers

4 have focused on afebrile bacteremia and have identified several comorbidities, including

5 chronic renal failure, hypothyroidism, alcoholism (33) and malignancy (15) as risk factors.

6 The only factors associated with atypical clinical signs in our study were diabetes and

7 infection with *S. aureus*. Diabetes is a known risk factor for atypical manifestation of

8 myocardial infarction (without chest pain) (34) and asymptomatic bacteriuria. Diabetic

9 patients are also more susceptible to *S. aureus* colonization (35) and bacteremia (36). Our

10 study showed a trend toward increased bacteremia associated with a cutaneous portal of

11 entry in the atypical group, which could explain the higher prevalence of *S. aureus* in this

12 group.

13 Bacteremia due to *S. aureus* are at higher risk of recurrence (37) especially in diabetic

14 patients. Since we found more atypical clinical manifestations in those patients, this could

15 suggest that they would need a closer follow-up in order to detect the first signs of a

16 recurrence even if they are not febrile or present chills. Nevertheless, only 11% of this cohort

17 was infected by *S. aureus* and we did not collect potential recurrences limiting any

18 recommendation. Another study would be necessary to assess if recurrences in those

19 patients are also atypical.

20 It is interesting to note that, even if only two-thirds of patients presented with fever $\geq 38.3^{\circ}\text{C}$

21 during bacteremia, 80% of patients showed temperature increases $>1.1^{\circ}\text{C}$ compared with

22 their baseline status. This increase of 1.1°C was defined by the IDSA as a criterion to suspect

23 infection in long-term care facilities residents (21). Our study suggests that it could be

24 applied to older patients ≥ 75 years old independently of their living place.

1 Our study confirms that bacteremia diagnosis can be challenging in older patients because
2 typical clinical manifestations may be missing. We noticed that elevated inflammatory
3 biological markers (C-reactive protein) were the reason why blood cultures were prescribed
4 even when patients had atypical manifestations of bacteremia. Procalcitonin levels were not
5 collected in the present study, but several studies suggest that this marker could be useful to
6 diagnose bacteremia even in older patients (38).

7 The key strengths of this study are its prospective design and the small number of patients
8 lost to follow-up at D90. Mortality, functional status and the institutionalization rate were
9 studied for 3 months after bacteremia episodes, making this study unique. To our
10 knowledge, this study is the first to consider atypical clinical manifestations of bacteremia
11 and its risk factors.

12 Our study has some limitations. First, no consensus has been reached on the definition of
13 atypical clinical manifestation. Most researchers have focused on afebrile bacteremia, but
14 we considered this definition to be too restrictive. Indeed, chills, hypothermia or
15 hypotension alert physicians to the possibility of bacteremia and lead to blood cultures. We
16 defined atypical presentation as closely as possible to what is considered to be “atypical” in
17 our clinical practice that is to say an absence of classical signs of bacteremia. Second, fever in
18 older patients is not easily defined. We chose 38.3°C as the cut-off value in the definition of
19 fever to increase the sensitivity of fever diagnosis. Patients remaining in the atypical group
20 would, therefore, be the most atypical. Moreover, this cut-off value is often used to define
21 fever in the existing literature (39).

22
23 To conclude, this study confirmed the poor prognosis of bacteremia in older patients.

24 Physicians should be aware of the vulnerability of these patients, who are at increased risk of

1 mortality and impaired functional status even months after the onset of such infection.
2 Atypical presentation occurs in at least 21% of patients and is an important mortality risk
3 factor. Diabetic patients are more likely to show fewer symptoms, and physicians should be
4 encouraged to perform blood culture more frequently in cases with nonspecific signs of
5 infection, but increased inflammatory markers.
6

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4

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7

8 **References**

- 9 1. World Health Organization. World report on ageing and health [Internet].WHO.2015.p.49-64.
10 Available from: <http://www.who.int/ageing/events/world-report-2015-launch/en/>
- 11 2. Duin D van. Diagnostic challenges and opportunities in older adults with infectious diseases. Clin
12 Infect Dis. 2012;54(7):97- 8.
- 13 3. Martin GS. The effect of age on the development and outcome of adult sepsis. Crit Care Med.
14 2006;34(1):15–21.
- 15 4. Mayr FB, Yende S, Linde-Zwirble WT *et al*. Infection rate and acute organ dysfunction risk as
16 explanations for racial differences in severe sepsis. JAMA. 2010;303(24):2495–503.
- 17 5. Yahav D, Eliakim-Raz N, Leibovici L, Paul M. Bloodstream infections in older
18 patients.Virulence.2015;0(0):1–12.
- 19 6. Crane SJ, Uslan DZ, Baddour LM. Bloodstream infections in a geriatric cohort: a population-based
20 study. Am J Med. 2007;120(12):1078–83.
- 21 7. Mylotte JM, Tayara A. Epidemiology of bloodstream infection in nursing home residents: evaluation in
22 a large cohort from multiple homes. Clin Infect Dis. 2002;35(12):1484–90.
- 23 8. Wester AL, Dunlop O, Melby KK *et al*. Age-related differences in symptoms, diagnosis and prognosis of
24 bacteremia. BMC Infect Dis. 2013;13:346.

- 1 9. Lee C-C, Chen S-Y. Comparison of clinical manifestations and outcome of community-acquired
2 bloodstream infections among the oldest old, elderly, and adult patients. *Medicine (Baltimore)*.
3 2007;86(3):138–44.
- 4 10. Hernández C, Fehér C, Soriano A *et al*. Clinical characteristics and outcome of elderly patients with
5 community-onset bacteremia. *J Infect*. 2015;70(2):135–43.
- 6 11. Green JE, Ariathianto Y, Wong SM *et al*. Clinical and inflammatory response to bloodstream
7 infections in octogenarians. *BMC Geriatr*. 2014;14:55.
- 8 12. Gavazzi G, Escobar P, Olive F *et al*. Nosocomial bacteremia in very old patients: predictors of
9 mortality. *Aging Clin Exp Res*. 2013;17(4):337–42.
- 10 13. Yoshikawa TT. Epidemiology and unique aspects of aging and infectious diseases. *Clin Infect*
11 *Dis*. 2000;30(6):931-3.
- 12 14. Coburn B, Morris AM, Tomlinson G, Detsky AS. Does this adult patient with suspected bacteremia
13 requires blood cultures? *JAMA*. 2012;308(5):502–11.
- 14 15. Yo C-H, Lee M-TG, Hsein Y-C *et al*. Risk factors and outcomes of afebrile bacteremia patients in an
15 emergency department. *Diagn Microbiol Infect Dis*. 2016;86(4):455–9.
- 16 16. Tokuda Y, Miyasato H, Stein GH, Kishaba T. The degree of chills for risk of bacteremia in acute febrile
17 illness. *Am J Med*. 2005;118(12):1417.
- 18 17. Fried LP, Tangen CM, Walston J *et al*. Frailty in older adults evidence for a phenotype. *J Gerontol A*
19 *Biol Sci Med Sci*. 2001;56(3):D3046–57.
- 20 18. Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care–associated
21 infection and criteria for specific types of infections in the acute care setting. *Am J Infect Control*.
22 2008;36(5):309–32.
- 23 19. Friedman ND, Kaye KS, Stout JE *et al*. Health care–associated bloodstream infections in adults: a
24 reason to change the accepted definition of community-acquired infections. *Ann Intern Med*.
25 2002;137(10):791–7.

- 1 20. Singer M, Deutschman CS, Seymour CW *et al.* The third international consensus definitions for sepsis
2 and septic shock (Sepsis-3). JAMA. 2016;315(8):801–10.
- 3 21. High KP, Bradley SF, Gravenstein S *et al.* Clinical Practice Guideline for the evaluation of fever and
4 infection in older adult residents of long-term care facilities :2008 update by the Infectious Diseases
5 Society of America. Clin Infect Dis. 2009 Jan 15;48(2):149-71.
- 6 22. Charlson ME, Pompei P, Ales KL. A new method of classifying prognostic comorbidity in longitudinal
7 studies: Development and validation. J Chronic Dis. 1987;40(5):373–83.
- 8 23. Katz S, Ford AB, Moskowitz RW *et al.* Studies of illness in the aged. The index of Activities of Daily
9 Living : a standardized measure of biological and psychosocial function. JAMA. 1963;185:914–9.
- 10 24. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of
11 daily living. The Gerontologist. 1969;9(3):179–86.
- 12 25. Søgaaard M, Schønheyder HC, Riis A *et al.* Short-term mortality in relation to age and comorbidity in
13 older adults with community-acquired bacteremia: a population-based cohort study. J Am Geriatr
14 Soc. 2008;56(9):1593–600.
- 15 26. Whitelaw DA, Rayner BL, Willcox PA. Community-acquired bacteremia in the elderly: a prospective
16 study of 121 cases. J Am Geriatr Soc. 1992;40(10):996–1000.
- 17 27. Leibovici L, Pitlik SD, Konisberger H, Drucker M. Bloodstream infections in patients older than eighty
18 years. Age Ageing. 1993;22(6):431–42.
- 19 28. Gavazzi G, Mallaret M-R, Couturier P *et al.* Bloodstream infection: differences between young-old,
20 old, and old-old patients. J Am Geriatr Soc. 2002;50(10):1667–73.
- 21 29. Retamar P, López-Prieto MD, Rodríguez-López F *et al.* Predictors of early mortality in very elderly
22 patients with bacteremia: a prospective multicenter cohort. Int J Infect Dis. 2014;26:83–7.
- 23 30. Deulofeu F, Cervelló B, Capell S *et al.* Predictors of mortality in patients with bacteremia: the
24 importance of functional status. J Am Geriatr Soc. 1998;46(1):14–8.
- 25 31. Leibovici L, Shraga I, Drucker M *et al.* The benefit of appropriate empirical antibiotic treatment in
26 patients with bloodstream infection. J Intern Med. 1998;244(5):379–86.

- 1 32. Prescott HC, Osterholzer JJ, Langa KM *et al.* Late mortality after sepsis: propensity matched cohort
2 study. *BMJ*. 2016;353.
- 3 33. Gleckman R, Hibert D. Afebrile bacteremia : a phenomenon in geriatric patients. *JAMA*.
4 1982;248(12):1478–81.
- 5 34. Breining A, Negers A, Mora L *et al.* Determinants of clinical presentation on outcomes in older
6 patients with myocardial infarction. *Geriatr Gerontol Int*. 2018;1–6.
- 7 35. Lipsky BA, Pecoraro RE, Chen MS *et al.* Factors affecting staphylococcal colonization among NIDDM
8 outpatients. *Diabetes Care*. 1987;10(4):483–6.
- 9 36. Bassetti M, Trecarichi EM, Mesini A *et al.* Risk factors and mortality of healthcare-associated and
10 community-acquired *Staphylococcus aureus* bacteremia. *Clin Microbiol Infect Dis*. 2012;18(9):862–9.
- 11 37. Chang FY, Peacock JE Jr, Musher DM *et al.* *Staphylococcus aureus* bacteremia: recurrence
12 and the impact of antibiotic treatment in a prospective multicenter study. *Medicine*
13 (Baltimore). 2003 Sep;82(5):333-9.
- 14 38. Lai CC, Chen SY, Wang JY *et al.* Diagnostic value of procalcitonin for bacterial infection in
15 elderly patients in the emergency department. *J Am Geriatr Soc*. 2010 Mar;58(3):518-22.
- 16 39. O’Grady NP, Barie PS, Bartlett JG *et al.* Guidelines for evaluation of new fever in critically ill adult
17 patients: 2008 update from the American College of Critical Care Medicine and the Infectious
18 Diseases Society of America. *Crit Care Med*. 2008;36(4):1330–49.
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- 25 Manuscript has been checked for spelling and grammar.

1 The English in this document has been checked by at least two professional editors, both
2 native speakers of English. For a certificate, please see:
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FIGURES

Figure legends :

Figure 1 : Etiologies of death over time after bacteremia

D, Day.

Figure 2 : Survival according to clinical presentation of bacteremia in 151 patients

Atypical presentation : absence of temperature $>38.3^{\circ}\text{C}$ or $<36^{\circ}\text{C}$, absence of chills and hypotension. Kaplan

Meier survival curve. p -values determined by log rank test. D, Day; n, number of patients.

Figure 3 : Evolution of Activities of Daily Living (ADL) score before and after bacteremia in 66 patients alive at Month 3 (D90).

ADL score 6/6 consisted in full independence. p -values determined by one-way ANOVA. *, $p<0.001$; D, Day; SD, Standard Deviation. ADL score was not available for 24 patients at D90.

1 **Figures :**

2 **Figure 1**

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2 **Figure 2**

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Time	Survival, n (%)			
	D0	D7	D30	D90
Typical signs	119 (100.0)	112 (94.1)	96 (81.4)	70 (64.8)
Atypical signs	32 (100.0)	27 (84.4)	22 (68.8)	12 (40.0)

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1 **Figure 3**

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Table 1. Descriptive data of 151 patients at baseline (at the time of blood collection)

	Baseline (n=151)	
	n	All patients
<i>Demographics</i>		
Age	151	85.4 (5.8)
Female sex	151	71 (47.0)
BMI (kg/m ²)	137	25.4 (5.3)
<i>Functional status</i>		
Living place: Home	151	122 (80.8)
ADL total score	151	3.8 (2.0)
IADL total score	146	2.4 (2.6)
<i>Comorbidities</i>		
Charlson total score	151	3.9 (2.7)
Chronic heart failure	151	61 (40.4)
COPD	151	20 (13.2)
Chronic renal failure	151	27 (17.9)
Cognitive impairment	148	70 (47.3)
Stroke	151	44 (29.1)
Diabetes mellitus	151	45 (29.8)
Solid/hematologic malignancy	151	42 (27.8)
Nb of medications	151	6.9 (3.4)
<i>Clinical manifestations</i>		
Severity	151	53 (35.1)

Temperature increase >1.1°C	131	106 (80.9)
Laboratory test		
Total protids (g/L)	144	66.9 (10.2)
Total leukocytes (giga/L)	150	13.9 (0.7)
GFR, (mL/min)	147	42.5 (28.5)
CRP (mg/L)	149	174.9 (118.7)

ADL, Activities of Daily Living; BMI, Body Mass Index; COPD, Chronic Obstructive Pulmonary Disease; CRP, C-Reactiv Protein; GFR, Glomerular Filtration Rate by Cockroft and Gault formula; IADL, Instrumental Activities of Daily living; Nb, number. Chronic renal failure was defined as chronic GFR <60mL/min. Severity was defined as bacteremia with ICU admission, organ failure or septic shock. Full independence consisted in ADL score 6/6 and IADL score 8/8. Quantitative variables are presented as mean (SD) and qualitative variables are presented as n (%).

Table 2. Microbiology and source of bacteremia

Bacteria identified, n (%)	163 (100)
Gram negative bacilli, n (%)	106 (65.0)
<i>Escherichia coli</i>	66 (40.5)
<i>Enterobacter</i> spp.	7 (5.0)
<i>Pseudomonas aeruginosa</i>	7 (4.3)
<i>Klebsiella pneumoniae</i>	6 (3.6)
<i>Proteus mirabilis</i>	5 (3.1)
<i>Acinetobacter</i> spp.	2 (1.2)
<i>Serratia</i> spp.	2 (1.2)
Other gram negative	9 (5.5)
Gram positive cocci, n (%)	57 (35.0)
<i>Streptococcus</i> spp.	27 (17.9)
<i>Staphylococcus aureus</i>	18 (11.0)
<i>Staphylococcus epidermidis</i>	4 (2.5)
Other Gram positive	9 (5.5)
Anaerobes, n (%)	10 (6.1)
Polymicrobial, n (%)	12 (7.9)
Multidrug resistant, n (%)	16 (9.8)
ESBL	12 (75.0)
MRSA	4 (25.0)
Source of bacteremia, n (%)	
Urinary tract	73 (48.3)
Digestive tract	25 (16.6)

Skin and soft tissue	20 (13.2)
Respiratory tract	13 (8.6)
Unknown	12 (7.9)
Other	19 (12.6)

ESBL, extended spectrum β -lactamase *Enterobacteriaceae*; MRSA,

Methicillin-Resistance *Staphylococcus Aureus*; n, number; spp,

species pluralis

Table 3 Factors associated with atypical presentation (uni and multivariate analyses)

	Atypical group	Typical group	Univariate analysis	Multivariate analysis
	(n=32)	(n=119)	OR (95%CI)	OR (95%CI)
<i>Demographics</i>				
Age	85.7 (6.5)	85.3 (5.6)	1.01 (0.95-1.08)	
Female sex	12 (37.5)	59 (49.6)	0.61 (0.27-1.36)	
BMI (kg/m ²)	24.5 (4.6)	25.6 (5.4)	0.96 (0.88-1.04)	
Living place: Home	25 (78.1)	97 (81.6)	0.81 (0.31-2.11)	
<i>Comorbidities</i>				
Congestive heart failure	16 (50.0)	45 (37.8)	1.64 (0.75-3.61)	
COPD	6 (18.8)	14 (11.8)	1.73 (0.61-4.94)	
Chronic renal disease	4 (12.5)	23 (19.3)	0.60 (0.19-1.87)	
Cognitive impairment	11 (36.7)	59 (50.0)	0.58 (0.25-1.32)	
Cerebrovascular disease	12 (37.5)	32 (26.9)	1.63 (0.72-3.71)	
Diabetes mellitus	13 (40.6)	32 (26.9)	1.86 (0.83-4.20)	2.96 (1.03-8.49)
Solid/hematologic malignancy	8 (25.0)	34 (28.6)	0.83 (0.34-2.04)	

Charlson total score	3.9 (2.8)	3.9 (2.6)	1.01 (0.87-1.17)	
Number of medications	7.3 (2.7)	6.8 (3.6)	1.05 (0.93-1.17)	
<i>Functional status</i>				
ADL total score	3.8 (2.1)	3.8 (2.0)	1.01 (0.83-1.23)	
IADL total score	2.7 (2.9)	2.3 (2.5)	1.06 (0.92-1.23)	
<i>Clinical manifestations</i>				
Delirium/altered mental status	16 (50.0)	52 (43.7)	1.29 (0.59-2.82)	
Functional decline	20 (62.5)	62 (52.1)	1.53 (0.69-3.41)	
Fall	6 (18.8)	13 (10.9)	1.88 (0.65-5.42)	
Acute urine retention/incontinence	6 (18.8)	20 (16.8)	1.14 (0.42-3.13)	
Comorbidity exacerbation	15 (46.9)	52 (43.7)	1.14 (0.52-2.49)	
Local signs of infection	11 (34.4)	39 (32.8)	0.77 (0.35-1.68)	
Secondary infection localizations	5 (17.9)	5 (4.5)	3.49 (0.99-12.28)	
<i>Laboratory tests</i>				
Total protids (g/L)	65.9 (14.8)	67.2 (8.6)	0.99 (0.95-1.03)	

Total leukocytes (giga/L)	14.4 (0.9)	13.7 (0.6)	1.00 (1.00-1.00)	
GFR (mL/min)	45.9 (43.3)	41.4 (23.5)	1.01 (0.99-1.02)	
CRP (mg/L)	188.5 (127.5)	171.1 (116.5)	1.00 (1.00-1.00)	
Potential confounding factors				
Recent antimicrobial treatment	7 (22.6)	27 (22.7)	0.99 (0.39-2.56)	
Prior use of paracetamol	8 (29.6)	20 (19.2)	1.77 (0.68-4.62)	
Betablocker treatment	17 (53.1)	45 (37.8)	1.86 (0.85-4.09)	
CSC/NSAID treatment	2 (9.1)	20 (22.0)	0.36 (0.08-1.65)	
Bacteria identified	33	126		
<i>Escherichia coli</i>	13 (40.6)	53 (44.5)	0.85 (0.39-1.88)	
<i>Streptococcus spp</i>	4 (12.5)	18 (15.1)	1.08 (0.39-2.94)	
<i>Staphylococcus aureus</i>	8 (25.0)	10 (8.4)	3.63 (1.30-10.17)	4.52 (1.16-17.56)
Multidrug resistant bacteria	4 (12.5)	18 (15.1)	0.80 (0.25-2.56)	
Nosocomial infection	6 (18.8)	35 (29.4)	0.55 (0.21-1.46)	
Appropriate antimicrobial treatment	23 (71.9)	94 (79.0)	0.68 (0.28-1.65)	

Time between symptoms and start of antimicrobial treatment (hours)	30.4 (35.8)	18.2 (25.2)	1.01 (1.00-1.03)	
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95% CI, 95% Confidence Interval; ADL, Activities of Daily Living ; BMI, Body Mass Index; COPD, Chronic Obstructive Pulmonary Disease; CRP, C-Reactive Protein; CSC, Corticosteroids; GFR, Glomerular Filtration Rate by Cockcroft and Gault formula; IADL, Instrumental Activities of Daily living ; NSAID, Non-Steroidal Anti-Inflammatory Drugs; OR, Odd Ratio; spp, species pluralis. Quantitative variables are presented as mean (Standard Deviation) and qualitative variables are presented as number (%). Univariate and multivariate analyses determined binary logistic regression.**Bold characters**, variables included in multivariate analysis