Risk factors for functional decline among survivors of Gram-negative bloodstream infection: A prospective cohort study

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Abstract

Objective
To identify risk factors for functional decline after hospitalization for Gram-negative bacteremia.

Patients and methods
A prospective cohort study based on a randomized controlled trial conducted between January 1, 2013 and August 31, 2017 in Israel and Italy. Hospitalized patients with Gram-negative bacteremia who survived until day 90 and were not bedridden at baseline were included. The primary end point was functional decline at 90 days.

Results
Five hundred and nine patients were included. The median age of the cohort was 71 years (interquartile range [IQR], 60–80 years), 46.4% (236/509) were male and 352 of 509 (69%) patients were independent at baseline. Functional decline at 90 days occurred in 24.4% of patients (124/509). In multivariable analysis; older age (odds ratio [OR], 1.03; for an one-year increment, 95% confidence interval [CI] 1.01–1.05), functional dependence in instrumental activities of daily living at baseline (OR, 4.64; 95% CI 2.5–8.6), low Norton score (OR, 0.87; 95% CI 0.79–0.96) and underlying comorbidities: cancer (OR, 2.01; 95% CI 1.14–3.55) and chronic pulmonary disease (OR, 2.23 95% CI 1.12–4.42) and longer length of hospital stay (OR 1.09; for one-day increment, 95% CI 1.04–1.15) were associated with
functional decline. Appropriate empirical antibiotic treatment was associated with lower rates of functional decline within 90 days (OR, 0.4; 95% CI 0.21–0.78).

Conclusions
Patients surviving bloodstream infections have poor long term trajectories after clinical recovery and hospital discharge. This has vast implications for patients, their family members and health policy makers.

Introduction
Gram-negative bacteremia is a major cause of morbidity and mortality in both hospitalized and community-dwelling patients. Bacteremia is the seventh ranked leading cause of death in the United States and Europe with in-hospital mortality rates of up to 30% [1–3]. The worldwide incidence of Gram-negative bacteremia has increased over the last decades. While the occurrence of bacteremia increased, mortality rates remained unchanged or in some cases decreased slightly [4–6]. Consequently, the number of bacteremia survivors is rising steadily [7]. The main focus of current management guidelines is interventions dealing with the reduction of short term mortality. Data regarding the long-term trajectory of sepsis and bacteremia among survivors are limited.

Functional decline among bloodstream infection survivors has major implications for patients, families, and the health care system. Following hospitalization due to sepsis, patients develop 1 to 2 new limitations of daily living activities which can negatively affect quality of life [8]. For the elderly, functional decline is the leading post discharge complication [9].

The present study was conducted on patients with Gram-negative bacteremia who participated in a randomized controlled trial (RCT) and survived until day 90 [10]. We aimed to determine risk factors for functional decline at 90 days among survivors of Gram-negative bacteremia and to evaluate the rate of functional decline in these patients.

Methods
Study design and patients
The design of the RCT has been described in detail previously [10]. Briefly, this was a randomized, multicenter, open-label, non-inferiority trial conducted between 2013 and 2017 in two academic centers in Israel (Rabin Medical Center, Beilinson Hospital; Rambam Health Care Campus) and one academic center in Italy (Hospital of Modena). Six hundred and four inpatients with Gram-negative bacteremia that were afebrile and hemodynamically stable for at least 48 hours, were randomized.

Bacteremia was defined as growth of Gram-negative bacteria in one or more blood cultures. Patients with bacteremia from the following sources were eligible for inclusion: urinary tract, intra-abdominal, respiratory tract, central venous catheter, or skin and soft tissue infection or an unknown source. Exclusion criteria were: other sources of infection requiring prolonged treatment, fever or hemodynamic instability in the 48 hours prior to randomization, uncontrolled focus of infection, polymicrobial growth involving Gram-positive bacteria, specific pathogens (Brucella, Salmonella), or immunosuppression (human immunodeficiency virus, neutropenia, or recent allogeneic stem cell transplantation). The RCT’s design as an
investigator initiated trial, particularly the broad inclusion criteria and the limited exclusion criteria, were meant to represent our target population.

Eligible patients were identified based on a daily review of microbiology laboratory reports of Gram-negative bacteremia. Patients fulfilling inclusion criteria were then approached by an infectious diseases physician from the study team. Patients that provided written informed consent were randomized in a 1:1 ratio to receive 7 days (intervention) or 14 days (control) antibiotic treatment. Functional capacity at baseline and hospital admission was documented for all participants in the RCT. Discharge, thirty and ninety day functional capacity were pre-planned secondary outcomes.

For the present observational prospective cohort study, we excluded: (i) Patients who did not survive until day 90 (N = 68) and (ii) patients who were bedridden before the acute infection (N = 27). The final analysis included 509 patients. The RCT and the observational study were approved by the local ethics board of each participating center: Rabin Medical Center Institutional Review Board (Israel), Rambam Institutional Review Board (Israel) and Comitato Etico dell’Area Vasta Emilia Nord (Italy). All RCT’s participants provided written informed consent before their inclusion.

Definitions and outcomes

The following data were obtained from the patient, family, attending physician and computerized medical records: baseline patient characteristics, demographics, cognitive status, comorbidities, presentation of infection, infection characteristics, antibiotic treatment, microbiological data, clinical management of infection and outcomes. Appropriate empirical treatment was defined as covering antibiotic therapy that matched the in vitro susceptibility of the Gram-negative pathogen in blood administered within 48 hours. Hospital acquired infections were defined as those occurring after 48 hours of hospital admission. Diarrhea was defined as ≥3 episodes per day for at least 2 days. Readmission was defined as any hospitalization occurring after discharge until 90 days.

Functional assessment was assessed at 5 time points: baseline, hospital admission, discharge from hospital, 30 days and 90 days; and coded into a 4-point scale: independent; functional dependence in instrumental activities of daily living (I-ADL): preparing meals, managing money, shopping, doing housework, using a telephone, leaving the house; functional dependence in basic ADL (B-ADL): eating, dressing, toileting, bathing, transferring; bedridden.

Data regarding functional status at baseline, hospital admission and discharge were collected in real time during hospital stay. Post discharge data related to functional capacity at 30 and 90 days after infection onset were collected via telephone interviews. Information was provided by the patient, the primary caretaker or the family physician.

The primary endpoint was functional decline, defined as a decline of 1-point or more from baseline.

Statistical analysis

Data were expressed as frequencies (percentages) for categorical variables, mean ± standard deviation for normally distributed continuous variables and as median and interquartile range (IQR, 25–75 percentiles) for non-normally distributed continuous variables.

Univariate analysis was conducted for all independent variables. Characteristics of subjects who had functional decline were compared to those who did not using the t-test or Mann–Whitney U-test (as appropriate based on their distribution) for continuous variables. The Chi-square test was used for categorical variables. Variables that were statistically significantly associated with functional decline (2-sided P value ≤ .05) were included in a multivariable analysis.
according to their clinical relevance. Multicollinearity was tested to examine the correlations between independent variables.

We used a logistic regression model to perform a multivariable analysis (Generalized Linear Models procedure of SPSS) and identify variables independently associated with 90-day functional decline. Four models were examined in order to adjust the best fit using the Akaike Information Criterion (AIC). Results are presented as odds ratios (OR) with 95% confidence intervals (CI). Statistical analyses were performed using IBM SPSS Statistics, version 25.

Results

Functional capacity of 604 bacteremia patients included in the RCT at 5 time-points

Functional capacity on a 4-point scale at baseline, hospital admission, hospital discharge, 30 and 90 day follow up is shown in Fig 1. At baseline, 376 patients were functionally independent, 97 patients were dependent for instrumental activities of daily living (IADL), 91 patients were dependent for basic activities of daily living (BADL) and 40 patients were bedridden (62.3%, 16.1%, 15.1%, 6.6%, respectively). At 90 days, 18% (69/376) of patients who were independent at baseline became non-independent to some degree. The rate of independent patients decreased from 62.3% (376/604) at baseline to 50.8% (307/604) at 90 days. Moreover, the rate of patients dependent for basic ADL has increased from 15.1% at baseline to 21.3%, 90 days after bacteremia onset (91/604 versus 129/604, respectively). The inconsistency in numbers of bedridden patients during the study period is explained by the number of deaths. The all-cause mortality rate within 90 days was 11.3% (68/604) (Fig 1).

Functional capacity of 536 bacteremia survivors at baseline and at day 90

The interaction between functional capacity of 536 bacteremia survivors at 2 time points: baseline and day 90, is presented in Table 1. One fifth of bacteremia survivors experienced functional decline (124/536) during study period, among them, almost 40% (46/124) had a
significant functional decline of 2 or more levels. No change in functional capacity was observed among 388 patients. Functional capacity improved in 24 patients. Among 536 survivors, 27 patients (5%) were bedridden at baseline, and therefore not included in the analysis (Table 1).

Characteristics of 509 patients included in the univariate analysis

Baseline characteristics of 509 inpatients with Gram-negative bacteremia that were not bedridden at baseline and survived to day 90 are presented in Tables 2 and 3. Patients’ median age was 71 years (interquartile range [IQR], 60–80 years), 46.4% (236/509) were male, and 73.5% lived with their families (374/509). While almost 70% of patients (352/509) were independent at baseline, most of the cohort was non-employed (80.6%, 400/509). The main source of bacteremia was the urinary tract (352/509 [69%]), and about one third were hospital-acquired (142/509).

Risk factors for functional decline

One out of four patients (124/509) showed functional decline at 90 days. In univariate analysis, patients who experienced functional decline tended to be older [76.5 years (IQR 64.3–83) vs. 69 years (IQR 58.5–78); \( P < .001 \)], were dependent for IADL at baseline and were unemployed [93.4% (114/124) vs. 76.5% (286/385); \( P < .001 \)] compared to those who did not show functional decline (Table 2). Other baseline characteristics associated with increased risk for functional decline were lower Norton score for risk of pressure ulcers (S1 Table [11]) and comorbidities including: congestive heart failure, cerebrovascular diseases, diabetes, chronic pulmonary disease, and malignancy. Infection characteristics associated with functional decline were higher Sequential Organ Failure Assessment (SOFA) score (S2 Table [12]) at infection onset and reduced consciousness at presentation. Hospital acquired bacteremia was also associated with increased risk of functional decline [38.7% (48/124) vs. 24.4% (94/385); \( P = .002 \)]. Inclusion in the RCT’s intervention arm (7 days antibiotic treatment) was similar among patients who experienced functional decline and those who did not [50% (62/124) vs. 50.1% (193/385), \( P = .98 \), respectively. Table 3].

Patients who experienced functional decline were given less often appropriate empirical antibiotic treatment [78.2% (97/124) vs. 88.1% (339/385), \( P = .007 \)]. During hospitalization patients who required oxygen supplementation, needed consultation of a physiotherapist or geriatric physician, experienced severe diarrhea or acquired pressure ulcers, were more prone to suffer from functional decline within 90 days. In addition, longer length of stay was associated with functional decline [7 days (IQR 5–12) vs. 5 days (IQR 4–7); \( P < .001 \), Table 3].
Multivariable analysis showed that older age (OR, 1.03; for an one-year increment, 95% CI 1–1.05), dependence for IADL at baseline (OR, 4.64; 95% CI 2.5–8.6), malignancy (OR, 2.01; 95% CI 1.14–3.55), chronic pulmonary disease (OR, 2.23 95% CI 1.12–4.42), low Norton score (OR, 0.87; 95% CI 0.79–0.96) longer hospital stay (OR 1.09; for an one-day increment, 95% CI 1.04–1.15) were independent risk factors for functional decline within 90 days. Appropriate empirical antibiotic treatment was associated with lower rates of functional decline within 90 days (OR, 0.4; 95% CI 0.21–0.78). SOFA score at infection onset and cerebrovascular disease were not independent risk factors for functional decline, Table 4.

Table 2. Patient characteristics a,b,c.

| Variable | No functional decline at 90 days, N = 385 | Functional decline at 90 days, N = 124 | Entire cohort N = 509 | P value |
|----------|-------------------------------------------|------------------------------------------|----------------------|---------|
| Age, median (IQR), years c | 69 (58.5–79) | 76.5 (64.3–83) | 71 (60–80) | < .001 |
| Sex, male | 173 (44.9) | 63 (30.8) | 236 (46.4) | .25 |
| Disturbed consciousness | 15 (3.9) | 10 (8.1) | 25 (4.9) | .06 |
| Marital status | | | | |
| Single | 23 (6) | 3 (2.4) | 26 (5.1) | |
| Married | 244 (63.4) | 80 (64.5) | 324 (63.7) | |
| Divorced | 38 (9.9) | 11 (8.9) | 49 (9.6) | |
| Widowed | 79 (20.5) | 29 (23.4) | 108 (21.2) | |
| Number of children, median (IQR) | 2 (1–3.5) | 3 (1–4) | 2 (1–4) | .3 |
| Functional capacity at baseline | | | | |
| Independent | 290 (75.3) | 62 (50) | 352 (69.2) | < .001 |
| Functional dependence in instrumental activities of daily living (IADL) | 34 (8.8) | 49 (39.5) | 83 (16.3) | |
| Functional dependence in basic activities of daily living (BADL) | 61 (15.8) | 13 (10.5) | 74 (14.5) | |
| Residency | | | | .36 |
| Home with family | 282 (73.2) | 92 (74.2) | 374 (73.5) | |
| Home alone | 66 (17.1) | 15 (12.1) | 81 (15.9) | |
| Nursing home | 15 (3.9) | 8 (6.5) | 23 (4.5) | |
| Other | 22 (5.7) | 9 (7.3) | 31 (6.1) | |
| No employment | 286 (76.5) | 114 (93.4) | 400 (80.6) | < .001 |
| Comorbidities | | | | |
| Charlson comorbidity score, median (IQR) d | 2 (0–3) | 2 (1–4) | 2 (1–3) | < .001 |
| Congestive heart failure | 21 (5.5) | 18 (14.5) | 39 (7.7) | .001 |
| Cerebrovascular disease | 40 (10.4) | 23 (18.5) | 63 (12.4) | .02 |
| Diabetes | | | | .02 |
| No diabetes | 251 (65.2) | 67 (54) | 318 (62.5) | |
| Diabetes without end-organ damage | 104 (27) | 38 (30.6) | 142 (27.9) | |
| Diabetes with end-organ damage | 30 (7.8) | 19 (15.3) | 49 (9.6) | |
| Chronic pulmonary disease | 37 (9.6) | 26 (21) | 63 (12.4) | .001 |
| Malignancy | 79 (20.5) | 36 (29) | 115 (22.6) | .05 |
| Norton score, median (IQR) | 19 (16–20) | 16 (14–18) | 18 (15–19) | < .001 |

a Data are presented as number (%) unless otherwise indicated.
b Abbreviations: IQR, interquartile range.
c Age-per one year increment
d S3 Table [24].
Table 3. Infection characteristics and management.*,b

| Variable                                  | No functional decline at 90 days, N = 385 | Functional decline at 90 days, N = 124 | Entire cohort N = 509 | P value |
|-------------------------------------------|------------------------------------------|----------------------------------------|-----------------------|---------|
| Predisposition                            |                                          |                                        |                       |         |
| Hospital-acquired infection               | 94 (24.4)                                | 48 (38.7)                              | 142 (27.9)            | .002    |
| Central venous catheter prior to infection | 28 (7.3)                                 | 7 (5.6)                                | 35 (6.9)              | .54     |
| Peripheral catheter prior to infection    | 73 (19)                                  | 43 (34.7)                              | 116 (22.8)            | < .001  |
| Infection characteristics and presentation |                                          |                                        |                       |         |
| Bacteria type c                           |                                          |                                        |                       | .11     |
| *Escherichia coli*                        | 260 (67.5)                               | 72 (58.1)                              | 332 (65.2)            |         |
| *Klebsiella* spp                          | 51 (13.2)                                | 16 (12.9)                              | 67 (13.2)             |         |
| Other *Enterobacteriaceae*                | 49 (12.7)                                | 18 (14.5)                              | 67 (13.2)             |         |
| *Acinetobacter* spp                       | 4 (1)                                    | 2 (1.6)                                | 6 (1.2)               |         |
| *Pseudomonas* spp                         | 18 (4.7)                                 | 14 (11.3)                              | 32 (6.3)              |         |
| Other                                     | 3 (0.8)                                  | 2 (1.6)                                | 5 (1)                 |         |
| Source of bacteremia                      |                                          |                                        |                       | .04     |
| Urinary tract                             | 269 (69.9)                               | 83 (66.9)                              | 352 (69.2)            |         |
| Primary, unknown source                   | 20 (5.2)                                 | 16 (12.9)                              | 36 (7.1)              |         |
| Abdominal/biliary                         | 55 (14.3)                                | 10 (8.1)                               | 65 (12.8)             |         |
| Respiratory                               | 14 (3.6)                                 | 6 (4.8)                                | 20 (3.9)              |         |
| Central venous catheter                   | 22 (5.7)                                 | 8 (6.5)                                | 30 (5.9)              |         |
| Skin and soft tissue                      | 5 (1.3)                                  | 1 (0.8)                                | 6 (1.2)               |         |
| SOFA score at onset, median (IQR) [min, max] | 2 (1–3) [0,11]                           | 2 (1–3) [0,15]                         | 2 (1–3) [0,15]        | .05     |
| Study arm-7 days                          | 193 (50.1)                               | 62 (50)                                | 255 (50.1)            | .98     |
| Vasopressor support                       | 7 (1.8)                                  | 3 (2.4)                                | 10 (2)                | .67     |
| Oxygen supplementation                    | 34 (8.8)                                 | 18 (14.5)                              | 52 (10.2)             | .07     |
| Infection management                      |                                          |                                        |                       |         |
| Appropriate empirical treatment administered within 48 h | 339 (88.1)                              | 97 (78.2)                              | 436 (85.7)            | .007    |
| Physiotherapy consultation during hospitalization | 55 (14.3)                              | 43 (34.7)                              | 98 (19.3)             | < .001  |
| Geriatrician consultation during hospitalization | 9 (2.3)                                | 9 (7.3)                                | 18 (3.5)              | .01     |
| Hospital-acquired Pressure ulcer          | 10 (2.6)                                 | 11 (8.9)                               | 21 (4.1)              | .002    |
| Severe diarrhea                           | 21 (5.5)                                 | 13 (10.5)                              | 34 (6.7)              | .05     |
| Length of hospital stay, median (IQR), days d | 1 (0–3)                                | 2 (0–6)                                | 1 (0–3)               | < .001  |
| Discharge disposition                     |                                          |                                        |                       | < .001  |
| Home with family                          | 280 (72.7)                               | 85 (68.5)                              | 365 (71.7)            |         |
| Home alone                                | 63 (16.4)                                | 12 (9.7)                               | 75 (14.7)             |         |
| Nursing home                              | 15 (3.9)                                 | 5 (4)                                  | 20 (3.9)              |         |
| Long term care facility                   | 1 (0.3)                                  | 3 (2.4)                                | 4 (0.8)               |         |
| Rehabilitation center                     | 4 (1)                                    | 10 (8.1)                               | 14 (2.8)              |         |
| Transferred to another hospital            | 0 (0)                                    | 1 (0.8)                                | 1 (0.2)               |         |
| Other                                     | 22 (5.7)                                 | 8 (6.5)                                | 30 (5.9)              |         |
| Hospital readmissions                     | 128 (33.2)                               | 63 (50.8)                              | 191 (37.5)            | < .001  |

* Data are presented as number. (%) unless otherwise indicated.

b Abbreviations: SOFA, sequential organ failure assessment.

c Fourteen patients with bloodstream infection with *Enterobacteriaceae* had a polymicrobial infection (9 patients in the group of patients who experienced functional decline and in 5 patients who did not show functional decline). Of these 14 patients, 9 had another *Enterobacteriaceae* as a co-pathogen, 3 had *Pseudomonas* spp., and 2 had *Aeromonas* spp.

d Length of hospital stay - per one day increment.

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In this observational study of 509 hospitalized patients with Gram-negative bacteremia, one out of four patients experienced functional decline within 90 days. Among patients who were functionally independent at baseline, 8% became dependent in basic ADL within 90 days of bacteremia onset. Furthermore, 13% of patients who were functionally dependent at baseline became bedridden within 90 days. Factors associated with increased risk for functional decline were: older age, dependency on others for IADL, malignancy, chronic pulmonary disease, low Norton score, inappropriate empirical treatment and higher length of hospital stay. High SOFA score at infection onset was associated with functional decline but did not emerge as such at multivariable analysis.

Dependent patients for IADL at baseline were at higher risk for functional decline within 90 days. Interestingly, patients with baseline dependence in basic ADL had low risk of functional decline. Similar results were demonstrated in a prospective study by Iwashyna et al. that showed sepsis patients with severe limitations at baseline did not experience significant functional decline compared to patients with normal functional capacity [8]. This finding was explained by a possible ceiling effect among this group of patients.

In our study, appropriate empiric antibiotic treatment was found to be a protective factor of functional decline. This outcome can be explained by a real effect or by a potential confounding factor that was not entered to our model. Studies investigating the impact of inappropriate empirical antibiotic therapy on short term mortality among patients with blood stream infections yielded conflicting results. While some studies have shown that inappropriate empirical antibiotic treatment increase mortality, [13–15] others have found no association [16, 17]. The controversy probably stems from heterogeneity in studies’ methodologies [13, 18, 19]. The impact of inappropriate empirical therapy on long term mortality was demonstrated in one study, showing significantly higher one-year mortality among patients with bacteremia receiving inappropriate empirical therapy [19]. However, the influence on functional capacity was not assessed.

### Table 4. Multivariable analysis for factors associated with functional decline among 90 days survivors*

| Risk factor                              | Multivariable logistic regression analysis OR (95% CI) | Univariate analysis OR (95% CI) |
|------------------------------------------|------------------------------------------------------|--------------------------------|
| Year of age b                            | 1.03 (1–1.05)*                                      | 1.04 (1.02–1.05)              |
| Functional capacity at baseline          | Reference                                            | Reference                      |
| Independent                              |                                                      |                                |
| Functional dependence in instrumental activities of daily living (IADL) | 4.64 (2.5–8.6)*                                    | 6.74 (4.02–11.3)              |
| Functional dependence in basic activities of daily living (BADL) | 0.24 (0.1–0.6)*                                    | 1 (0.52–1.93)                 |
| Malignancy                               | 2.01 (1.14–3.55)*                                   | 1.59 (1–2.51)                 |
| Cerebrovascular disease                  | 1.99 (0.97–4.08)                                    | 1.96 (1.12–3.43)              |
| Chronic pulmonary disease                | 2.23 (1.12–4.42)*                                   | 2.5 (1.44–4.32)               |
| Norton score                             | 0.87 (0.79–0.96)*                                   | 0.86 (0.8–0.92)               |
| SOFA score at presentation               | 1.12 (0.98–1.28)                                    | 1.12 (1.01–1.25)              |
| Hospital-acquired infection              | 1.65 (0.92–2.95)                                    | 1.96 (1.27–3.01)              |
| Appropriate empirical treatment administered within 48 h | 0.4 (0.21–0.78)*                                 | 0.49 (0.29–0.83)              |
| Length of hospital stay                  | 1.09 (1.04–1.15)*                                   | 1.12 (1.08–1.17)              |

*a Abbreviations: OR, odds ratio; CI, confidence interval.

*b Age-per one year increment; Length of hospital stay: per one day increment.

Statistically significant $P < .05$.

Multivariable analysis using generalized linear models (GLM). $N = 491$, Akaike’s Information Criterion (AIC)– 428.936, constant $\beta = -1.562$.

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### Discussion

In this observational study of 509 hospitalized patients with Gram-negative bacteremia, one out of four patients experienced functional decline within 90 days. Among patients who were functionally independent at baseline, 8% became dependent in basic ADL within 90 days of bacteremia onset. Furthermore, 13% of patients who were functionally dependent at baseline became bedridden within 90 days. Factors associated with increased risk for functional decline were: older age, dependency on others for IADL, malignancy, chronic pulmonary disease, low Norton score, inappropriate empirical treatment and higher length of hospital stay. High SOFA score at infection onset was associated with functional decline but did not emerge as such at multivariable analysis.

Dependent patients for IADL at baseline were at higher risk for functional decline within 90 days. Interestingly, patients with baseline dependence in basic ADL had low risk of functional decline. Similar results were demonstrated in a prospective study by Iwashyna et al. that showed sepsis patients with severe limitations at baseline did not experience significant functional decline compared to patients with normal functional capacity [8]. This finding was explained by a possible ceiling effect among this group of patients.

In our study, appropriate empiric antibiotic treatment was found to be a protective factor of functional decline. This outcome can be explained by a real effect or by a potential confounding factor that was not entered to our model. Studies investigating the impact of inappropriate empirical antibiotic therapy on short term mortality among patients with blood stream infections yielded conflicting results. While some studies have shown that inappropriate empirical antibiotic treatment increase mortality, [13–15] others have found no association [16, 17]. The controversy probably stems from heterogeneity in studies’ methodologies [13, 18, 19]. The impact of inappropriate empirical therapy on long term mortality was demonstrated in one study, showing significantly higher one-year mortality among patients with bacteremia receiving inappropriate empirical therapy [19]. However, the influence on functional capacity was not assessed.
We found that a large proportion of hospitalized patients with Gram-negative bacteremia experienced functional loss. Similar trends were observed in previously published studies. In a multicenter, prospective cohort study of 1,279 adults who were hospitalized for acute medical illnesses, 31% experienced functional decline between preadmission and hospital discharge. After three months, 40% of the cohort experienced disabilities in daily activities [20]. In concordance with our study results, a systematic review aimed to identify predictors of functional decline revealed that the most common risk factors are age, lower functional status, cognitive impairment, depression and length of hospital stay [21].

This study has several limitations. First, our study included only Gram-negative bacteremia patients who gave consent to participate in the RCT, this could limit the generalization of results. However, one of the RCT strengths was its nonrestrictive inclusion criteria that enabled a representative cohort of eligible patients [10]. Second, functional capacity at 30 and 90 days was assessed through telephone interviews. This could result in a self-reporting bias leading to either underestimation or overestimation of the outcome according to the patient’s subjective perception. Third, definitions and measurement methods of functional decline may differ between studies leading to difficulty in assessment of functional capacity. While many studies, including our RCT, examined all-cause mortality or other objectively assessed outcomes, this study assessed outcomes that impact patient’s quality of life; whether they will return to baseline activity level, what are the risk factors for functional decline and whether they can be prevented. In order to do this we only addressed patients who were alive on day 90.

Conclusions

Functional decline is associated with an increased risk of mortality, and with higher health care costs [22, 23]. This study contributes to the identification of patients at risk of functional deterioration after hospitalization. We cannot expect patients with severe infections to return rapidly to their pre-infection functional status. At 90 days a quarter of patients surviving Gram-negative sepsis had a functional decline. These patients need support. Understanding the risk factors for functional decline is essential to clinicians, patients, their family members and health policy makers.

Supporting information

S1 Table. Norton score for risk of pressure ulcers.
(DOCX)

S2 Table. Sequential Organ Failure Assessment (SOFA) score.
(DOCX)

S3 Table. Charlson comorbidity index.
(DOCX)

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All the authors were responsible for revision of final manuscript for submission.

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**References**

1. Goto M, Al-Hasan MN. Overall burden of bloodstream infection and nosocomial bloodstream infection in North America and Europe. Clin Microbiol Infect. 2013; 19(6):501–509. https://doi.org/10.1111/1469-0691.12195 PMID: 23473333

2. Bates DW, Pruess KE, Lee TH. How bad are bacteremia and sepsis? Outcomes in a cohort with suspected bacteremia. Arch Intern Med. 1995; 155(6):593–598. https://doi.org/10.1001/archinte.1995.00430060050006 PMID: 7887754

3. Haug JB, Harthug S, Kalager T, Digranes A, Solberg CO. Bloodstream Infections at a Norwegian University Hospital, 1974–1979 and 1988–1989: Changing Etiology, Clinical Features, and Outcome. Clin Infect Dis. 1994; 19(2):246–256. https://doi.org/10.1093/clinids/19.2.246 PMID: 7986895

4. Segaaard M, Nergaard M, Dethlefsen C, Schønheyder HC. Temporal changes in the incidence and 30-day mortality associated with bacteremia in hospitalized patients from 1992 through 2006: a population-based cohort study. Clin Infect Dis. 2011; 52(1):61–69. https://doi.org/10.1093/cid/ciq069 PMID: 21148521

5. Madsen KM, Schønheyder HC, Kristensen B, Sørensen HT. Secular trends in incidence and mortality of bacteremia in a Danish county 1981–1994. APMIS. 1999; 107(3):346–352. https://doi.org/10.1111/j.1699-0463.1999.tb01563.x PMID: 10223938

6. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. Crit Care Med. 2008; 36(1):296–327. https://doi.org/10.1097/01.CCM.0000288158.12101.41 PMID: 18158437

7. Leibovici L. Long-term consequences of severe infections. Clin Microbiol Infect. 2013; 19(6):510–512. https://doi.org/10.1111/1469-0691.12160 PMID: 23397980
8. Iwashyna TJ, Ely EW, Smith DM, Langa KM. Long-term cognitive impairment and functional disability among survivors of severe sepsis. JAMA. 2010; 304(16):1787–1794. https://doi.org/10.1001/jama.2010.1553 PMID: 20978258

9. Inouye SK, Bogardus ST, Baker DI, Leo-Summers L, Cooney LM. The Hospital Elder Life Program: a model of care to prevent cognitive and functional decline in older hospitalized patients. Hospital Elder Life Program. J Am Geriatr Soc. 2000; 48(12):1697–1706. https://doi.org/10.1111/j.1532-5415.2000.tb03885.x PMID: 11129764

10. Yahav D, Franceschini E, Koppel F, Turjeman A, Babich T, Bitterman R, et al. Seven Versus 14 Days of Antibiotic Therapy for Uncomplicated Gram-negative Bacteremia: A Noninferiority Randomized Controlled Trial. Clin Infect Dis. 2018; 69(7):1091–1098. https://doi.org/10.1093/cid/ciy1054 PMID: 30535100

11. Norton D. Calculating the risk: reflections on the Norton scale. Decubitus. 1989; 2(3):24–31. PMID: 2775471

12. Vincent JL, Moreno R, Takala J, Willatts S, De Mendonça A, Bruining H, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. Intensive Care Med. 1996; 22(7):707–710. https://doi.org/10.1007/BF01709751 PMID: 8844239

13. Paul M, Shani V, Muchtar E, Kariv G, Robenshtok E, Leibovici L. Systematic review and meta-analysis of the efficacy of appropriate empiric antibiotic therapy for sepsis. Antimicrob Agents Chemother. 2010; 54(11):4861–4863. https://doi.org/10.1128/AAC.00627-10 PMID: 20733044

14. Kang CI, Kim SH, Park WB, Lee KD, Kim HB, Kim EC, et al. Bloodstream infections caused by antibiotic-resistant gram-negative bacilli: risk factors for mortality and impact of inappropriate initial antimicrobial therapy on outcome. Antimicrob Agents Chemother. 2005; 49(2):760–766. https://doi.org/10.1128/AAC.49.2.760-766.2005 PMID: 15673761

15. Retamar P, Portillo MM, López-Prieto MD, Rodríguez-López D, De Cueto M, García MV, et al. Impact of inadequate empirical therapy on the mortality of patients with bloodstream infections: a propensity score-based analysis. Antimicrob Agents Chemother. 2012; 56(1):472–478. https://doi.org/10.1128/AAC.00462-11 PMID: 22005999

16. Zaragoza R, Artero A, Camarena JJ, Sancho S, González R, Nogueira JM. The influence of inadequate empirical antimicrobial treatment on patients with bloodstream infections in an intensive care unit. Clin Microbiol Infect. 2003; 9(5):412–418. https://doi.org/10.1046/j.1469-0691.2003.00656.x PMID: 12848754

17. Thom KA, Schweizer ML, Osih RB, McGregor JC, Furuno JP, Perencevich EN, et al. Impact of Empiric Antimicrobial Therapy on Outcomes in Patients with Escherichia coli and Klebsiella pneumoniae Bacteremia: A Cohort Study. BMC Infect Dis. 2008; 8(1):116. https://doi.org/10.1186/1471-2334-8-116 PMID: 18793400

18. McGregor JC, Rich SE, Harris AD, Perencevich EN, Osih R, Lodise TP Jr, et al. A systematic review of the methods used to assess the association between appropriate antibiotic therapy and mortality in bacteremic patients. Clin Infect Dis. 2007; 45(3):329–337. https://doi.org/10.1086/519283 PMID: 17599310

19. Gradel KO, Jensen US, Schenhuyder HC, Østergaard C, Knudsen JD, Wehberg S, et al. Impact of appropriate empirical antibiotic treatment on recurrence and mortality in patients with bacteraemia: a population-based cohort study. BMC Infect Dis. 2017; 17(1):122. https://doi.org/10.1186/s12879-017-2233-z PMID: 28186732

20. Sager MA, Franke T, Inouye SK, Landefeld CS, Morgan TM, Rudberg MA, et al. Functional outcomes of acute medical illness and hospitalization in older persons. Arch Intern Med. 1996; 156(6):645–652. https://doi.org/10.1001/archinte.1996.00440060067008 PMID: 8629876

21. Hoogerdijn JG, Schuurmans MJ, Duijnstee MSH, de Rooij SE, Grypdonck MFH. A systematic review of predictors and screening instruments to identify older hospitalized patients at risk for functional decline. J Clin Nurs. 2007; 16(1):46–57. https://doi.org/10.1111/j.1365-2702.2006.01579.x PMID: 17181666

22. Yeh KP, Lin MH, LiuLK, Chen LY, Peng LN, Chen LK. Functional decline and mortality in long-term care settings: Static and dynamic approach. J Clin Gerontol Geriatr. 2014; 5(1):13–17. https://doi.org/10.1016/j.jcgg.2013.08.001

23. Schupf N, Tang MX, Albert SM, Costa R, Andrews H, Lee JH, et al. Decline in cognitive and functional skills increases mortality risk in nondemented elderly. Neurology. 2005; 65(8):1218–1226. https://doi.org/10.1212/01.wnl.0000180970.07386.cb PMID: 16247048

24. Charlson M, Pompei P, Ales K, MacKenzie C. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. J Chronic Dis. 1987; 40(5):373–383. https://doi.org/10.1016/0021-9681(87)90171-8 PMID: 3558716