

# Impact of a Multistep Bundles Intervention in the Management and Outcome of Gram-Negative Bloodstream Infections: A Single-Center “Proof-of-Concept” Study

Davide Fiore Bavaro,<sup>1,\*</sup> Lucia Diella,<sup>1,\*</sup> Alessandra Belati,<sup>1,\*</sup> Nicolò De Gennaro,<sup>1</sup> Deborah Fiordelisi,<sup>1</sup> Roberta Papagni,<sup>1</sup> Giacomo Guido,<sup>1</sup> Elda De Vita,<sup>1</sup> Luisa Frallonardo,<sup>1</sup> Michele Camporeale,<sup>1</sup> Carmen Pellegrino,<sup>1</sup> Sofia Denicolò,<sup>2</sup> Enrica Ranieri,<sup>2</sup> Michele Fabiano Mariani,<sup>1</sup> Gaetano Brindicci,<sup>1</sup> Luigi Ronga,<sup>2</sup> Francesco Di Gennaro,<sup>1</sup> Adriana Mosca,<sup>2</sup> and Annalisa Saracino<sup>1</sup>

<sup>1</sup>Department of Biomedical Sciences and Human Oncology, Clinic of Infectious Diseases, University of Bari “Aldo Moro,” Bari, Italy, and <sup>2</sup>Section of Microbiology and Virology, University of Bari, Bari, Italy

**Background.** This is a “proof-of-concept” study aiming to evaluate the impact of a multistep bundles intervention in the management and outcomes of patients with gram-negative bloodstream infections (GN-BSIs).

**Methods.** This was a single-center, quasi-experimental design study. In the pre-phase (January 2019 to May 2020), patients were retrospectively enrolled. During the post-phase (June 2020 to September 2021), all patients were prospectively enrolled in a nonmandatory 3-step bundles intervention arm including (i) step 1: imaging to detect deep foci of infection, follow-up blood cultures and procalcitonin monitoring; (ii) step 2: early targeted antibiotic treatment and surgical source control; (iii) step 3: discontinuation of antibiotics within 7–10 days in case of uncomplicated BSI. Patients were followed up to 28 days from BSI onset. The primary outcome was 28-day mortality.

**Results.** A total of 271 patients were enrolled: 127 and 144 in the pre- vs post-phase, respectively. Full application of step 1 (67% vs 42%;  $P < .001$ ), step 2 (83% vs 72%;  $P = .031$ ), and step 3 (54% vs 2%;  $P < .001$ ) increased in the post-phase. Overall, the intervention reduced 28-day mortality (22% vs 35%, respectively;  $P = .016$ ) and the median duration of total (11 vs 15 days;  $P < .001$ ) and targeted (8 vs 12 days;  $P = .001$ ) antibiotic therapy. Finally, the multivariate Cox regression confirmed the independent protective effect of adherence to step 1 (adjusted hazard ratio [aHR], 0.36; 95% CI, 0.20–0.63) and step 2 (aHR, 0.48; 95% CI, 0.29–0.81) on risk of 28-day mortality.

**Conclusions.** Clinical management and outcomes of patients with GN-BSIs may be improved by providing a pre-established multistep bundles intervention.

**Keywords.** gram negative; antimicrobial resistance; antimicrobial stewardship; bloodstream infections.

Diagnostic and therapeutic management of patients with gram-negative bloodstream infections (GN-BSIs) has been widely investigated in recent years [1]; however, some important questions are still unsolved in this field.

Currently, areas of debate extend far beyond appropriate targeted therapies for different pathogens. For instance, strategies to recognize potential foci that should be properly controlled and follow-up approaches to quickly detect complications or

determine the duration for each patient of tailored antibiotic treatment are still under investigation [2, 3].

Prior successful experiences have raised the importance of managing patients with gram-positive BSIs using multiple bundles, including assessment of infection source, detection of persistent bacteremia, and ideal exposure to antibiotics. These bundles are currently defined as quality-of-care indicators (QCI) for *Staphylococcus aureus* BSI management [4, 5].

However, bundles for management of patients with GN-BSIs are still not available. As recently shown in a survey on the management of patients with GN-BSI among infectious diseases (ID) specialists [6], the lack of guidelines likely explains the large heterogeneity in clinical practice and the non-evidence-based management of these patients, who are already at significant risk of mortality due to sepsis.

Nevertheless, certain interventions derived from prior experience on gram-positive BSIs could be protective also in case of GN-BSIs and need to be further investigated as possible QCIs. For instance, early surgical source control of the deep site of

Received 10 June 2022; editorial decision 13 September 2022; accepted 15 September 2022; published online 17 September 2022

\*Equal contribution.

Correspondence: Bavaro Davide Fiore, MD, Clinic of Infectious Diseases, University of Bari, Piazza G. Cesare, 11, 70124 Bari, Italy (davidebavaro@gmail.com).

Open Forum Infectious Diseases®

© The Author(s) 2022. Published by Oxford University Press on behalf of Infectious Diseases Society of America. This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs licence (<https://creativecommons.org/licenses/by-nc-nd/4.0/>), which permits non-commercial reproduction and distribution of the work, in any medium, provided the original work is not altered or transformed in any way, and that the work is properly cited. For commercial re-use, please contact journals.permissions@oup.com  
<https://doi.org/10.1093/ofid/ofac488>

infection was demonstrated to be protective for mortality in patients with intra-abdominal infection and associated BSIs [7, 8]; however, standardized use of abdominal and/or thoracic imaging to identify sources of infection and to exclude deep abscesses as a possible strategy to guarantee early source control has been poorly explored in the literature, and mostly in the setting of BSIs from urinary sources [9, 10]. The use of follow-up blood cultures (FUBCs), however, showed a potential protective role when performed in patients with complicated infections [11], but these data are still not generalizable to all kinds of infections [12].

Finally, some important studies have redefined the concept of treatment duration for BSIs, showing that “shorter is better” when possible [13]: The crucial point is the identification of patients eligible for short-term therapy and not at higher risk of recurrence/relapse of the infection.

In accordance with these data, a multistep bundles strategy for the management of GN-BSI was established in our hospital, including a series of literature-based QICs. The aim of this study was to evaluate the impact of this intervention on the management and outcomes of patients with GN-BSIs.

## METHODS

### Study Design and Study Population

This was a comparative cohort study, with a quasi-experimental design, that evaluated the efficacy of a pre-established multistep management bundles intervention on outcomes of GN-BSI.

All consecutive adult (aged  $\geq 18$  years) patients who developed a BSI caused by at least 1 gram-negative bacterium (including polymicrobial BSIs) and who were evaluated by an infectious diseases specialist from January 1, 2019, to September 30, 2021, were included in this study.

Episodes of GN-BSIs by different bacteria occurring in the same patient were analyzed independently only when the index blood cultures were separated by at least 7 days.

Exclusion criteria were informed refusal and/or patients who (1) were younger than 18 years, (2) died before the administration of at least 1 active antibiotic, (3) did not have any documented gram-negative pathogen at blood cultures, (4) had no evaluation by an ID specialist.

As this work aimed to assess the efficacy of specific bundles on GN-BSI management and outcome, the abovementioned exclusion criteria (especially #2 and #4), were based on the following considerations: (i) in order to minimize the possible effect on mortality of inappropriate antimicrobial therapies (in terms of drugs, dosage, route of administration) prescribed without the supervision of a specialist of antibiotic therapy; (ii) in order to limit the impact on outcomes of patients who died immediately after the onset of GN-BSI, for whom none of these bundles would be applicable.

Patients with GN-BSI were discharged only in case of available oral or outpatient antimicrobial therapy (based on

antibiogram of pathogen isolated) and clinical stability. The duration of therapy was completed as planned by the ID specialist independent of discharge.

Patients were followed until discharge or until the day of death. In case of discharge, mortality was evaluated using information from hospital records, which were linked to a municipal records database. Our hospital information system allows us access to patient personal data (living or deceased status, date of death). For this reason, we have no patients lost to follow-up in mortality analyses.

### Microbiologic Diagnosis

Index BCs were performed at the discretion of the attending physician and were not mandated by a study protocol. Samples were collected for the microbiology assessment before starting empirical antimicrobial therapy. According to current guidelines, blood cultures were performed by collecting 15–20 mL of blood per culture set. Two bottles per set were used and immediately placed into a BACT/ALERT 3D instrument (Biomérieux Inc., Marcy-l'Étoile, France). Positive aerobic blood cultures were subcultured on MacConkey agar, CNA blood agar, Sabouraud dextrose agar, mannitol-salt agar, and chocolate agar and incubated aerobically at 37°C for 24 hours.

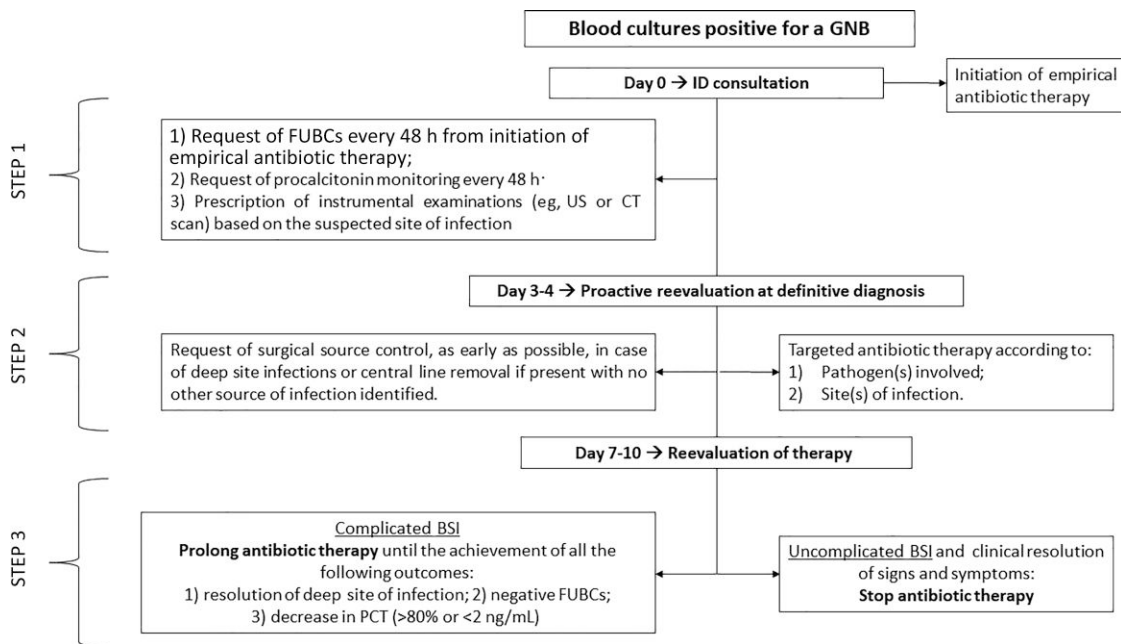
Identification and antibacterial susceptibility were tested on the automated VITEK 2 system and VITEK MS (Biomérieux) according to the manufacturer's instructions. The interpretative breakpoints of minimum inhibitory concentration values were based on the criteria of the European Committee on Antimicrobial Susceptibility Testing (EUCAST).

The presence of the *bla* genes for carbapenemases, including KPC and NDM, was determined by polymerase chain reaction using the GeneXpert System (Cepheid).

### Intervention

Patients included in this comparative study were divided into 2 groups:

- (a) Pre-intervention group: all patients retrospectively enrolled from January 1, 2019, to May 31, 2020. According to the hospital internal guidelines, these patients were treated with at least 10–14 days of antibiotic therapy after the index blood culture, and discontinuation of antibiotics was decided on the basis of improvement demonstrated on clinical and blood tests. Any other instrumental or microbiological investigations after the initiation of treatment was based on clinical judgment.
- (b) Postintervention group: all patients treated according to our nonmandatory internal multistep management bundles and prospectively enrolled from June 1, 2020, to September 30, 2021.



**Figure 1.** Multistep management bundles for gram-negative BSIs. Abbreviations: BSI, bloodstream infection; CT, computed tomography; FUBCs, follow-up blood cultures; GNB, gram-negative bacteria; ID, infectious disease; PCT, procalcitonin; US, ultrasonography.

Importantly, during the study period, no other significant events occurred in our hospital that could have influenced the ID team treatment strategies of GN-BSI (eg, large outbreak of a resistant GNR, modification in ID team, change in policy of antibiotic treatment, etc.).

#### Multistep Management Bundles for Gram-Negative BSIs

The multistep management bundles were based on multiple QICs, according to current literature and arbitrary choice of members of our ID team, applied following the identification of a gram-negative bloodstream infection (Figure 1).

Step 1 (when blood cultures turned positive for at least 1 gram-negative bacterium) performed along with the initiation of empirical antibiotic therapy:

- (1) Request of follow-up blood cultures (FUBCs) every 48 hours (1 set for aerobes and anaerobes every 48 hours from peripheral vein and central lines if present until the first negative result) until 1 negative result [11, 12, 14, 15].
- (2) Request of procalcitonin monitoring every 48 hours until reduction of >80% or absolute value <2 ng/mL [16].
- (3) In all cases, prescription of at least ultrasonography of the abdomen was part of baseline tests requested at the time of first ID evaluation. Importantly, in case of suspected deep site of infection, other types of instrumental examination (eg, computed tomography) were immediately requested in order to confirm the presence of drainable abscesses [9, 10].

Step 2 (proactive re-evaluation after 72 hours at the acquisition of definitive antibiogram and/or definition of source of infection):

- (1) Targeted antibiotic therapy according to pathogen(s) involved and site(s) of infection.
- (2) Request of surgical source control as early as possible in case of deep site infections, or central line removal if present with no other source of infection identified [7, 8].

Step 3 (pro-active re-evaluation at days 7–10 of therapy after index blood culture):

- (1) Discontinuation of treatment in all cases of uncomplicated BSI (uBSI) with absence of fever and clinical stability, or therapy prolongation in cases of complicated BSI (cBSI) [13, 17].

GN-BSIs were defined as “uncomplicated” by the following criteria at day 7: (a) negative FUBCs (after at least 3 days of culture); (b) complete control of any deep site of infection; (c) decrease in procalcitonin (PCT) or serum values by at least 80%, or an absolute value <2 ng/mL; (d) afebrile from at least 72 hours and hemodynamically stable.

The remaining cases were considered complicated BSI. The discontinuation of antimicrobials was reevaluated every 5–7 days by an ID specialist checking for resolution of the deep site of infection, achievement of negative FUBCs, and decrease in PCT or serum values by at least 80%, or an absolute value <2 ng/mL.

## Outcomes

The primary end point was mortality (all-cause 14-day and 28-day mortality).

Secondary end points were:

- (i) adherence to QCI multistep management bundles;
- (ii) total duration of antibiotic therapy;
- (iii) severe (grade 3–5) adverse events to antibiotic therapy (evaluated within 14 days of discontinuation);
- (iv) number of BSIs requiring a surgical source control;
- (v) 30-day and 90-day recurrence/relapse of the initial infection, defined as any infection caused by the same pathogen within 30 or 90 days of discontinuation of therapy. In case of deep-site infections, any recrudescence of signs of infection in the same site was considered recurrence.
- (vi) 90-day mortality.

## Other Definitions

Acute severity of illness was assessed using the qPitt bacteremia score, measured retrospectively on the day before GN-BSI was diagnosed [18]; primary sources of GN-BSI were defined according to the Centers for Disease Control and Prevention [19].

Empirical antibiotic treatment was considered appropriate if at least 1 active drug according to in vitro susceptibility results had been initiated in the first 12 hours after the blood culture was obtained.

We defined targeted therapy as any antibiotic selected on the basis of the agent responsible for the BSI and its susceptibility pattern.

Patients were defined as “severely immunocompromised” if at specific risk for opportunistic infection: recent solid organ transplantation, prolonged neutropenia with absolute neutrophil count <500 cells/mL during the BSI treatment course, CD4 cell count <200 cells/mL in HIV patients, or chronic corticosteroids and/or other immunomodulator therapy in those at risk for severe infections.

Clinical stability was defined using Halm’s criteria [20].

Any infection occurring in the course of treatment of BSI that required additional treatments, independent of the site of infection, was considered a breakthrough infection.

## Statistical Analysis

All data were anonymized and collected on an electronic database.

Descriptive statistics were produced for demographic, clinical, and laboratory characteristics of patients. Medians and interquartile ranges (q1–q3) were produced for continuous variables, and numbers and percentages were produced for categorical variables.

The distribution of outcomes, clinical findings, and laboratory findings between groups (standard-of-care and intervention groups) was analyzed with univariate parametric and nonparametric tests, with Kruskal-Wallis and Mann-Whitney *U* tests (where appropriate) for continuous variables, and with

Pearson’s  $\chi^2$  test (Fisher’s exact test where appropriate) for categorical variables, according to data distribution.

In order to assess predictors of all-cause 14-day and 28-day mortality, a univariate Cox regression model was produced for variables of interest. Then, a stepwise multivariable Cox regression was applied to control for potential confounders and was adjusted for variables associated ( $P < .1$ ) with end points on univariate analysis or considered significant according to the current literature. In the final model, full adherence to step 1 and step 2 was included as a proxy for intervention, because immortal time bias could not be entirely ruled out for step 3 (only those surviving at least 7 days could be included in step 3).

Finally, Kaplan-Meier curve estimates were also performed for variables of interest. In all cases, a  $P$  value <.05 was considered statistically significant. Statistical analysis was performed using STATA “Special Edition,” version 16.1 (StataCorp, College Station, TX, USA).

## RESULTS

### General Characteristics of the Study Population

During the study time frame, 271 eligible patients with a gram-negative BSI were included (Table 1). A total of 127 patients were managed in the pre-intervention phase, while 144 were managed in the postintervention phase.

Overall, 158 subjects (58%) were males, with a median (q1–q3) age of 68 (57–79) years; the median age was lower in the postintervention group compared with pre-intervention patients (64 vs 72 years, respectively;  $P = .002$ ). Conversely, all other characteristics (ward of evaluation, Charlson comorbidity index, incidence of concurrent coronavirus disease 2019, and comorbidities) were similar in the 2 groups, with the exception of solid neoplasia, which was more frequent in the postintervention group (26% vs 10%;  $P = .001$ ).

In analyzing the clinical picture associated with GN-BSIs (Table 1), some differences were noted. At first, the source of infection was significantly dissimilar in the 2 groups, with a higher incidence of primary/urinary-source BSIs in the pre-phase (30% vs 61%;  $P < .001$ ), while in the post-phase a higher incidence of intra-abdominal (28% vs 13%;  $P = .003$ ), skin and soft tissue (10% vs 3%;  $P = .019$ ), and endovascular sources (8% vs 2%;  $P = .019$ ) was recorded.

Similarly, the incidence of septic shock at presentation was more frequent in the pre-phase (37% vs 26%;  $P = .044$ ).

Finally, no differences were noted in terms of Sequential Organ Failure Assessment (SOFA) score or qPitt bacteremia score at presentation, antimicrobial resistance pattern of GN bacteria involved in BSIs, incidence of polymicrobial BSIs, or appropriate empirical antibiotic therapy.

### Analysis of the Impact of Intervention on BSIs Management

A crude comparison of adherence to QCIs between the pre-intervention and postintervention periods is shown in

**Table 1. General Characteristics of the Study Population**

	Overall (n = 271)	Pre-intervention (n = 127)	Postintervention (n = 144)	P Value
<b>General characteristics</b>				
Age, median (q1–q3), y	68 (57–79)	72 (60–81)	64 (54–76)	<b>.002</b>
Male sex, No. (%)	158 (58)	68 (54)	90 (62)	.136
Ward of evaluation, No. (%)				
Medical unit	182 (67)	92 (72)	90 (62)	.052
Surgical unit	58 (21)	19 (15)	39 (27)	
Intensive care unit	31 (12)	16 (13)	15 (11)	
Charlson comorbidity index, median (q1–q3)	5 (3–7)	5 (3–7)	5 (3–7)	.694
Concurrent SARS-CoV-2 infection, No. (%)	33 (12)	16 (13)	17 (12)	.842
Comorbidity, No. (%)				
Severe cardiovascular disease	22 (8)	7 (6)	15 (10)	.140
Chronic obstructive pulmonary disease	47 (17)	23 (18)	24 (17)	.754
Type II diabetes	75 (28)	39 (31)	36 (25)	.295
Chronic kidney diseases (eGFR < 60 mL/min)	81 (30)	41 (32)	40 (28)	.419
Dialysis	21 (8)	9 (7)	12 (8)	.702
Obesity (BMI > 30 kg/m <sup>2</sup> )	26 (10)	12 (9)	14 (10)	.939
Solid neoplasia	50 (18)	13 (10)	37 (26)	<b>.001</b>
Hematologic neoplasia	14 (5)	10 (8)	4 (3)	.059
Severe immunocompromission, No. (%)	46 (17)	23 (18)	23 (16)	.640
<b>Clinical presentation of BSIs and therapies</b>				
Source of bloodstream infection, No. (%)				
Urinary tract	94 (35)	58 (46)	36 (25)	<b>&lt; .001<sup>a</sup></b>
CVC-related	43 (16)	16 (13)	27 (19)	
Intra-abdominal	57 (21)	17 (13)	40 (28)	
Lung	13 (5)	8 (6)	5 (3)	
Skin and soft tissue	19 (7)	4 (3)	15 (10)	
Endovascular	13 (5)	2 (2)	11 (8)	
Osteoarticular	6 (2)	3 (2)	3 (2)	
Primary BSI	26 (9)	19 (15)	7 (5)	
Antimicrobial resistance pattern of GNB, No. (%)				
Extensively sensitive	51 (19)	23 (18)	28 (19)	.514
Resistant to third-generation cephalosporins	38 (14)	16 (13)	22 (15)	
Extended-spectrum beta-lactamases	56 (21)	23 (18)	33 (23)	
Carbapenem-resistant	126 (46)	65 (51)	61 (42)	
Monomicrobial infections, No. (%)	215 (79)	103 (81)	112 (78)	.500
<i>E. coli</i>	61 (28)	30 (29)	31 (28)	.858
<i>K. pneumoniae</i>	64 (30)	30 (29)	34 (30)	
<i>A. baumannii</i>	44 (21)	23 (22)	21 (19)	
Other gram-negative	46 (21)	20 (20)	26 (23)	
Polymicrobial infections, No. (%) <sup>b</sup>	56 (21)	24 (19)	32 (22)	.500
Only gram-negative	16 (29)	5 (21)	11 (34)	.721
Gram-negative and gram-positive	20 (36)	9 (37)	11 (34)	
Gram-negative and <i>Candida</i> spp.	8 (14)	4 (17)	4 (13)	
Gram-negative, gram-positive, and <i>Candida</i> spp. <sup>a</sup>	12 (21)	6 (25)	6 (19)	
qPitt bacteriemia score >2, No. (%)	60 (22)	32 (25)	28 (19)	.255
SOFA score, median (q1–q3)	4 (2–7)	4 (2–7)	4 (2–7)	.364
Septic shock at presentation, No. (%)	84 (31)	47 (37)	37 (26)	<b>.044</b>
Appropriate empirical therapy, No. (%)	102 (47%)	49 (45)	53 (49)	.364
Definitive antibiotic therapy for BSI, No. (%)				
Monotherapy	71 (27)	36 (28)	35 (24)	.450
Combination therapy	200 (73)	91 (72)	109 (76)	

Boldface means statistically significant ( $P < .05$ ).

Abbreviations: BMI, body mass index; BSI, bloodstream infection; CVC, central venous catheter; eGFR, estimated glomerular filtration rate; GNB, gram-negative bacteria; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SOFA, Sequential Organ Failure Assessment.

<sup>a</sup>Urinary tract:  $P < .001$ ; CVC-related:  $P = .1666$ ; intra-abdominal:  $P = .003$ ; lung:  $P = .277$ ; skin and soft tissue:  $P = .019$ ; endovascular:  $P = .019$ ; osteoarticular:  $P = .999$ ; primary BSI:  $P = .004$ .

<sup>b</sup>*S. aureus* (10 cases, 6 and 4 in the pre-phase and post-phase, respectively); *E. faecalis* (17 cases, 7 and 10 in the pre-phase and post-phase, respectively).

**Table 2. Adherence to Quality-of-Care Indicators and Associated Risk of Mortality**

Quality-of-Care Indicators Included in Multistep Gram-Negative BSI Management Bundles	Adherence in Pre-intervention	Adherence in Postintervention	P Value	HR (95% CI) for 14-Day Mortality Risk Reduction	HR (95% CI) for 28-Day Mortality Risk Reduction
<b>STEP 1 (BSI onset; n = 271)</b>					
FUBCs every 48 h from index blood culture until 1 negative result	59/127 (46)	99/144 (69)	<b>&lt;.001</b>	0.57 (0.33–0.99)*	0.42 (0.26–0.69)**
Procalcitonin monitoring every 48 h until reduction of >80% or absolute value <2 ng/mL	95/127 (75)	114/144 (79)	.393	0.27 (0.15–0.46)**	0.24 (0.15–0.39)**
Performance of imaging to detect infection source within 72 h of diagnosis	54/127 (42)	101/144 (70)	<b>&lt;.001</b>	0.46 (0.26–0.80)*	0.30 (0.18–0.50)**
Full adherence to bundles included in step 1 (all 3 QCIs)	53/127 (42)	97/144 (67)	<b>&lt;.001</b>	0.41 (0.23–0.73)*	0.28 (0.16–0.47)**
<b>STEP 2 (microbiological diagnosis of BSI; n = 271)</b>					
Source control in case of deep-site infection within 72 h of diagnosis of deep-site infection (n = 95)	5/26 (20)	42/69 (62)	<b>&lt;.001</b>	0.14 (0.03–0.65)*	0.09 (0.02–0.42)*
Targeted antimicrobial therapy within 72 h of index blood culture	91/127 (72)	119/144 (83)	<b>.031</b>	0.35 (0.20–0.61)**	0.41 (0.25–0.67)**
Full adherence to bundles included in step 2 (both QCIs, when applicable)	91/127 (72)	119/144 (83)	<b>.031</b>	0.28 (0.16–0.48)**	0.31 (0.19–0.51)**
<b>STEP 3 (days 7–9 of antimicrobial therapy; n = 236)<sup>a</sup></b>					
Discontinuation of treatment according to type of BSI (uncomplicated vs complicated)	2/108 (2)	69/128 (54)	<b>&lt;.001</b>	1.03 (0.37–2.83)	0.58 (0.22–1.51)

Boldface means statistically significant ( $P < .05$ ).

Abbreviations: BSI, bloodstream infection; FUBCs, follow-up blood cultures; HR, hazard ratio; QCIs, quality-of-care indicators.

\* $P < .05$ ; \*\* $P < .001$ .

<sup>a</sup>Excluded patients who died within 7 days.

**Table 2.** Importantly, during the post-phase period, adherence to QCIs significantly improved in all 3 steps. In particular, for step 1, a higher frequency of FUBCs and imaging investigations within 72 hours of BSI onset was observed in the post-phase ( $P < .001$  in both cases), while for step 2 source control within 72 hours of index blood culture in cases of deep-site infection was the QCI that showed the most important improvement in adherence (62% vs 20%;  $P < .001$ ).

Finally, early discontinuation of therapy according to type of BSI (uncomplicated vs complicated) also showed a significant improvement in adherence in the post-phase (54% vs 2%;  $P < .001$ ).

Moreover, in **Table 2**, the predicted mortality risk (at day 14 and day 28) associated with the application of each of the QCIs is shown.

Among all QCIs included, it was noteworthy that a short treatment duration according to type of BSI, and in particular early (days 7–9) discontinuation of therapy, was chosen in 86% of uBSIs (data not shown in the table) and was not associated with a significant increase of 14-day or 28-day mortality. Interestingly, among the 64 eligible patients (affected by uncomplicated BSI in the post-phase), 25 (39%) were treated with a 7-day treatment, without significantly increased incidence of mortality or recurrence (data not shown in the table).

#### Analysis of Primary and Secondary Outcomes

Overall, 28-day mortality and 90-day mortality were significantly lower in the post- vs pre-phase (22% vs 35%;  $P = .016$ ;

and 24% vs 38%;  $P = .016$ ; respectively), while 14-day mortality was not statistically influenced by the period of enrollment. However, the intervention markedly reduced the median duration of total (11 vs 15 days;  $P < .001$ ) and targeted (8 vs 12 days;  $P = .001$ ) antibiotic therapy. Interestingly, a higher number of BSIs that were eligible for surgical source control were found in the post-phase (48% vs 20%;  $P < .001$ ).

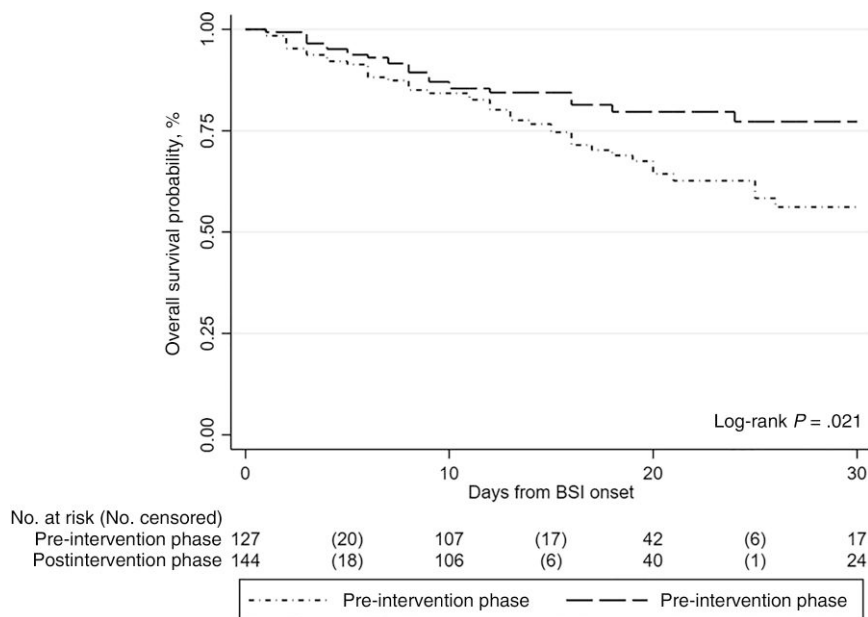
Finally, in analyzing other secondary outcomes, no differences were demonstrated in terms of recurrence/relapse of primary BSIs or incidence of breakthrough infections, while a nonsignificant reduction of incidence of severe adverse events to antibiotics (grade 3–5 according to Common Toxicity Criteria for Adverse Events) was noted postintervention (4% vs 10%;  $P = .051$ ).

**Supplementary Table 1** shows the distribution of primary and secondary outcomes in the pre- and postintervention phases.

#### Survival Analysis

Twenty-eight-day mortality risk was then explored by Kaplan-Meier curves. Interestingly, the postintervention phase was associated with reduced risk of death ( $P = .021$ ) (**Figure 2**) when compared with the pre-phase.

In order to identify other possible variables associated with 14-day and 28-day mortality, a univariate Cox regression was performed (**Supplementary Table 2**), followed by a



**Figure 2.** Kaplan-Meier survival analysis. Abbreviation: BSI, bloodstream infection.

multivariable model excluding all factors not reaching statistical significance. Finally, in the definitive multivariable models (Table 3), age >65 years, septic shock at presentation, and BSI caused by a carbapenem-resistant GN bacteria were

**Table 3. Multivariate Cox Regression Analysis of Variables Associated With 14-Day and 28-Day Mortality**

	Multivariate Analysis		
	aHR	95% CI	P Value
<b>14-d mortality</b>			
Age, per 1-y increase	1.04	1.01–1.06	<b>.002</b>
Charlson comorbidity index	0.99	0.89–1.09	.862
Septic shock at presentation	2.26	1.25–4.07	<b>.007</b>
BSI requiring surgical source control	1.40	0.73–2.66	.302
BSI caused by a carbapenem-resistant GNB	2.20	1.11–4.35	<b>.023</b>
Appropriate empirical therapy	0.86	0.43–1.72	.687
Adherence to management bundles			
Full adherence to step 1	0.59	0.32–1.11	.104
Full adherence to step 2	0.41	0.22–0.73	<b>.003</b>
<b>28-d mortality</b>			
Age, per 1-y increase	1.03	1.01–1.05	<b>.003</b>
Charlson comorbidity index	1.00	0.91–1.09	.924
Septic shock at presentation	1.94	1.17–3.21	<b>.010</b>
BSI requiring surgical source control	1.39	0.79–2.44	.246
BSI caused by a carbapenem-resistant GNB	1.99	1.10–3.58	<b>.022</b>
Appropriate empirical therapy	0.72	0.39–1.32	.290
Adherence to management bundles			
Full adherence to step 1	0.36	0.20–0.63	<b>&lt;.001</b>
Full adherence to step 2	0.48	0.29–0.81	<b>.006</b>

Boldface means statistically significant ( $P < .05$ ).

Abbreviations: aHR, adjusted hazard ratio; BSI, bloodstream infection; GNB, gram-negative bacteria.

independently associated with 14-day and 28-day mortality. On the contrary, adherence to step 1 was protective for 28-day mortality (adjusted hazard ratio [aHR], 0.36; 95% CI, 0.20–0.63), while adherence to step 2 was protective for both 14-day mortality (aHR, 0.41; 95% CI, 0.22–0.73) and 28-day mortality (aHR, 0.48; 95% CI, 0.29–0.81).

Finally, a sensitivity analysis was performed by repeating the multivariable Cox regression model only in patients with monomicrobial GN-BSI (Supplementary Table 3); the reduced mortality in subjects who were treated according to GN-BSI bundles was confirmed in this analysis.

## DISCUSSION

To the best of our knowledge, this is the first study evaluating the use of a structured multistep bundles intervention on the management and outcome of patients with gram-negative BSI.

This work is in line with recent papers highlighting the importance of identifying additional treatment and diagnostic strategies to improve the outcome of GN-BSIs [17, 21, 22]. Indeed, excluding early targeted antimicrobial therapy and adequate vital support, another widely recognized pivotal aspect to reduce mortality risk includes the identification of potential foci of infection, which should be quickly controlled [23], while the selection of patients with uncomplicated BSI who can be treated with short-course antimicrobials is crucial to reducing antimicrobial resistance, potential adverse events, and health care costs [23]. According to our data, a full application of the QCI was quite unsatisfactory in the pre-intervention phase, when patients were managed without pre-established

bundles, resulting in a higher rate of unfavorable outcomes, despite appropriate empirical antibiotic therapy in half of the cases and targeted treatment administration within 72 hours of BSI onset in almost 3 out of 4 patients. Nevertheless, it should be noted that the mortality reported in this work is quite high if compared with the general GN-BSI literature (around 15%). However, this study included a high number of BSIs caused by carbapenem-resistant gram-negative bacteria (46%) and also polymicrobial infections, which are both associated with higher mortality if compared with other GN-BSIs. Second, this work was conducted in a tertiary care hospital that manages subjects with multiple comorbidities and severe clinical conditions; this, in turn, is associated with a higher “baseline” mortality risk of the population.

As QCI is considered a useful tool for evaluating and monitoring different aspects of health care procedures [24], our ID team decided to incorporate several literature-based QCIs in a standardized management protocol for GN-BSIs.

Notably, QCIs for gram-negative bacteria (GNB)-BSI management had not been established yet; a recent work highlighting the “research agenda” of management of GNB-BSI tried to explore this topic, suggesting a few possible QCIs [25]. Still, according to current knowledge, short treatment duration in nonimmunocompromised patients with uncomplicated GN-BSI and the use of FUBCs are supported by robust evidence [14, 15]; on the contrary, studies investigating the use of systematic imaging to identify foci of infections are limited to few observational data.

Interestingly, during the first step of our intervention, systematic use of FUBCs and requests for imaging were included, along with procalcitonin monitoring every 48 hours until a reduction of >80% or an absolute value <2 ng/mL was obtained. While the latter bundle performed similarly pre- and postintervention, we noticed a remarkable increase in adherence to FUBCs and early imaging postintervention. Importantly, use of FUBCs was associated with reduced 14-day and 28-day mortality risk in this analysis. This result, which is concordant with previous studies on FUBCs in the context of GN-BSI [11, 12], is probably explainable by the high rate of deep-site infections and BSIs presenting with septic shock included in the cohort; these types of infections are at higher risk of persistent bacteremia and are probably better managed when FUBCs are performed. Differently from previous studies [9, 10], in our work early (within 72 hours of diagnosis) systematic imaging also influenced mortality risk; nevertheless, it should be acknowledged that the GN-BSIs included in this analysis originated from several sites and organs, and not only from the urinary tract, where incidence of drainable abscesses is lower. It should also be acknowledged that in this intervention the use of PCT was preferred over the use of C-reactive protein to guide antimicrobial therapy, despite the latter being supported by strong evidence in cases of uncomplicated BSI [26].

Nevertheless, in our setting, we also included complicated BSI, and, more importantly, we included patients affected by multiple comorbidities or even treated with concurrent surgical procedures. In these cases, C-reactive protein values may be influenced and unreliable. PCT was preferred as it showed a more linear and predictable trend in these situations [16].

Unsurprisingly, the QCIs of step 2, including targeted antibiotic therapy and surgical source control of deep site of infection, were both significantly associated with increased survival. Notably, in the postintervention period, the number of patients who underwent source control within 72 hours of diagnosis of deep-site infection increased significantly, probably due to a superior awareness of this aspect of care and early performance of imaging. On the other hand, although an improvement was noticed, the number of patients with targeted therapy within 72 hours of diagnosis changed only by a little in the post-phase. The main reason for this result is the absence of rapid microbiologic diagnostic testing in our hospital; therefore, in most cases the definitive therapy was possible only after culture results.

Finally, the third step, early discontinuation of therapy in cases of uncomplicated BSI, was one of the most important QCIs introduced with the intervention: Importantly, our data confirmed, also in a “real life” setting, that reducing the duration of therapy in selected subjects without complicated BSI is not associated with increased recurrence/relapse or mortality. In addition, in the postintervention group, we noticed a reduced incidence of adverse reactions to antibiotics.

In fact, antimicrobial drugs are potentially harmful, and they could lead to adverse events such as renal or hepatic toxicity; moreover, they cause selective pressure, a major issue promoting the rise of antibiotic resistance [27]. Accordingly, these data encourage the implementation of antimicrobial stewardship protocols and early discontinuation of treatments when possible.

In producing univariate survival curves, reduced mortality was noted when classifying patients according to post-phase attendance. However, this might be due to immortal time bias: Indeed, only patients with sufficient survival can undergo all 3 steps of the intervention, biasing results in favor of the intervention. Therefore, each step was also analyzed individually in the multivariable analysis in order to identify its impact on survival, confirming a significant reduction in mortality risk [28].

Finally, a few points should be considered when reading our results. This study was conducted as a “proof-of-concept” work to evaluate the possible efficacy of a multistep bundles intervention on management and outcomes of GN-BSIs, taking inspiration from previous studies on *Staphylococcus aureus* bacteremia. Accordingly, all cases of GN-BSIs were included, independent of the involved pathogen(s), site of infection, presence of polymicrobial BSIs, or antimicrobial resistance pattern of GNB. This obviously hampers the generalizability of our



results but increases the real-life applicability of the data as well as the interest in studying and sharpening these interventional strategies under different conditions. Moreover, the intervention required a proactive ID consultation in any case of GN-BSI, which was possible in our large tertiary care teaching hospital with sufficient medical staff resources, but this approach may not be reproducible in all facilities. However, proactive reevaluation at the time of acquisition of definitive antibiogram and imaging was able to determine indication for targeted antimicrobial therapy (including both deescalation and escalation) and to assess the need for surgical source control or central venous catheter removal; both of these QCIs were strongly associated with reduced mortality, suggesting the importance of implementing this approach. In fact, by analyzing the impact of each QCI on mortality risk, the most effective bundles in reducing mortality were early targeted antimicrobial therapy and surgical source control within 72 hours of diagnosis of deep-site infection; in addition, FUBCs and imaging within 72 hours of BSI onset influenced mortality, although these last 2 probably were indirectly related, as they resulted in better management of the BSI. Moreover, our study confirmed that a shorter duration of antibiotic therapy was not associated with a different mortality or infection recurrence rate when compared with a longer course.

The study has several limitations. First, it should be remembered that patients were not randomized to receive a specific management protocol. Therefore, unobserved biases (eg, improvement of general patient care in the post-phase period, Hawthorne effect, and others) may have influenced results. For instance, differences in the 2 groups were observed in the rate of metastatic solid cancer, which was found more frequently in the postintervention period, whereas onset with septic shock was more frequent in the pre-phase.

Second, in this study the provided antimicrobial therapy was not analyzed in detail. Indeed, we acknowledge that several factors, including pharmacokinetics/pharmacodynamic (PK/PD) dosage optimization, use of mono or combination therapies, and route of administration (intravenous or oral), significantly impact survival of patients. However, all therapies were prescribed by an ID specialist during the pre- and postintervention periods according to good clinical practice principles and hospital internal guidelines and were assumed to be appropriate; accordingly, no significant modification was expected in the post-phase.

Another potential limitation could be represented by the fact that in some patients several bundles were also applied in the pre-phase: Indeed, the management of GN-BSIs was guided by ID consultation requested by the attending physicians of all enrolled patients, even in the pre-phase. Nevertheless, quasi-experimental study designs applied to quality improvement projects represent, by definition, real-life clinical experience. In addition, it should be stated that this study may be

underpowered to detect differences in infection recurrence/relapse rates.

Lastly, as this was a single-center study, external validation is warranted.

In conclusion, our study shows that improving adherence to selected QCI indicators was effective in reducing mortality, duration of antibiotic treatment, and adverse events to antibiotics, without increasing the risk of recurrence/relapse of infections.

### Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

### Acknowledgments

**Potential conflicts of interest.** All authors: no reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

**Ethical approval.** This study was performed with the formal approval of our Ethical Committee (study number: 6527) and in accordance with the Declaration of Helsinki and national and institutional standards. Finally, data were previously pseudo-anonymized, according to the requirements set by Italian data protection code (leg. Decree 196/2003) and European general data protection regulation (GDPR 2016/679).

**Patient consent.** The patients provided written informed consent (available from the corresponding author) for the use of their data for research purposes.

### References

1. Rodríguez-Baño J, de Cueto M, Retamar P, Gálvez-Acebal J. Current management of bloodstream infections. *Exp Rev Anti Infect Ther* **2010**; 8:815–29.
2. Minton J, Clayton J, Sandoe J, Gann HM, Wilcox M. Improving early management of bloodstream infection: a quality improvement project. *BMJ* **2008**; 336: 440–3.
3. Seifert H. The clinical importance of microbiological findings in the diagnosis and management of bloodstream infections. *Clin Infect Dis* **2009**; 48(Suppl 4): S238–45.
4. López-Cortés LE, Del Toro MD, Gálvez-Acebal J, et al. Impact of an evidence-based bundle intervention in the quality-of-care management and outcome of *Staphylococcus aureus* bacteremia. *Clin Infect Dis* **2013**; 57:1225–33.
5. Goto M, Schweizer ML, Vaughan-Sarrazin MS, et al. Association of evidence-based care processes with mortality in *Staphylococcus aureus* bacteremia at Veterans Health Administration hospitals, 2003–2014. *JAMA Intern Med* **2017**; 177:1489–97.
6. Diallo K, Thilly N, Luc A, et al. Management of bloodstream infections by infection specialists: an international ES-CMID cross-sectional survey. *Int J Antimicrob Agents* **2018**; 51:794–8.
7. Tellor B, Skrupky LP, Symons W, High E, Micek ST, Mazuski JE. Inadequate source control and inappropriate antibiotics are key determinants of mortality in patients with intra-abdominal sepsis and associated bacteremia. *Surg Infect (Larchmt)* **2015**; 16:785–93.
8. Lagunes L, Rey-Pérez A, Martín-Gómez MT, et al. Association between source control and mortality in 258 patients with intra-abdominal candidiasis: a retrospective multi-centric analysis comparing intensive care versus surgical wards in Spain. *Eur J Clin Microbiol Infect Dis* **2017**; 36:95–104.
9. Sørensen SM, Schonheyder HC, Nielsen H. The role of imaging of the urinary tract in patients with urosepsis. *Int J Infect Dis* **2013**; 17:e299–303.
10. Yu TY, Kim HR, Hwang KE, Lee J-M, Cho JH, Lee JH. Computed tomography findings associated with bacteremia in adult patients with a urinary tract infection. *Eur J Clin Microbiol Infect Dis* **2016**; 35:1883–7.
11. Giannella M, Pascale R, Pancaldi L, et al. Follow-up blood cultures are associated with improved outcome of patients with gram-negative bloodstream infections: retrospective observational cohort study. *Clin Microbiol Infect* **2020**; 26:897–903.

12. Wiggers JB, Xiong W, Daneman N. Sending repeat cultures: is there a role in the management of bacteremic episodes? (SCRIBE study). *BMC Infect Dis* **2016**; 16:286.
13. Spellberg B, Rice LB. The shorter is better movement: past, present, future. *Clin Microbiol Infect* **2022**;S1198-743X(22)00209-9. doi: [10.1016/j.cmi.2022.04.005](https://doi.org/10.1016/j.cmi.2022.04.005).
14. Maskarinec SA, Park LP, Ruffin F, et al. Positive follow-up blood cultures identify high mortality risk among patients with gram-negative bacteraemia. *Clin Microbiol Infect* **2020**; 26:904–10.
15. Amipara R, Winders HR, Justo JA, Bookstaver PB, Kohn J, Al-Hasan MN. Impact of follow up blood cultures on outcomes of patients with community-onset gram-negative bloodstream infection. *EClinicalMedicine* **2021**; 34:100811.
16. Covington EW, Roberts MZ, Dong J. Procalcitonin monitoring as a guide for antimicrobial therapy: a review of current literature. *Pharmacotherapy* **2018**; 38:569–81.
17. Erickson RM, Tritle BJ, Spivak ES, Timbrook TT. Impact of an antimicrobial stewardship bundle for uncomplicated gram-negative bacteremia. *Open Forum Infect Dis* **2019**; 6:XXX–XX.
18. Battle SE, Augustine MR, Watson CM, et al. Derivation of a quick Pitt bacteremia score to predict mortality in patients with gram-negative bloodstream infection. *Infection* **2019**; 47:571–8.
19. Garner JS, Jarvis WR, Emori TG, Horan TC, Hughes JM. CDC definitions for nosocomial infections, 1988. *Am J Infect Control* **1988**; 16:128–40.
20. Halm EA, Fine MJ, Marrie TJ, et al. Time to clinical stability in patients hospitalized with community-acquired pneumonia: implications for practice guidelines. *JAMA* **1998**; 279:1452–7.
21. Claeys KC, Heil EL, Hitchcock S, Johnson JK, Leekha S. Management of gram-negative bloodstream infections in the era of rapid diagnostic testing: impact with and without antibiotic stewardship. *Open Forum Infect Dis* **2020**; 7:XXX–XX.
22. Walsh TL, Bremmer DN, Moffa MA, et al. Impact of an antimicrobial stewardship program-bundled initiative utilizing accelerate Pheno™ system in the management of patients with aerobic gram-negative bacilli bacteremia. *Infection* **2021**; 49:511–9.
23. Evans L, Rhodes A, Alhazzani W, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. *Intensive Care Med* **2021**; 47:1181–247.
24. Mainz J. Developing evidence-based clinical indicators: a state of the art methods primer. *Int J Qual Health Care* **2003**; 15:i5–11.
25. Giannella M, Malosso P, Scudeller L, et al. Quality of care indicators in the MANageMENT of BLOODstream infections caused by Enterobacteriaceae (MAMBOO-E study): state of the art and research agenda. *Int J Antimicrob Agents* **2021**; 57:106320.
26. von Dach E, Albrich WC, Brunel AS, et al. Effect of C-reactive protein-guided antibiotic treatment duration, 7-day treatment, or 14-day treatment on 30-day clinical failure rate in patients with uncomplicated gram-negative bacteremia: a randomized clinical trial. *JAMA* **2020**; 323:2160–9.
27. Zhang L, Levy K, Trueba G, et al. Effects of selection pressure and genetic association on the relationship between antibiotic resistance and virulence in *Escherichia coli*. *Antimicrob Agents Chemother* **2015**; 59:6733–40.
28. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chron Dis* **1987**; 40:373–83.