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Original Article

Impact of Implementing an Antimicrobial Stewardship Program for Optimizing Antibiotic Treatment in Gram-negative Bacilli Bacteremia

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ABSTRACT

Background: Antibiotic Stewardship Programs (ASP) have improved empirical and directed antibiotic treatment in Gram-negative Bacilli (GNB) bloodstream infections. A decrease in mortality, readmission, and length of hospitalization has been reported.

Materials and Methods: A pre-post-quasi-experimental study was conducted between November and April 2015–2016 (pre-intervention period), 2016–2017, 2017–2018, and 2018–2019 (post-intervention periods), to analyse the impact of ASP on empirical, directed, and entire treatment optimization, as well as mortality, readmission, and length of hospitalization, in hospitalized patients with Gram-negative bacilli (GNB) bloodstream infections.

Results: One hundred seventy-four patients were included (41 in the pre-intervention group, 38 in the first-year post-intervention group, 50 in the second-year post-intervention group, and 45 in the third-year post-intervention group). There was a significant improvement in directed treatment optimization (43.9% in the pre-intervention group, 68.4% in the first-year post-intervention group, 74% in the second-year post-intervention group, and 88.9% in the third-year post-intervention group, P <0.001), as well as in entire treatment optimization (19.5%, 34.2%, 40.0%, and 46.7%, respectively, P=0.013), with increased optimal directed (adjusted odds ratio [aOR], 3.71; 95% confidence interval [CI], 1.60–8.58) and entire treatment (aOR, 3.31; 95% CI, 1.27–8.58). Although a tendency toward

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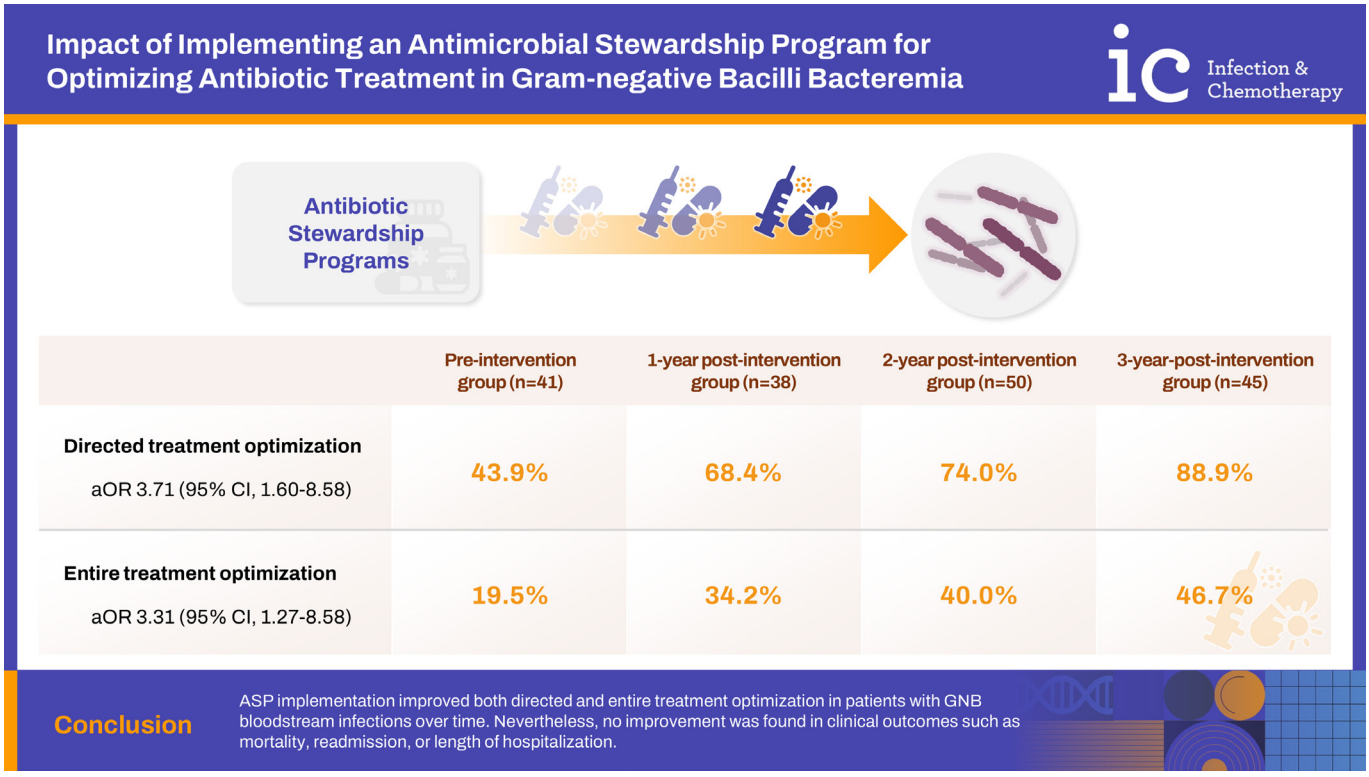
improvement was observed in empirical treatment after ASP implementation, it did not reach statistical significance (41.5% *vs.* 57.9%, *P*=0.065). No changes in mortality, readmission, or length of hospitalization were detected.
Conclusion: ASP implementation improved both directed and entire treatment optimization in patients with GNB bloodstream infections over time. Nevertheless, no improvement was found in clinical outcomes such as mortality, readmission, or length of hospitalization.

Keywords: Antibiotic stewardship programs; Bloodstream infections; Gram-negative bacilli

GRAPHICAL ABSTRACT



BACKGROUND

Antibiotic Stewardship Programs (ASP) are designed to optimize the use of antimicrobials, improve clinical outcomes of patients with infections, minimize adverse effects, and ensure cost-effective treatments [1, 2]. One of the main strategies consists of prospective audits formulated through individualized non-compulsory recommendations that help to optimize antibiotic treatment [1, 2]. The ASP represents an important educational task for the prescribing physician because the recommendations can be applied in future prescriptions [1], resulting in learning by both parties, consultant, and prescriber. One of the scenarios for these interventions is bacteremia [1], specifically in patients with Gram-negative bacilli (GNB) infections. Some authors have shown an improvement in optimizing antibiotic treatment for bacteremia after establishing an ASP [3-9], including GNB bacteremia [10, 11]. Improvement in clinical outcomes such as mortality [3, 6, 12] and mean length of hospital stay [9, 13] have also been observed. Different studies have analysed the impact of an ASP intervention on GNB bacteremia. However, after reviewing the literature, we have not found studies evaluating the improvement in antibiotic treatment optimization and its evolution over time, as well as changes in mortality, hospital stay, or readmissions.

In this retrospective study, we compared the optimization rate of antibiotic treatment (empirical, directed, and

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entire) before and after implementing an ASP-bundled intervention in patients hospitalized with GNB bacteremia. As secondary endpoints, we tried to assess the acceptance of recommendations, made by the ASP team, mortality, readmission rates, and hospital length.

MATERIALS AND METHODS

1. Study design and population

We conducted a retrospective pre-/post-intervention study to analyse the impact on antibiotic prescription and clinical outcomes of an ASP intervention focalized on hospitalized patients with GNB bacteremia. The inclusion criteria were critically ill adult patients admitted to the Hospital Clínico Universitario of San Juan de Alicante, Spain, a 400-bed tertiary care teaching facility, for at least 24 hours, with GNB isolated from blood cultures, before and after the implementation of an ASP- bundled initiative. The pre-intervention period was from November 1st, 2015, to April 30th, 2016, and the three post-intervention periods were the same in 2016–2017, 2017–2018, and 2018–2019.

Exclusion criteria for the study were: 1) patients whose blood cultures were collected in an Intensive Care Unit admission, 2) patients admitted to the Infectious Diseases ward, due to the bias of belonging to the ASP, 3) patients who died before the results of the blood cultures were available, 4) polymicrobial bacteremia, and 5) patients who had already been evaluated with the same GNB bacteremia.

In the pre-intervention period, the microbiological procedure used for the diagnosis of bacteremia was a qualitative automated system of continuous monitoring of cultures (BD BACTEC™ FX), using Plus Aerobic/F and Plus Anaerobic/F culture bottles. A maximum incubation time of five days was used. In the case of microbiological growth, blood cultures were extracted, performing an extension with a Gram stain. Depending on the staining, it was grown in various media and sensitivity panels. Reports containing the provisional results of the Gram stain and definitive result with an antibiogram were issued, and they were recorded in the patient's medical history. No recommendations or assessments were made by the ASP, except at the request of the responsible medical team.

In the post-intervention period, microbiological procedures were similar, but provisional and definitive blood culture results were directly reported to the ASP team. No microbiological rapid diagnostic techniques were used in any period.

Since May 2016, an ASP multidisciplinary team, composed of (at least one of each) clinical experts in infectious diseases, internal medicine and intensive care physicians, pharmacists, and microbiologists, convened daily on weekdays to review the treatment of bacteremia in hospitalized patients. Whenever any positive blood culture was reported, non-compulsory treatment recommendations were formulated in the patient's electronic medical records by the ASP physicians: one based on Gram stain information, either altering or maintaining the scheduled empirical treatment; and another after bacterial identification and obtaining the antibiogram, indicating the recommended antibiotic (both intravenous and oral), the duration of treatment, and if other complementary investigations were needed. These recommendations were conducted every weekday, for each positive blood culture. During weekends, positive blood cultures were reported to the on-call physician by the on-call microbiologist, and they were reviewed by the ASP team on the following workday. Periodic educational interventions, such as training sessions, were also conducted to improve acceptance of recommendations.

2. Ethics statement

The Research Ethics Committee of the Hospital Clínico Universitario of San Juan de Alicante approved this study (IRB code number 21/009). Obtaining informed consent was not compulsory due to the retrospective nature of the study. Data management was conducted according to the current legislation on the protection and confidentiality of data on methods, risks, and treatment (December 5th Organic Law 3/2018 for Protection of Personal Data and Guarantee of Digital Rights & 2016/679 Regulation of the European Parliament and of the Council of the 27th of April 2016).

3. Data collection and definitions

We identified the patients with GNB, isolated from one or more blood culture bottles, via a formal query in our microbiology laboratory database repository. Demographic characteristics, patient comorbidities, clinical profile, microbiological data, and outcome variables were collected retrospectively through the patient's electronic medical record. The severity of the illness was retrospectively assessed with the Pitt Bacteremia Score from the medical history [14].

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Empirical treatment was defined as the antibiotic administered in the first 24 hours after the extraction of blood cultures. Directed treatment was defined as the antibiotic administered after the identification of the microorganism and the antibiogram. Treatment was defined as optimal if there was *in vitro* activity against the isolated pathogen, if it was appropriate for clinical practice guidelines [3, 14, 15] if the dose and duration were adequate, and if oral route therapy had been performed. The optimal entire treatment was when both the empirical and directed treatments were considered optimal for patients. A recommendation made by the ASP team was considered accepted if the patient's attending medical team followed it. The source of bacteremia, as well as its acquisition, was established according to the definitions of the Centers for Disease Control and Prevention [16, 17]. The classification of microorganisms according to antimicrobial resistance was conducted based on the criteria of Magiorakos et al. [18].

4. Data analysis

Differences in the continuous variables between the pre-intervention and post-intervention groups were assessed using the Kruskal–Wallis test. Differences in the categorical variables were assessed using the Chi-square test or Fisher's exact test when appropriate (when the expected frequency in one of the cells was less than 5). A value of P <0.05 was considered statistically significant. All the statistical analyses were performed using IBM SPSS software (version 26.0, IBM, Armonk, NY, USA).

An analysis of the association between qualitative variables was also performed by estimating the odds ratio (OR) in the univariate analysis (using Pearson's Chi-square test for dichotomous variables and logistic regression for non-dichotomous variables) and the adjusted odds ratio (aOR) for the different covariates and confounding factors (all other variables associated with the independent variable in the univariate analysis) obtained through a multivariate analysis using logistic regression. Both values were reported with their 95% confidence intervals (CI).

RESULTS

1. Population baseline characteristics

After applying the exclusion criteria (**Fig. 1**), a sample of 174 patients with GNB bacteremia was obtained. The

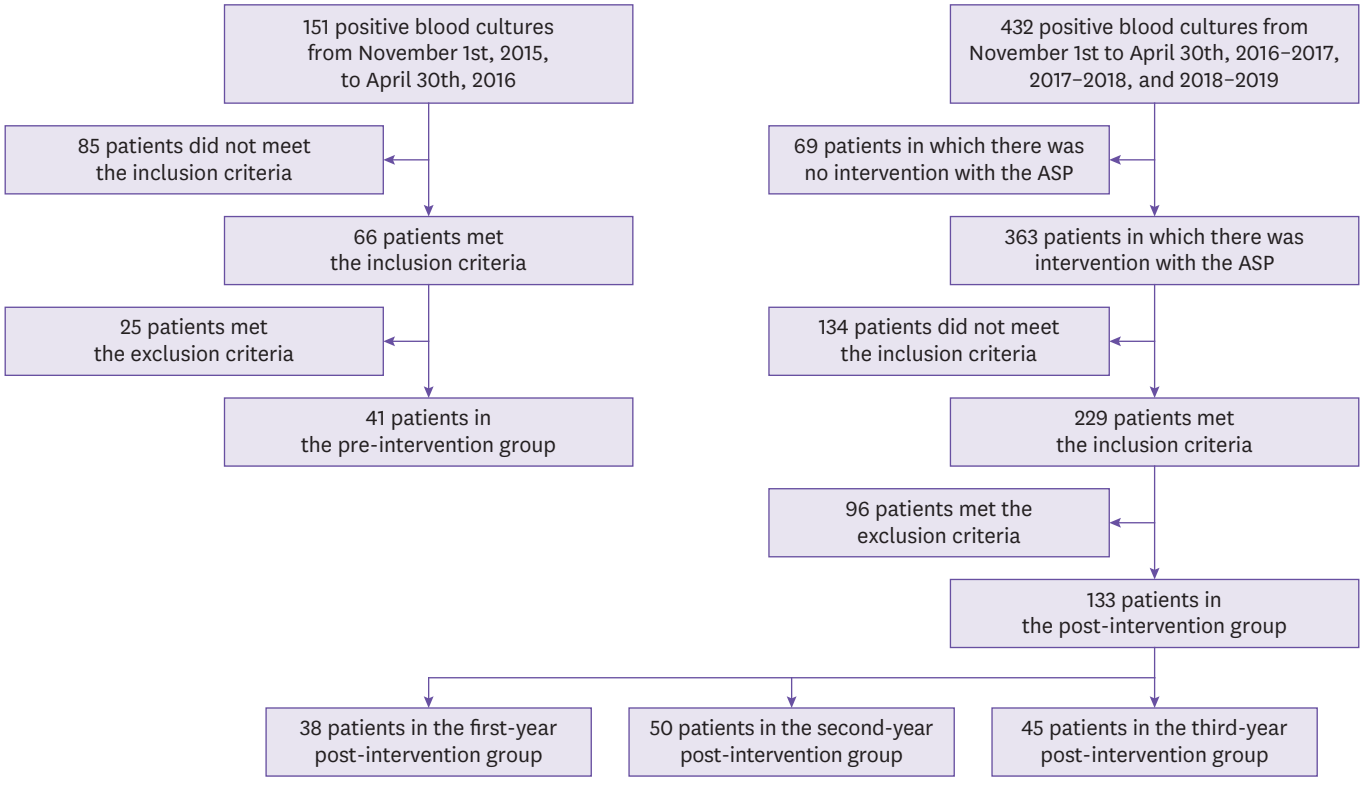

Figure 1. Flow chart for patient selection and inclusion and exclusion criteria.

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pre-intervention group included forty-one patients, and the three post-intervention period groups included 133 patients (38, 50, and 45 patients, respectively).

Demographic, clinical, and microbiological characteristics are shown in **Table 1**.

Table 1. Demographic, clinical, and microbiological characteristics of the patients, by group

Variable	Total N=174	Pre- intervention[a] N=41	Post-intervention 1st year[b] N=38	Post-intervention 2nd year[c] N=50	Post-intervention 3rd year[d] N=45	*P*-value[e]
Sex						0.488
Woman	88 (50.6)	21 (51.2)	23 (60.5)	22 (44.0)	22 (48.9)	
Man	86 (49.4)	20 (48.8)	15 (39.5)	28 (56.0)	23 (51.1)	
Age (years)	75 (66-85)	72 (63-84.5)	74.50 (62-84)	75 (65.75-86)	80 (68-86.5)	0.528[f]
Service						0.853
Medical	145 (83.3)	34 (82.9)	32 (84.2)	40 (80.0)	39 (86.7)	
Surgical	29 (16.7)	7 (17.1)	6 (15.8)	10 (20.0)	6 (13.3)	
Diabetes mellitus	43 (24.7)	14 (34.1)	4 (10.5)	13 (26.0)	12 (26.7)	0.102
Cardiovascular disease	53 (30.5)	14 (34.1)	16 (42.1)	11 (22.0)	12 (26.7)	0.196
Neurological disease	44 (25.3)	9 (22.0)	9 (23.7)	14 (28.0)	12 (26.7)	0.912
Chronic pneumopathy	41 (23.6)	8 (19.5)	10 (26.3)	17 (34.0)	6 (13.3)	0.104
Chronic liver disease	12 (6.9)	10 (24.4)	0	2 (4.0)	0	<0.001
Chronic renal disease	65 (37.4)	12 (29.3)	15 (39.5)	15 (30.0)	23 (51.1)	0.111
Neoplasm						0.982
Solid	52 (29.9)	12 (29.3)	11 (28.9)	16 (32.0)	13 (28.9)	
Hematologic	8 (4.6)	1 (2.4)	2 (5.3)	2 (4.0)	3 (6.7)	
Immunosuppression	24 (19.5)	7 (17.1)	6 (15.8)	13 (26.0)	8 (17.8)	0.590
Focus						0.197
Urinary	61 (35.1)	13 (31.7)	9 (23.7)	20 (40.0)	19 (42.2)	
Unknown	50 (28.7)	16 (39.0)	10 (26.3)	10 (26.3)	13 (28.9)	
Abdominal	35 (20.1)	7 (17.1)	8 (21.1)	8 (21.1)	9 (20.0)	
Respiratory	14 (8.0)	1 (2.4)	8 (21.1)	4 (8.0)	1 (2.2)	
Venous	5 (2.9)	2 (4.9)	0	2 (4.0)	1 (2.2)	
Urinary other	9 (5.2)	2 (4.9)	3 (7.9)	2 (4.0)	2 (4.4)	
Origin						0.073
Community	82 (47.1)	19 (46.3)	18 (47.4)	27 (54.0)	18 (40.0)	
Healthcare	61 (35.1)	12 (29.3)	9 (23.7)	4 (8.0)	6 (13.3)	
Nosocomial	31 (17.8)	10 (24.4)	11 (28.9)	9 (38.0)	21 (46.7)	
Pitt Index[g]	1 (0-2)	1 (0-2)	1 (0-2)	1 (0-2)	0 (0-2)	0.724[f]
Microorganism						0.314
Escherichia coli	101 (58.0)	24 (28.5)	18 (47.4)	31 (62.0)	28 (62.2)	
Klebsiella pneumoniae	19 (10.9)	7 (17.1)	6 (15.8)	2 (4.0)	4 (8.9)	
Pseudomonas aeruginosa	12 (6.9)	3 (7.3)	2 (5.3)	5 (10.0)	2 (4.4)	
Haemophilus influenzae	7 (4.0)	0	4 (10.5)	2 (4.0)	1 (2.2)	
Klebsiella oxytoca	5 (2.9)	1 (2.4)	1 (2.6)	1 (2.0)	2 (4.4)	
Enterobacter cloacae	5 (2.9)	2 (4.9)	1 (2.6)	0	2 (4.4)	
Morganella morganii	5 (2.9)	2 (4.9)	0	1 (2.0)	2 (4.4)	
Proteus mirabilis	4 (2.3)	1 (2.4)	0	3 (6.0)	0	
Others	16 (9.2)	1 (2.4)	6 (15.8)	5 (10.0)	4 (8.9)	
Multi-resistance						0.243
MDR	55 (31.6)	13 (31.7)	7 (18.4)	16 (32.0)	19 (42.2)	
XDR	1 (0.6)	0	0	1 (2.0)	0	

Quantitative variables are expressed as N (%). Qualitative variables are expressed as median (interquartile range).
Disease.
[a]November 2015-April 2016.
[b]November 2016-April 2017.
[c]November 2017-April 2018.
[d]November 2018-April 2019.
[e]*P*-values based on Chi-square test, unless otherwise indicated.
[f]Kruskall-Wallis test.
[g]Pitt bacteremia acute severity rating index.
MDR, multidrug-resistant; XDR, extremely resistant.

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2. Assessment of prescription quality

Regarding the degree of treatment optimization (**Table 2**, **Fig. 2**), progressive and statistically significant increases in the directed (43.9%, 68.4%, 74.0%, and 88.9%, *P* <0.001) and entire treatments (19.5%, 34.2%, 40.0%, and 46.7%, *P*=0.013) were obtained. In contrast, non-statistically significant differences were found in the empirical treatment. Nevertheless, a trend towards improvement was observed when comparing the pre-intervention group with the combined set of the 3 post-intervention groups (41.5% compared to 57.9%, *P*=0.065). Univariate and multivariate analyses were performed for optimal antibiotic treatment (**Table 3**, and **Table 4**) for each category (empirical, directed, and entire). The ASP group intervention was significantly associated with the optimal directed treatment (aOR, 3.71; 95% CI, 1.60–8.58, *P*=0.002) and the entire treatment (aOR, 3.31; 95% CI, 1.27–8.58; *P*=0.014). In addition, when we analysed this association depending on the period after the ASP intervention, we found positive effects of the ASP intervention in the second year (aOR, 3.26; 95% CI, 1.25–8.50; *P*=0.015 for the directed treatment, and aOR, 3.07; 95% CI, 1.08–8.74; *P*=0.035 for the entire treatment) and in the third year (aOR, 9.23; 95% CI, 2.60–32.69; *P*=0.001 for the directed, and aOR, 5.14; 95% CI, 1.73–15.31; *P*=0.003 for the entire).

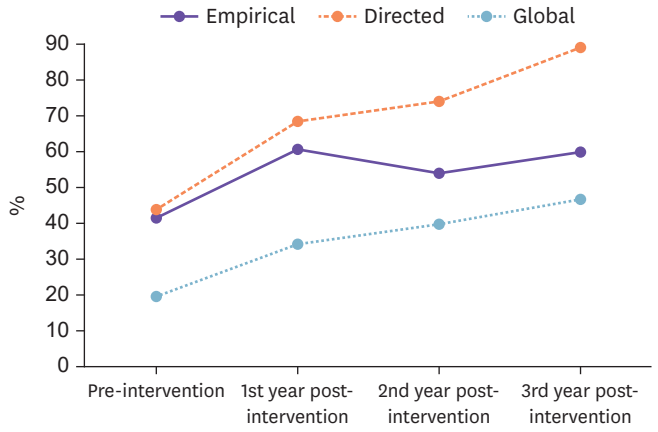

Figure 2. Degree of treatment optimization distributed by periods.

Table 2. Optimization of treatment, exitus, readmissions, and hospital stay in the different periods of the study

Variable	Total N=174	Pre- intervention[a] N=41	Post-intervention 1st year[b] N=38	Post-intervention 2nd year[c] N=50	Post-intervention 3rd year[d] N=45	*P*-value[e]
Optimal empirical treatment	94 (54.0)	17 (41.5)	23 (60.5)	27 (54.0)	27 (60.0)	0.273
Optimal directed treatment	121 (69.5)	18 (43.9)	26 (68.4)	37 (74.0)	40 (88.9)	<0.001
Optimal entire treatment	65 (37.4)	8 (19.5)	13 (34.2)	20 (40.0)	21 (46.7)	0.013
Duration of treatment (days)	14 (10-14)	14 (11-16.5)	14 (10-16.2)	14 (10-14)	14 (10-14)	0.615[f]
Exitus at 30 days	23 (13.2)	6 (14.6)	6 (15.8)	6 (12.0)	5 (11.1)	0.912
Readmission at 30 days	24 (13.8)	6 (14.6)	3 (7.9)	9 (18.0)	6 (13.3)	0.596
Hospital stays (days)	7 (4-12)	8 (5-15.5)	9.5 (5.7-20.7)	6 (4-9)	5 (4-8)	0.001[f]

Quantitative variables are expressed as N (%). Qualitative variables are expressed as median (interquartile range).
[a]November 2015-April 2016.
[b]November 2016-April 2017.
[c]November 2017-April 2018.
[d]November 2018-April 2019.
[e]*P*-values based on Chi-square test, unless otherwise indicated.
[f]Kruskall-Wallis test.

Table 3. Multivariate analysis of the probability of improvement from empirical, directed, and entire treatment

Variable	Optimal empirical treatment		Optimal directed treatment		Optimal entire treatment	
	aOR[a] (95% CI)	*P*-value	aOR[a] (95% CI)	*P*-value	aOR[a] (95% CI)	*P*-value
ASP intervention	2.06 (0.92-4.61)	0.078	3.71 (1.60-8.58)	0.002	3.31 (1.27-8.58)	0.014
Study period						
Pre-intervention[b]	1 (Reference)		1 (Reference)		1 (Reference)	
Post-intervention 1st year[c]	2.31 (0.84-6.31)	0.103	2.28 (0.80-6.49)	0.123	2.18 (0.69-6.82)	0.183
Post-intervention 2nd year[d]	1.72 (0.70-4.26)	0.240	3.26 (1.25-8.50)	0.015	3.07 (1.08-8.74)	0.035
Post-intervention 3rd year[e]	2.43 (0.93-6.41)	0.072	9.23 (2.60-32.69)	0.001	5.14 (1.73-15.31)	0.003

[a]Adjusted Odds Ratio for the rest of the variables in the Table.
[b]November 2015-April 2016.
[c]November 2016-April 2017.
[d]November 2017-April 2018.
[e]November 2018-April 2019.
aOR, adjusted odds ratio; CI, confidence interval.

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Table 4. Multivariate analysis of the association between the intervention and clinical outcome variables

Variable	Mortality after 30 days		Readmissions after 30 days		Hospital stay >7 days	
	aOR[a] (95% CI)	*P*-value	aOR[a] (95% CI)	*P*-value	aOR[a](95% CI)	*P*-value
ASP intervention	0.87 (0.27–2.80)	0.814	0.81 (0.26–2.58)	0.725	0.69 (0.27–1.73)	0.424
Period of study						
Pre-intervention[b]	1 (Reference)		1 (Reference)		1 (Reference)	
Post-intervention 1st year[c]	1.99 (0.42–9.37)	0.386	0.23 (0.04–1.43)	0.116	1.91 (0.62–5.93)	0.261
Post-intervention 2nd year[d]	0.76 (0.18–3.14)	0.701	1.50 (0.40–5.56)	0.546	0.65 (0.22–1.90)	0.436
Post-intervention 3rd year[e]	0.57 (0.13–2.54)	0.462	0.73 (0.17–3.13)	0.671	0.24 (0.70–0.82)	0.023

[a]Adjusted Odds Ratio for the remaining variables with potential associations.
[b]November 2015-April 2016.
[c]November 2016-April 2017.
[d]November 2017- April 2018.
[e]November 2018-April 2019.
aOR, adjusted odds ratio; CI, confidence interval.

Table 5. Optimization of treatment, exitus, readmissions, and hospital comparing the Pre-intervention period and the whole post-intervention period

Variable	Total N=174	Pre-intervention[a] N=41	Post-intervention[b] N=133	*P*-value[c]
Optimal empirical treatment	94 (54.0)	17 (41.5)	77 (57.9)	0.065
Optimal directed treatment	121 (69.5)	18 (43.9)	103 (77.4)	<0.001
Optimal entire treatment	65 (37.4)	8 (19.5)	57 (42.9)	0.007
Duration of treatment (days)	14 (10–14)	14 (11–16.5)	14 (10–14)	0.429[d]
Exitus at 30 days	23 (13.2)	6 (14.6)	17 (12.8)	0.759
Readmission at 30 days	24 (13.8)	6 (14.6)	18 (13.5)	0.858
Hospital stays (days)	7 (4–12)	8 (5–8)	7 (4–7)	0.116[d]

Quantitative variables are expressed as N (%). Qualitative variables are expressed as Median (Interquartile range).
[a]November 2015-April 2016.
[b]November 2016-April 2019.
[c]*P*-values based on Chi-square test, unless otherwise indicated.
[d]Kruskall-Wallis test.

3. ASP acceptance rate recommendations

The overall acceptance rate was 82.5%, with 93.9% for recommendations on empirical treatment, 79.3% for those on directed treatment, and 73.1% for treatment duration. No significant differences were found between medical and surgical services (83.6% *vs.* 80.4%, *P*=0.800).

4. Clinical outcome (Table 2 and Table 5)

Length of hospitalization was significantly and progressively reduced over the periods studied from 9.5 days (95% CI, 5.75–10.75) in the pre-intervention period to 8 days (95% CI, 5–15.5), 6 days (95% CI, 4–9), and 5 days (95% CI, 4–8), respectively, in the three post-intervention ASP periods.

Although ASP intervention was not associated with reduced mortality or readmission rates, an association with a reduced length of hospitalization (greater than 7 days) was observed in the univariate analysis (OR, 0.47; 95% CI, 0.23–0.96; *P*=0.035). However, in the multivariate analysis, this association was not found (aOR, 0.69; 95% CI, 0.27–1.73; *P*=0.424).

DISCUSSION

Few studies have described an ASP approach to non-critically ill patients with GNB bacteraemia. Like most of these series, our ASP program intervention significantly improved and optimized targeted antibiotic treatment in GNB bloodstream infections.

Regarding the quality of the prescription analysis, our results are also like those described in other GNB bacteremia ASP interventions. Elligsen et al. showed an improvement (44% to 55%) after the implementation of an ASP based on predictive models [10]. Similarly, Yanai et al. showed an increase in the degree of adequacy of antibiotic treatments (53.2% to 89.3%) in bacteremic urinary tract infections [11]. Other studies have also described similar prescription quality improvements after ASP implementation [3, 4, 8]. In a recent Spanish study, the establishment of a bacteremic ASP intervention was associated with a 2-fold increased probability of having an optimal directed treatment [5].

Most of those studies evaluated the ASP intervention on GNB bacteremia in before-after periods, but an evaluation over time was not reported. In contrast, in the present study, the results have shown that the rate of optimal targeted treatment significantly increased over time (43.9% in the pre-intervention period and 68.4%, 74%, and 88.9% in subsequent post-intervention periods). In addition, the latest post-intervention periods were associated with an increased probability (2–4-fold) of optimal targeted treatment in the multivariate analysis. These data suggest that ASP establishment not only has a short beneficial effect on directed treatment, but it can also be maintained for years. The educational role played by ASP intervention is beneficial to both the prescriber and the consultant. This process is linked to a progressive improvement in optimization rates.

Although the improvement in empirical treatment did not significantly increase during the intervention, a trend was reported between the pre-and post-intervention groups (41.5% and 57.9%), as in other series [6–9, 12, 13, 19]. It is possible that if a larger sample size had been obtained, a better and larger difference would have been achieved. Because ineffective empirical treatment has previously been associated with increased mortality in patients with bacteremia [19–21], further efforts should be made to improve prescribing.

Regarding the entire treatment, no other ASP series has analysed this concept. However, we thought it was interesting to take it into account as an important prescription quality index. In addition, it is worth noting that, although our ASP intervention did not significantly improve the rate of empirical treatment, as an entire prescription, (empirical and targeted treatment together), the rate of optimization improved over time (19.5%, 34.2%, 40%, and 46.7% respectively).

In the multivariate analysis with the clinical outcomes (mortality at 30 days, length of hospitalization, and readmissions at 30 days), no significant association was found, due to the small number of study subjects, which may result in low statistical power. Previous studies have shown different results; whereas some of them reported an association between ASP treatment and mortality rates [3, 6, 12], readmission rates [22, 23], and length of hospitalization [9, 13], other studies did not find differences [5, 8, 24], including no differences in mortality and recurrence rates in GNB bacteremia [23]. These discrepancies across studies can be explained by many other factors, such as infection severity, comorbidities, or the source of the infection.

It is possible that significant differences in mortality rates, length of hospitalization, etc. could not be identified. These discrepancies across studies can be explained by many other factors, such as infection severity, comorbidities, or the source of the infection. Another potential limitation is that the study was conducted at a single center. As this is an observational study conducted at a single institution with 400 beds, it is difficult to generalize the results and may also be difficult to apply to other large institutions.

In conclusion, as previously described, an ASP improves the prescription of directed and entire treatment in GNB bacteraemia. ASP recommendations are beneficial because they produce change in prescribers, due to their formative and educational nature. More studies are needed to assess the extent to which this improvement occurs, and which interventions are most appropriate for each scenario.

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REFERENCES

1. Rodríguez-Baño J, Paño-Pardo JR, Alvarez-Rocha L, Asensio Á, Calbo E, Cercenado E, Cisneros JM, Cobo J, Delgado O, Garnacho-Montero J, Grau S, Horcajada JP, Hornero A, Murillas-Angoiti J, Oliver A, Padilla B, Pasquau J, Pujol M, Ruiz-Garbajosa P, San Juan R, Sierra R. GEIH-SEIMC; SEFH; SEMPSPH. Programas de optimización de uso de antimicrobianos (PROA) en hospitales españoles: documento de consenso GEIH-SEIMC, SEFH y SEMPSPH [Programs for optimizing the use of antibiotics (PROA) in Spanish hospitals: GEIH-SEIMC, SEFH and SEMPSPH consensus document]. Farm Hosp 2012;3633:e1-30.
2. Barlam TF, Cosgrove SE, Abbo LM, MacDougall C, Schuetz AN, Septimus EJ, Srinivasan A, Dellit TH, Falck-Ytter YT, Fishman NO, Hamilton CW, Jenkins TC, Lipsett PA, Malani PN, May LS, Moran GJ, Neuhauser MM, Newland JG, Ohl CA, Samore MH, Seo SK, Trivedi KK. Implementing an Antibiotic Stewardship Program: Guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. Clin Infect Dis 2016;62:e51-77. PUBMED | CROSSREF
3. Niwa T, Watanabe T, Goto T, Ohta H, Nakayama A, Suzuki K, Shinoda Y, Tsuchiya M, Yasuda K, Murakami N, Itoh Y. Daily review of antimicrobial use facilitates the early optimization of antimicrobial therapy and improves clinical outcomes of patients with bloodstream infections. Biol Pharm Bull 2016;39:721-7. PUBMED | CROSSREF
4. Bias TE, Vincent WR 3rd, Trustman N, Berkowitz LB, Venugopalan V. Impact of an antimicrobial stewardship initiative on time to administration of empirical antibiotic therapy in hospitalized patients with bacteremia. Am J Health Syst Pharm 2017;74:511-9. PUBMED | CROSSREF
5. Merino E, Caro E, Ramos JR, Boix V, Gimeno A, Rodríguez JC, Riera G, Más P, Sanchéz-Paya J, Reus S, Torrús D, Portilla J. Impact of a stewardship program on bacteraemia in adult inpatients. Rev Esp Quimioter 2017.30:257-63. PUBMED
6. Tsukamoto H, Higashi T, Nakamura T, Yano R, Hida Y, Muroi Y, Ikegaya S, Iwasaki H, Masada M. Clinical effect of a multidisciplinary team approach to the initial treatment of patients with hospital-acquired bloodstream infections at a Japanese university hospital. Am J Infect Control 2014;42:970-5. PUBMED | CROSSREF
7. Ehren K, Meißner A, Jazmati N, Wille J, Jung N, Vehreschild JJ, Hellmich M, Seifert H. Clinical impact of rapid species identification from positive blood cultures with same-day phenotypic antimicrobial susceptibility testing on the management and outcome of bloodstream infections. Clin Infect Dis 2020.70:1285-93. PUBMED
8. Kim M, Song KH, Kim CJ, Song M, Choe PG, Park WB, Bang JH, Hwang H, Kim ES, Park SW, Kim NJ, Oh MD, Kim HB. Electronic alerts with automated consultations promote appropriate antimicrobial prescriptions. PLoS One 2016;11:e0160551. PUBMED | CROSSREF
9. Murri R, Taccari F, Spanu T, D'Inzeo T, Mastrorosa I, Giovannenze F, Scoppettuolo G, Ventura G, Palazzolo C, Camici M, Lardo S, Fiori B, Sanguinetti M, Cauda R, Fantoni M. A 72-h intervention for improvement of the rate of optimal antibiotic therapy in patients with bloodstream infections. Eur J Clin Microbiol Infect Dis 2018;37:167-73. PUBMED | CROSSREF
10. Elligsen M, Pinto R, Leis JA, Walker SAN, Daneman N, MacFadden DR. Improving decision making in empiric antibiotic selection (IDEAS) for Gram-negative bacteremia: a prospective clinical implementation study. Clin Infect Dis 2021;73:e417-25. PUBMED | CROSSREF
11. Yanai M, Ogasawara M, Hayashi Y, Suzuki K, Takahashi H, Satomura A. Impact of interventions by an antimicrobial stewardship program team on appropriate antimicrobial therapy in patients with bacteremic urinary tract infection. J Infect Chemother 2018;24:206-11. PUBMED | CROSSREF
12. Aillet C, Jammes D, Fribourg A, Léotard S, Pellat O, Etienne P, Néri D, Lameche D, Pantaloni O, Tournoud S, Roger PM. Bacteraemia in emergency departments: effective antibiotic reassessment is associated with a better outcome. Eur J Clin Microbiol Infect Dis 2018;37:325-31. PUBMED | CROSSREF
13. Pogue JM, Mynatt RP, Marchaim D, Zhao JJ, Barr VO, Moshos J, Sunkara B, Chopra T, Chidurala S, Kaye KS. Automated alerts coupled with antimicrobial stewardship intervention lead to decreases in length of stay in patients with gram-negative bacteremia. Infect Control Hosp Epidemiol 2014;35:132-8. PUBMED | CROSSREF
14. Cisneros-Herreros JM, Cobo-Reinoso J, Pujol-Rojo M, Rodríguez-Baño J, Salavert-Lletí M. Guía para el diagnóstico y tratamiento del paciente con bacteriemia. Guías de la Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica (SEIMC). Guidelines for the diagnosis and treatment of patients with bacteriemia. Enferm Infecc Microbiol Clin 2007;25:111-30. PUBMED | CROSSREF
15. Rodríguez-Baño J, de Cueto M, Retamar P, Gálvez-Acebal J. Current management of bloodstream infections. Expert Rev Anti Infect Ther 2010;8:815-29. PUBMED | CROSSREF
16. Friedman ND, Kaye KS, Stout JE, McGarry SA, Trivette SL, Briggs JP, Lamm W, Clark C, MacFarquhar J, Walton AL, Reller LB, Sexton DJ. Health care--associated bloodstream infections in adults: a reason to change the accepted definition of community-acquired infections. Ann Intern Med 2002;137:791-7. PUBMED | CROSSREF
17. Garner JS, Jarvis WR, Emori TG, Horan TC, Hughes JM. CDC definitions for nosocomial infections, 1988. Am J Infect Control 1988;16:128-40. PUBMED | CROSSREF
18. Magiorakos AP, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG, Harbarth S, Hindler JF, Kahlmeter G, Olsson-Liljequist B, Paterson DL, Rice LB, Stelling J, Struelens MJ, Vatopoulos A, Weber JT, Monnet DL. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. Clin Microbiol Infect 2012;18:268-81. PUBMED | CROSSREF
19. Retamar P, Portillo MM, López-Prieto MD, Rodríguez-López F, de Cueto M, García MV, Gómez MJ, Del Arco A, Muñoz A, Sánchez-Porto A, Torres-Tortosa M, Martín-Aspas A, Arroyo A, García-Figueras C, Acosta F, Corzo JE, León-Ruiz L, Escobar-Lara T, Rodríguez-Baño J; SAEI/SAMPAC Bacteremia Group. Impact of inadequate empirical therapy on the mortality of patients with bloodstream infections: a propensity score-based analysis.

Antimicrob Agents Chemother 2012;56:472-8. PUBMED | CROSSREF

20. Leibovici L, Shraga I, Drucker M, Konigsberger H, Samra Z, Pitlik SD, Pitlik . The benefit of appropriate empirical antibiotic treatment in patients with bloodstream infection. J Intern Med 1998;244:379-86. PUBMED | CROSSREF
21. Micek ST, Welch EC, Khan J, Pervez M, Doherty JA, Reichley RM, Hoppe-Bauer J, Dunne WM, Kollef MH. Resistance to empiric antimicrobial treatment predicts outcome in severe sepsis associated with Gram-negative bacteremia. J Hosp Med 2011;6:405-10. PUBMED | CROSSREF
22. Mahrous AJ, Thabit AK, Elarabi S, Fleisher J. Clinical impact of pharmacist-directed antimicrobial stewardship guidance following blood culture rapid diagnostic testing. J Hosp Infect 2020;106:436-46. PUBMED | CROSSREF
23. 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:ofz490. PUBMED | CROSSREF
24. Rodríguez-Baño J, Pérez-Moreno MA, Peñalva G, Garnacho-Montero J, Pinto C, Salcedo I, Fernández-Urrusuno R, Neth O, Gil-Navarro MV, Pérez-Milena A, Sierra R, Estella Á, Lupión C, Irastorza A, Márquez JL, Pascual Á, Rojo-Martín MD, Pérez-Lozano MJ, Valencia-Martín R, Cisneros JM; PIRASOA Programme Group. Outcomes of the PIRASOA programme, an antimicrobial stewardship programme implemented in hospitals of the Public Health System of Andalusia, Spain: an ecologic study of time-trend analysis. Clin Microbiol Infect 2020;26:358-65. PUBMED | CROSSREF