






Impact of the Inclusion of an Aminoglycoside to the Initial Empirical Antibiotic Therapy for Gram-Negative Bloodstream Infections in Hematological Neutropenic Patients: a Propensity-Matched Cohort Study (AMINOLACTAM Study)

 A. Albasanz-Puig,^{a,b,c}  C. Gudiol,^{a,b,c,d,e} P. Puerta-Alcalde,^{c,f} C. M. Ayaz,^g M. Machado,^h F. Herrera,ⁱ P. Martín-Dávila,^j J. Laporte-Amargós,^{a,b,c} C. Cardozo,^f M. Akova,^g A. Álvarez-Uría,^h D. Torres,ⁱ J. Fortún,^j C. García-Vidal,^{c,f}  P. Muñoz,^h A. Bergas,^a H. Pomares,^k S. Mercadal,^k X. Durà-Miralles,^{a,b,c} E. García-Lerma,^l N. Pallarès,^j J. Carratalà^{a,b,c,d}

^aInfectious Disease Department, Bellvitge University Hospital, L'Hospitalet de Llobregat, Barcelona, Spain

^bInfections of the Respiratory Tract and in Immunocompromised Patients Research Group, Infectious Diseases and Transplantation Program, Institut d'Investigació Biomèdica de Bellvitge, L'Hospitalet de Llobregat, Barcelona, Spain

^cSpanish Network for Research in Infectious Disease, Instituto de Salud Carlos III, Madrid, Spain

^dUniversity of Barcelona, Barcelona, Spain

^eInstitut Català d'Oncologia, L'Hospitalet de Llobregat, Barcelona, Spain

^fInfectious Diseases Department, Hospital Clínic i Provincial, Barcelona, Spain

^gHacettepe University School of Medicine, Ankara, Turkey

^hClinical Microbiology and Infectious Diseases Department, Hospital General Universitario Gregorio Marañón, Madrid, Spain

ⁱInfectious Diseases Section, Department of Medicine, Centro de Educación Médica e Investigaciones Clínicas, Buenos Aires, Argentina

^jInfectious Diseases Department, Ramón y Cajal Hospital, Madrid, Spain

^kHematology Department, Institut Català d'Oncologia, L'Hospitalet de Llobregat, Barcelona, Spain

^lBioStatistics Unit, Institut d'Investigació Biomèdica de Bellvitge, L'Hospitalet de Llobregat, Barcelona, Spain

ABSTRACT To test the hypothesis that the addition of an aminoglycoside to a β -lactam antibiotic could provide better outcomes than β -lactam monotherapy for the initial empirical treatment of hematological neutropenic patients with subsequently documented Gram-negative bacillus (GNB) bloodstream infection (BSI), a multinational, retrospective, cohort study of GNB BSI episodes in hematological neutropenic patients in six centers (2010 to 2017) was conducted. Combination therapy (β -lactam plus aminoglycoside) was compared to β -lactam monotherapy. The primary endpoint was the case fatality rate, assessed at 7 and 30 days from BSI onset. Secondary endpoints were nephrotoxicity and persistent BSI. Propensity score (PS) matching was performed. Among 542 GNB BSI episodes, 304 (56%) were initially treated with combination therapy, with cefepime plus amikacin being most common (158/304 [52%]). Overall, *Escherichia coli* (273/304 [50.4%]) was the main etiological agent, followed by *Pseudomonas aeruginosa*, which predominated in the combination group (76/304 [25%] versus 28/238 [11.8%]; $P < 0.001$). Multidrug resistance rates were similar between groups (83/294 [28.2%] versus 63/233 [27%]; $P = 0.95$). In the multivariate analysis, combination therapy was associated with a lower 7-day case fatality rate (odds ratio [OR], 0.37; 95% CI, 0.14 to 0.91; $P = 0.035$) with a tendency toward lower mortality at 30 days (OR, 0.56; 95% CI, 0.29 to 1.08; $P = 0.084$). After PS matching, these differences remained for the 7-day case fatality rate (OR, 0.33; 95% CI, 0.13 to 0.82; $P = 0.017$). In addition, aminoglycoside use was not significantly associated with renal function impairment (OR, 1.12; 95% CI, 0.26 to 4.87; $P = 0.9$). The addition of an aminoglycoside to the initial empirical therapy regimen for febrile neutropenic hematological patients should be considered.

KEYWORDS febrile neutropenia, hematological patients, aminoglycosides, combination empirical treatment, Gram-negative bloodstream infection

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Address correspondence to C. Gudiol, cgudiol@iconcologia.net.

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Patients with hematological malignancies are at high risk of Gram-negative bacillus bloodstream infections (GNB BSI), especially those with severe and prolonged neutropenia. Multidrug-resistant (MDR) GNB BSI, including those caused by extended-spectrum β -lactamase (ESBL)-producing *Enterobacterales* and carbapenem-resistant (CR) GNB, are increasing worldwide in cancer patients (1–3). This is of special concern in hematological neutropenic patients, in whom a delay in initiating adequate empirical antibiotic therapy can negatively affect outcomes (4–6). Currently, the optimal initial empirical therapy for high-risk hematological patients with febrile neutropenia (FN) remains a matter of intense debate.

A prospective study including patients with severe GNB BSI found reduced mortality in the subgroup of neutropenic patients who received empirical combination therapy with a β -lactam plus an aminoglycoside (7). However, a later meta-analysis by the same group failed to confirm the benefit of combination therapy over β -lactam monotherapy in neutropenic cancer patients (8). Of note, whereas the 2011 Infectious Diseases Society of America (IDSA) guidelines advocate monotherapy with an antipseudomonal β -lactam for FN treatment (9), the most recent European Conference on Infections in Leukaemia (ECIL) guidelines recommend escalation or de-escalation strategies based on the clinical presentation and individual risk of MDR infections (10). The administration of a β -lactam plus an aminoglycoside facilitates using noncarbapenem β -lactams while ensuring broad empirical antibiotic coverage that can later be narrowed according to microbiological results. In fact, reducing carbapenem use is a cornerstone of limiting the development of antibiotic resistance.

In the current era of widespread antimicrobial resistance, it can be hypothesized that adding an aminoglycoside to a β -lactam may broaden the antibiotic spectrum, improve empirical treatment adequacy, and thereby reduce mortality (11). Moreover, aminoglycosides have pharmacological properties that offer additional advantages, such as their rapid bactericidal activity, postantibiotic effect, and potential synergy with β -lactams (12). The main limitation of this strategy is the potential for aminoglycoside-associated nephrotoxicity (13). However, it is difficult to determine aminoglycosides' net contribution to nephrotoxicity because relevant confounders, such as septic shock, prolonged treatment courses, and the use of other nephrotoxic agents, may overestimate this adverse event (14). Therefore, a short-course aminoglycoside treatment could reliably improve outcomes without significantly affecting renal function.

We aimed to test the hypothesis that the addition of a short-course aminoglycoside regimen to a broad-spectrum β -lactam could provide better outcomes than β -lactam monotherapy, without significant renal function impairment, for the empirical treatment of hematological neutropenic patients with GNB BSI.

RESULTS

Clinical characteristics and BSI etiology. Among the 605 eligible episodes, 63 met at least one of the exclusion criteria and were excluded from analysis, leaving 542 included episodes (Fig. 1). Table 1 shows the episodes' baseline characteristics. Patients in the monotherapy group had more comorbidities, including diabetes mellitus, and were more likely to have received previous corticosteroids. Conversely, more patients in the combination group presented with severe neutropenia and septic shock when compared to the monotherapy group. Nevertheless, all the above-mentioned variables were balanced between groups in the propensity score (PS)-matched cohort (see Table S4 in the supplemental material).

Microbiological results are detailed in Table 2. We observed no differences regarding BSI etiology between groups with the exception of *Pseudomonas aeruginosa* isolates, which were more frequently identified in the combination group.

Overall, 146 episodes were caused by MDR strains, with ESBL production being present in 66 (45.2%) of them. When the BSI episodes caused by *Escherichia coli* and *Klebsiella pneumoniae* were analyzed, 41/273 isolates (15%) of the former and 21/98

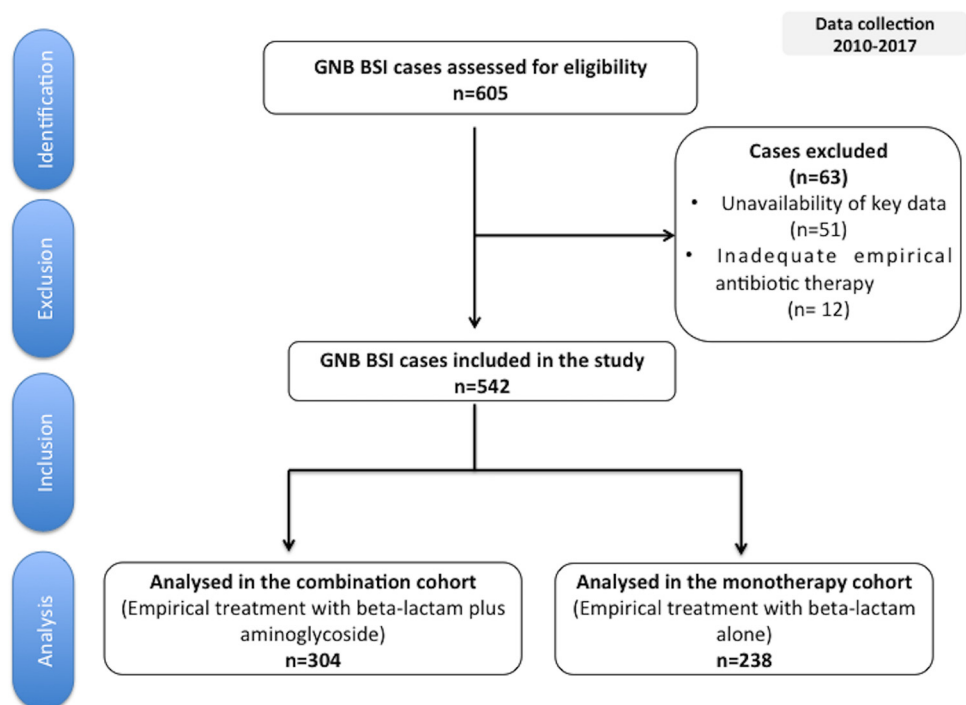


FIG 1 Selection flowchart for episodes of bloodstream infection caused by Gram-negative bacilli. Abbreviations: GNB, Gram-negative bacilli; BSI, bloodstream infection.

isolates (21.4%) of the latter were ESBL producers. Carbapenemase expression was identified in 12/146 isolates (8.2%), particularly in *K. pneumoniae* (8/12).

Focusing on *P. aeruginosa*, 29/104 isolates (27.8%) were MDR, and among these, 25/29 (86.2%) were CR. However, only 4/29 isolates (13.8%) were carbapenemase producers. Among the 25 remaining non-carbapenemase-producing *P. aeruginosa* isolates, 8/25 (32%) were MDR and 17/25 (68%) were extensively drug resistant. All MDR *P. aeruginosa* isolates tested were susceptible to amikacin. Of note, the rate of MDR *P. aeruginosa* BSI was significantly higher in the combination group.

Empirical antibiotic treatment. The empirical antibiotic therapy is detailed in Table 3. Carbapenems were predominantly used in the monotherapy group, whereas cefepime and piperacillin-tazobactam were more frequently administered in the combination group. In the combination group, 56/304 episodes (18.4%) received only one active antibiotic, with the aminoglycoside being the active drug in 47/56 (83.9%) of them. Detailed information regarding the 47 episodes in which patients received an aminoglycoside as the only active antibiotic in the combination group is provided in Table S10.

Study endpoints. Table 4 details the study endpoints. In the multivariate analysis, empirical combination therapy was associated with a lower 7-day case fatality rate (adjusted odds ratio [aOR], 0.37; 95% confidence interval [CI], 0.14 to 0.91; $P=0.035$) and showed a tendency toward lower mortality at 30 days (aOR, 0.56; 95% CI, 0.29 to 1.08; $P=0.084$). Moreover, there was no significant renal function impairment (aOR, 1.77; 95% CI, 0.56 to 5.63; $P=0.3$) after adjusting for baseline renal insufficiency and concomitant nephrotoxic agents. In addition, combination therapy was associated with a lower risk of persistent GNB BSI than monotherapy (aOR, 0.35; 95% CI, 0.12 to 0.89; $P=0.033$). The intraclass correlation index, which measures the amount of variability explained by the hospital cluster effect, was 0.07 in the 7-day-mortality model and 0.20 in the 30-day-mortality and nephrotoxicity model. These figures suggest a low cluster effect in the 7-day-mortality model and a moderate effect in the 30-day-mortality and nephrotoxicity model. More detailed information regarding case fatality rates according to the active empirical antibiotic therapy is provided in Table S11.

TABLE 1 Baseline characteristics of patients with bloodstream infections due to Gram-negative bacilli by treatment group

Parameter ^a	Value for study population ^b			P ^c
	Total (n = 542)	Combination therapy (n = 304 [56%])	Monotherapy (n = 238 [44%])	
No. (%) at center				
Bellvitge University Hospital	216 (39.8)	168 (77.8)	48 (22.2)	<0.001
Hospital Clínic I Provincial de Barcelona	128 (23.6)	73 (57)	55 (43)	0.885
Hacettepe University School of Medicine	82 (15.1)	1 (1.2)	81 (98.8)	<0.001
Hospital General Universitario Gregorio Marañón	53 (9.8)	39 (73.6)	14 (26.4)	0.011
Centro de Educación Médica e Investigaciones Clínicas	32 (5.9)	9 (28.1)	23 (71.9)	0.002
Ramón y Cajal Hospital	31 (5.7)	14 (45.2)	17 (54.8)	0.282
Age (yr) (mean ± SD)	53.7 ± 16.3	54.2 ± 15.5	53.1 ± 17.3	0.48
No. (%) of males	311 (57.4)	179 (58.9)	132 (55.5)	0.48
No. (%) with:				
Comorbidities ^d	121 (22.4)	42 (13.8)	79 (33.3)	<0.001
Diabetes mellitus	41 (7.6)	15 (4.9)	26 (10.9)	0.01
Acute leukemia	251 (46.3)	133 (43.8)	118 (49.6)	0.20
HSCT	160 (29.5)	87 (28.6)	73 (30.7)	0.67
Previous corticosteroid treatment (1 mo)	252 (46.7)	127 (41.9)	125 (52.7)	0.02
Duration of previous neutropenia (days) (median [IQR])	4 [2–10]	4 [2–9]	5 [3–11.5]	0.001
No. (%) with:				
Profound neutropenia at presentation (<100 neutrophils/mm ³)	429 (80.3)	261 (85.9)	168 (73)	<0.001
Previous antibiotic treatment (1 mo)	268 (49.6)	145 (47.7)	123 (52.1)	0.35
Quinolone prophylaxis	165 (30.5)	74 (24.3)	91 (38.4)	0.001
Previous BSI episode	39 (7.2)	18 (5.9)	21 (8.8)	0.3
Previous hospital admission (1 mo)	384 (71.6)	230 (76.2)	154 (65.8)	0.01
Kidney failure at presentation (GFR < 60 ml/min/1.73 m ²)	88 (16.3)	46 (15.2)	42 (17.7)	0.49
Concomitant nephrotoxic treatment	90 (16.6)	50 (16.4)	40 (16.8)	1
Nosocomial acquisition	353 (65.4)	196 (64.5)	157 (66.5)	0.68
High-risk BSI	145 (26.9)	86 (28.3)	59 (25.0)	0.682
High-risk MASCC index score (<21)	289 (53.3)	155 (51)	134 (56.3)	0.25
Septic shock at presentation	104 (19.3)	71 (23.4)	33 (14)	0.008
Source of BSI				
Endogenous	236 (43.7)	139 (45.7)	97 (41.1)	0.32
Unknown origin	75 (13.8)	41 (13.5)	34 (14.3)	0.89
Catheter infection	53 (9.8)	21 (6.9)	32 (13.6)	0.015
Urinary tract infection	33 (6.11)	17 (5.6)	16 (6.8)	0.7
Respiratory tract infection	32 (5.9)	18 (5.9)	14 (5.9)	1
Neutropenic enterocolitis	28 (5.2)	20 (6.6)	8 (3.4)	0.14
Perianal infection	24 (4.4)	15 (4.9)	9 (3.8)	0.67
Skin and soft tissue infection	17 (3.1)	8 (2.6)	9 (3.8)	0.59
Mucositis	12 (2.2)	8 (2.6)	4 (1.7)	0.66
Other sources	32 (5.9)	17 (5.6) ^e	15 (6.3) ^f	0.87

^aAbbreviations: BSI, bloodstream infection; HSCT, hematopoietic stem cell transplant; GFR, glomerular filtration rate; MASCC, Multinational Association for Supportive Care in Cancer.

^bQualitative data are expressed as number (percent), unless otherwise indicated. Quantitative data are expressed as means ± standard deviation (SD) or median and interquartile range (IQR, 25th to 75th percentiles), as appropriate.

^cQualitative data were tested by the chi-square test. Quantitative data expressed as means ± SD were tested by the *t* test, and quantitative data expressed as medians and IQR were tested by the Kruskal-Wallis test.

^dComorbidities are defined as the presence of one or more of the following diseases: chronic obstructive pulmonary disease, heart or hepatic disease, diabetes mellitus, renal failure, and cerebrovascular disease.

^eIncludes peritonitis (*n* = 1), cholangitis (*n* = 1), other abdominal infections (*n* = 11), and sinusitis (*n* = 4).

^fIncludes peritonitis (*n* = 2), cholangitis (*n* = 1), other abdominal infections (*n* = 11), and odontogenic infection (*n* = 1).

For the PS analysis, we were able to match 147 pairs of episodes treated empirically with combination therapy or monotherapy. Baseline characteristics of the PS-matched cohort are detailed in Table S4. In this cohort, combination therapy was still associated with a lower 7-day case fatality rate (aOR, 0.33; 95% CI, 0.13 to 0.82; *P* = 0.017). In contrast, there was no association when the 30-day case fatality rate was assessed (aOR, 0.79; 95% CI, 0.41 to 1.51; *P* = 0.5). Persistent BSI could not be assessed due to the low

TABLE 2 Isolated microorganisms in patients with bloodstream infections due to Gram-negative bacilli by treatment group

Organism or infection ^a	No. (%) in study population			P ^b
	Total (n = 542)	Combination therapy (n = 304)	Monotherapy (n = 238)	
<i>Escherichia coli</i>	273 (50.4)	147 (48.4)	126 (52.9)	0.33
<i>Pseudomonas aeruginosa</i>	104 (19.2)	76 (25)	28 (11.8)	<0.001
<i>Klebsiella pneumoniae</i>	98 (18.1)	52 (17.1)	46 (19.3)	0.58
<i>Enterobacter cloacae</i>	26 (4.8)	12 (3.95)	14 (5.88)	0.4
Other	41 (7.6)	17 (5.6)	24 (10)	0.072
MDR BSI ^c	146 (27.7)	83 (28.2)	63 (27)	0.95
<i>E. coli</i>	78 (14.8)	40 (13.6)	38 (16.3)	0.25
<i>K. pneumoniae</i>	29 (5.5)	13 (4.4)	16 (6.7)	0.26
<i>P. aeruginosa</i>	29 (5.5)	25 (8.5)	4 (1.7)	0.001
Other	10 (1.9)	5 (1.7)	5 (2.1)	0.7

^aAbbreviations: BSI, bloodstream infection; MDR, multidrug resistant.

^bQualitative data were tested by the chi-square test.

^cPercentages are calculated based on the available data regarding MDR BSI (total study population, n = 527; monotherapy population, n = 233; combination therapy population, n = 294).

number of events in the PS-matched cohort. Regarding nephrotoxicity, combination therapy continued to have no association with significant renal function impairment (aOR, 1.12; 95% CI, 0.26 to 4.87; P = 0.9).

The results obtained after performing the sensitivity analysis and an inverse probability of treatment weighting (IPTW)-based approach did not show significant differences compared to those observed with the PS analysis (Table S12 and Fig. S1).

DISCUSSION

In this multicenter, international observational study of a large cohort of neutropenic hematological patients with GNB BSI, adding a short-course aminoglycoside to the empirical therapy with a β -lactam significantly improved the 7-day case fatality rate, without significantly impairing renal function.

Our findings differ from those of other studies that failed to demonstrate a benefit from combination therapy on survival, including an important meta-analysis (8). Nevertheless, most of the randomized clinical trials (RCT) included in that meta-analysis were performed between 1983 and 2012, when the burden of bacterial resistance had not yet reached the levels we currently face (15). Thus, their results may not represent the true impact of combined treatment in the current era of multidrug resistance. Interestingly, our findings do agree with those reported in a later study of neutropenic cancer patients with BSI, where combination therapy was associated with lower mortality in hematological patients (16).

TABLE 3 Treatment regimens of patients with bloodstream infections due to Gram-negative bacilli by treatment group

Treatment	No. (%) in study population			P ^a
	Total (n = 542)	Combination therapy (n = 304)	Monotherapy (n = 238)	
β -Lactam antibiotic				
Meropenem	173 (31.9)	78 (25.7)	95 (39.9)	0.001
Cefepime	164 (30.3)	158 (52)	6 (2.5)	<0.001
Piperacillin-tazobactam	120 (22.1)	46 (15.1)	74 (31.1)	<0.001
Imipenem-cilastatin	67 (12.4)	15 (4.9)	52 (21.8)	<0.001
Other β -lactams	18 (3.3)	7 (2.3) ^b	11 (4.6) ^c	0.210
Aminoglycosides ^d	304 (56)	304 (100)	0	

^aQualitative data were tested by the chi-square test. Quantitative data were tested by the Kruskal-Wallis test.

^bIncludes ceftazidime (n = 4), aztreonam (n = 1), ceftolozane-tazobactam (n = 1), and ertapenem (n = 1).

^cIncludes cefoperazone-sulbactam (n = 3), ceftazidime (n = 1), ceftriaxone (n = 3), doripenem (n = 1), ertapenem (n = 2), and amoxicillin-clavulanate (n = 1).

^dAll episodes in the combination group received amikacin at a dose of 15 mg/kg once daily or equivalent dosing if renal failure was present. The median number of days of aminoglycoside treatment was 2 (IQR 1–3).

TABLE 4 Case fatality and nephrotoxicity rates at different assessment points

Treatment	No. (%) in study population			P ^a
	Total (n = 542)	Combination therapy (n = 304)	Monotherapy (n = 238)	
7-day case fatality rate	49 (9)	18 (5.92)	31 (13)	0.007
30-day case fatality rate	115 (21.2)	48 (15.8)	67 (28.1)	0.001
Persistent BSI ^b	24 (4.4)	7 (2.4)	17 (7.20)	0.014
Incidence of nephrotoxicity at end of antibiotic treatment	40 (7.4)	18 (5.9)	22 (9.2)	0.2

^aQualitative data were tested by the chi-square test.

^bBSI: bloodstream infection. Percentages are calculated based on the available data regarding persistent BSI (total study population, n = 533; monotherapy population, n = 236; combination therapy population, n = 297).

We observed relevant differences regarding the β -lactam used between treatment groups. These findings may be explained because the use of a combination therapy, based on the addition of an aminoglycoside, allows using a carbapenem-sparing β -lactam while ensuring a wide antibiotic coverage. This is of paramount importance, since a reduction of carbapenem consumption is a cornerstone in the fight against antimicrobial resistance. However, when monotherapy is used, carbapenems seem to be preferred, probably due to their activity against ESBL producers, which are currently the most prevalent multidrug-resistant microorganisms in our setting.

Importantly, the benefit of combined therapy for the 7-day case fatality rate remained statistically significant after PS-matching analysis. This is particularly relevant because the impact of an empirical antibiotic regimen on outcomes is probably better assessed by taking early mortality into consideration. These results may be explained by different factors. First, in the combination group, 47/304 episodes (15.5%) showed an improvement empirical treatment adequacy with the aminoglycoside addition. Of note, 26 of these 47 episodes (55.3%) were caused by *P. aeruginosa*, with the majority of them being CR strains. This is of special concern, since 11/26 (42.3%) of these episodes were empirically treated with carbapenems, and the 7-day case fatality rate was particularly high among them (9/10). An expected finding was that case fatality rates of patients who received aminoglycoside monotherapy were higher than those of patients treated with β -lactam monotherapy. However, if the aminoglycoside had not been added to the empirical treatment, an inadequate empirical antibiotic therapy would have been administered, leading to a clinical scenario associated with very high mortality rates. (4, 17). Second, despite the similar rates of multidrug resistance between groups, persistent BSI occurred less often in the combination group, suggesting an enhanced bactericidal effect that may facilitate microbiological and clinical cure (12, 18). In addition, the lowest mortality rate was observed in the combination group when both antibiotic agents were active against the causative microorganism.

It remains controversial whether a short-course aminoglycoside regimen can benefit severely ill patients. Notably, we found improved early mortality among patients receiving combination therapy, who presented more frequently with septic shock, consistent with other reports (19, 20). However, an important meta-analysis (21) and a recent prospective observational cohort study of 648 ICU patients (22) failed to show this association. In the latter, there was no association with a faster reversal of shock or an improved 14-day survival. However, that study mainly included general nonimmunocompromised patients, and only 4% received inadequate empirical antibiotic therapy, probably due to low local levels of antibiotic resistance (22). The potential nephrotoxicity of aminoglycosides is a major concern that limits their clinical use. However, its nephrotoxicity is usually mild when it is administered in a nephroprotective once-daily dosing regimen and in a short course (13, 23). As reported in the above-mentioned meta-analysis, the mean duration of aminoglycoside treatment in most of the included trials was >7 days (8), which could explain the resulting increased nephrotoxicity. In contrast, the median duration of aminoglycoside treatment in our study was only 2 days, which might explain the lack of renal impairment.

Finally, in the current era of emerging resistance, choosing the optimal initial empirical β -lactam according to individual risk of resistance is crucial. In this regard, the new available β -lactam antibiotics play a very important role.

This study benefitted from including a large cohort and having a multicenter design, facilitating generalization. In addition, to account for possible bias, logistic regression models were adjusted by PS analysis. Nevertheless, this study has some limitations that should be acknowledged. First, this was not an RCT; thus, the choice of therapy could have been influenced by several patient-related variables and the clinical presentation. In this regard, patients who received monotherapy had more comorbidities, including diabetes mellitus, which could lead to bias if clinicians considered these patients more susceptible to developing nephrotoxicity and, consequently, avoided the use of aminoglycosides. However, the presence of renal function impairment at baseline is a well-known factor associated with increased nephrotoxicity, and in our cohort, the rate of kidney failure at baseline was not significantly different between treatment groups, which may reduce the potential treatment bias.

Second, the planned sample size was not achieved in the monotherapy group, because the final number of episodes included in the combination group was higher than initially expected. However, the difference in 30-day case fatality between treatment groups was slightly higher than expected, so the study was not underpowered to detect clinically relevant differences. Third, we included only patients with a documented BSI episode, so the results may not be applicable to all febrile neutropenic patients. Fourth, some information may have been lost due to the retrospective design, and we may not have adequately controlled for certain confounders. Fifth, the commonly used antimicrobial susceptibility testing methods may have not been able to detect piperacillin-tazobactam resistance. Finally, despite the differences among centers regarding the number of included episodes and empirical treatments, these inter-variability differences had only a moderate influence on the 30-day case fatality and nephrotoxicity rates at the end of treatment.

In conclusion, we found that therapy with a broad-spectrum β -lactam plus a short-course aminoglycoside regimen significantly improved the 7-day case fatality rate for the empirical treatment of GNB BSI in hematological neutropenic patients, with no significant renal function impairment. In addition to choosing the optimal empirical β -lactam according to individual risk of resistance, our results support reconsidering the inclusion of short-course aminoglycoside therapy in combination with the β -lactam for the treatment of febrile hematological neutropenic patients. Further RCTs are warranted to assess the impact of such combination therapy in these high-risk patients.

MATERIALS AND METHODS

Study design and setting. This was a multicenter, retrospective cohort study of prospectively collected data, conducted from January 2010 to August 2017 in six university hospitals in Spain (4 centers), Argentina (1 center), and Turkey (1 center).

Ethics. The study was approved by the Institutional Review Board at Bellvitge University Hospital (reference number EPA052/17) and by the local research ethics committees of participating centers. It was conducted according to the Declaration of Helsinki guidelines. The need for informed consent was waived by the Clinical Research Ethics Committee due to the retrospective design. The study results are reported following the STROBE recommendations (24).

Participants. All adult (≥ 18 years old) hematological neutropenic patients, including hematopoietic stem cell transplant (HSCT) recipients, were eligible for the study if they were diagnosed with at least one episode of GNB BSI for which they received adequate initial empirical antibiotic therapy for at least 48 h. Empirical antibiotic therapy was classified into a combination therapy group (β -lactam plus aminoglycoside) and a monotherapy group (β -lactam). The exclusion criteria were unavailability of key data (related to empirical therapy and death), receipt of inadequate empirical antibiotic therapy, use of a combination other than a β -lactam plus aminoglycoside, and death within the first 48 h from BSI onset. The follow-up period was 30 days from BSI onset.

Variables. Data regarding baseline characteristics, clinical and microbiological features, and endpoints were collected. Creatinine and glomerular filtration rate were recorded at the moment of initiation and at the end of antibiotic treatment. Empirical antibiotic therapy was defined as antibiotic therapy administered before reception of definitive susceptibility results. Adequate empirical antibiotic therapy was defined as treatment of BSI episodes with at least one *in vitro* active antibiotic against the causative pathogen for at least 48 h. In the monotherapy group, all episodes were treated exclusively with an

empirical β -lactam, which was active against the infecting microorganism. In the combination group, adequate empirical combination therapy was considered to have occurred when the β -lactam and/or the aminoglycoside was active against the causative microorganism and was administered for at least 48 h. In this group, receiving monotherapy with an active aminoglycoside was considered an adequate combination treatment. Inadequate treatment was considered when the empirical treatment did not include any antibiotic with *in vitro* activity. The antipseudomonal β -lactams were uniformly administered at the doses recommended by the international guidelines for the management of febrile neutropenia (9, 10): cefepime, 2 g/8 h; piperacillin-tazobactam, 4.5 g/6 h; meropenem, 1 g/8 h; imipenem-cilastatin, 500 mg/6 h; and ceftazidime, 2 g/8 h. In the case of renal impairment, the dosing was adjusted accordingly.

Endpoints. The primary endpoint was the case fatality rate, assessed at 7 and 30 days from BSI onset. Secondary endpoints included the incidence of nephrotoxicity and persistent BSI. Nephrotoxicity incidence was considered in patients developing acute kidney injury, grade ≥ 2 (25), defined as an increase in serum creatinine value of ≥ 2.0 times the baseline, and was recorded at the termination of antibiotic treatment in both treatment groups. Persistent BSI was considered if blood cultures were positive after the first 48 h of adequate antibiotic therapy.

Microbiological studies. Clinical samples were processed at the microbiology laboratories of each participating center in accordance with standard operating procedures. GNB were identified using standard microbiological techniques, and *in vitro* susceptibility was determined according to EUCAST recommendations, except at the center in Argentina, where CLSI cutoffs were used (26). MDR GNB were defined as described elsewhere (27). ESBL production was studied in isolates with reduced susceptibility to third-generation cephalosporins and was confirmed by phenotypic methods, such as disk diffusion or Etest, or molecular characterization by PCR, depending on the participating center. Isolates were considered carbapenemase producers if a carbapenemase gene was detected by a molecular method. Due to the retrospective nature of the study, the analysis of isolates was not able to be performed in a central microbiology laboratory, and it was performed in each participating center.

Definitions. Patients diagnosed with acute myeloid or acute lymphoblastic leukemia were classified as having acute leukemia. Neutropenia was defined as an absolute neutrophil count of $<0.5 \times 10^9$ cells/mm³. The Multinational Association for Supportive Care in Cancer (MASCC) score was calculated as described elsewhere (28). Previous corticosteroid treatment was defined as the administration of ≥ 20 mg of prednisone, or equivalent dosing, for at least 4 weeks within the last 30 days from BSI onset.

BSI sources were established using standard U.S. Centers for Disease Control and Prevention criteria for secondary BSI (29). In addition, we defined an endogenous source of BSI in neutropenic patients with absent or mild gastrointestinal symptoms, in whom gut translocation was suspected. Neutropenic enterocolitis was defined in patients with severe (grade III or IV) extensive mucositis, involving the upper and lower gastrointestinal tract. Mucositis was considered present in patients with ulcerative lesions involving only the oral cavity. An unknown source was considered when no clear source of BSI was identified due to mixed clinical presentations and/or lack of adequate complementary diagnostic procedures. BSIs were considered low risk when originating from the urinary tract, a catheter, or endogenous sources but high risk when originating from other sources.

Comorbidities were defined as the presence of one or more of the following diseases: chronic obstructive pulmonary disease, heart disease, hepatic disease, diabetes mellitus, renal failure, and cerebrovascular disease. Baseline renal failure was defined as a glomerular filtration rate of <60 ml/min/1.73 m², measured by the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation. Vancomycin and colistin were considered concomitant nephrotoxic drugs if used during the study period.

Sample size. For the whole cohort, we expected a similar number of episodes to be treated with both regimens. The 30-day case fatality rates in the monotherapy and combination groups were expected to be 25% and 15%, respectively. Thus, 278 episodes was the ideal minimum sample size required to perform an unadjusted test to reject the null hypothesis of equal case fatality rates between monotherapy and combination groups, with a power of 80% and a type I error of 5%. A 10% dropout rate was assumed for the sample size estimation.

Statistical analysis. Continuous quantitative variables were compared using the Mann-Whitney *U* test or the *t* test, as appropriate. Categorical variables were compared using Fisher's exact test or Pearson's χ^2 test as appropriate. Incidence rates and 95% confidence intervals (CIs) were reported.

To assess potential risk factors for mortality, logistic regression was used to calculate crude and multivariable adjusted ORs with their 95% CIs. Four logistic regression models were developed, with 7- and 30-day mortality, persistent BSI, and nephrotoxicity as dependent variables. To account for the clustered data within each hospital, a mixed-model approximation was assessed. The cluster effect was found to be relevant only for 30-day mortality and nephrotoxicity; thus, a logistic mixed-effects model for both outcomes was estimated. Missing imputation was not performed because missing key data was an exclusion criterion. Predefined independent variables were tested based on clinical plausibility, as were interactions considered clinically significant. The final multivariate model included age, sex, HSCT, acute leukemia (AL), comorbidities, neutrophil count (<100 or >100 /mm³), MASCC index, MDR GNB BSI, corticosteroids, BSI risk, and the interaction between combination therapy and MDR GNB BSI. The Akaike information criterion was used to assess model goodness of fit.

A major source of bias in this study was the choice of empirical therapy. To address this and to limit the differences between treatment groups, we conducted PS matching based on the estimated probability that a patient would be in the combination group based on the clinical profile. We matched episodes from each treatment group with the nearest-neighbor algorithm, using a maximum tolerance distance between matched subjects of 0.2 standard deviation (30). The PS-confounding variables were age,

gender, AL, HSCT, MASCC index, diabetes mellitus, comorbidities (yes/no), length of previous neutropenia (<7 days versus ≥7 days), BSI risk, BSI acquisition, quinolone prophylaxis, prior antibiotics, urinary catheter, corticosteroids, intensive care unit (ICU) admission (previous or during hospitalization), prior BSI, severe mucositis, parenteral nutrition, hypotension, septic shock, and renal failure at presentation. We identified the imbalanced variables between groups after PS matching by calculating the standardized mean difference and included these as covariates in subsequent logistic regression models. Analyses were performed with R software version 3.4.1. (31). All models used for the multivariate and PS analysis are detailed in Tables S1 to S8. In addition, and in order to further address the potential treatment bias, we performed an inverse probability of treatment weighting (IPTW) analysis and a sensitivity analysis by center, which are detailed in Tables S9 and Fig. S1.

SUPPLEMENTAL MATERIAL

Supplemental material is available online only.

SUPPLEMENTAL FILE 1, PDF file, 0.6 MB.

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