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Influence of Empiric Therapy with a β-Lactam Alone or Combined with an Aminoglycoside on Prognosis of Bacteremia Due to Gram-Negative Microorganisms▽

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Evidence supporting the combination of aminoglycosides with β-lactams for Gram-negative bacteremia is inconclusive. We have explored the influence on survival of empirical therapy with a β-lactam alone versus that with a β-lactam-aminoglycoside combination by retrospectively analyzing a series of bacteremic episodes due to aerobic or facultative Gram-negative microorganisms treated with single or combination therapy. The outcome variable was a 30-day mortality. Prognostic factors were selected by regression logistic analysis. A total of 4,863 episodes were assessed, of which 678 (14%) received combination therapy and 467 (10%) were fatal. Factors independently associated with mortality included age greater than 65 (odds ratio [OR], 2; 95% confidence interval [CI], 1.6 to 2.6), hospital acquisition (OR, 1.5; 95% CI, 1.2 to 1.9), a rapidly or ultimately fatal underlying disease (OR, 2.5; 95% CI, 2 to 3.2), cirrhosis (OR, 1.9; 95% CI, 1.4 to 2.6), prior corticosteroids (OR, 1.5; 95% CI, 1.1 to 2), shock on presentation (OR, 8.8; 95% CI, 7 to 11), pneumonia (OR, 2.8; 95% CI, 1.9 to 4), and inappropriate empirical therapy (OR, 1.8; 95% CI, 1.3 to 2.5). Subgroup analysis revealed that combination therapy was an independent protective factor in episodes presenting shock (OR, 0.6; 95% CI, 0.4 to 0.9) or neutropenia (OR, 0.5; 95% CI, 0.3 to 0.9). Combination therapy improved the appropriateness of empirical therapy in episodes due to extended-spectrum β-lactamase (ESBL)- or AmpC-producing *Enterobacteriaceae* and *Pseudomonas aeruginosa*. In patients with Gram-negative bacteremia, we could not find an overall association between empirical β-lactam-aminoglycoside combination therapy and prognosis. However, a survival advantage cannot be discarded for episodes presenting shock or neutropenia, hence in these situations the use of combination therapy may still be justified. Combination therapy also should be considered for patients at risk of being infected with resistant organisms, if only to increase the appropriateness of empirical therapy.

Evidence favoring the addition of an aminoglycoside to a β-lactam antibiotic for the treatment of patients with sepsis due to Gram-negative microorganisms is rather tenuous. Two systematic reviews of more than 100 randomized clinical trials conducted in neutropenic and nonneutropenic patients have indicated that the only discernible effect of combination therapy is an increased rate of toxicity attributable to the aminoglycoside component (14, 16). Thus, the prospects of β-lactam-aminoglycoside combination therapy for an increased efficacy based on the *in vitro* observation of synergy and less selection of resistant mutants have not yet been fulfilled *in vivo*. The only infections for which some doubts persist regarding a putative survival benefit of combination therapy are those due to *Pseudomonas aeruginosa* and other potentially resistant Gram-negative bacilli (15, 17).

Despite the evidence that monotherapy with aminoglycosides may fall short of being the optimal treatment for serious infections other than those affecting the urinary tract (9), the current surge of multiple β-lactam and quinolone resistance in Gram-negative bacilli and the scarcity of new compounds to face it justify a renewed interest in this class of antibiotics. Several recent observations have made it clear that adding an aminoglycoside to the empirical regimen administered to seriously ill patients infected by *P. aeruginosa* or other potentially resistant Gram-negative organisms may help to avoid the ominous pitfall of fully inadequate initial therapy and may increase survival (3, 5).

In the present study, we report our experience with a large cohort of patients with Gram-negative bacteremia who received as empirical therapy a β-lactam-aminoglycoside combination or a single β-lactam. The primary aim of the study was to look for any indication that combination therapy could be associated with a better prognosis than single-β-lactam treatment.

MATERIALS AND METHODS

Setting. The study was carried out in a 700-bed university center in Barcelona, Spain. Since 1991, our unit has been prospectively identifying and monitoring all patients with bacteremia admitted to our hospital. The present report refers to all patients admitted during 12 consecutive years (January 1997 to December 2008) with monomicrobial bacteremia due to aerobic or facultative Gram-negative microorganisms who received as empirical therapy either β-lactams alone or β-lactams plus an aminoglycoside. The study was approved by the ethics committee board of our institution.

Assessed clinical variables. The following clinical variables were collected prospectively from all patients: demographics, place of acquisition (community, hospital, health care related), comorbidities, prognosis of underlying disease according to a modification of McCabe and Jackson criteria (10, 11), selected exposures within the previous month (antibiotics, corticosteroids, surgery, and indwelling bladder catheter), source of bacteremia, shock on presentation, ap-

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TABLE 1. β-Lactams administered to patients receiving and not receiving aminoglycosides as empirical therapy

Antibiotic	No.[a] (%; n = 4,863)	No. (%) receiving:		OR (95% CI)	P
		Combination therapy (n = 678)	β-Lactam only (n = 4,185)		
Ampicillin	380 (8)	43 (6)	377 (8)	0.8 (0.5–1.1)	0.1
Amoxicillin-clavulanate	249 (5)	3 (0.4)	246 (6)	0.1 (0.02–0.2)	<0.0001
Non-antipseudomonal cephalosporin	2,490 (51)	117 (17)	2,373 (57)	0.2 (0.1–0.3)	<0.0001
Antipseudomonal cephalosporin	354 (7)	186 (27)	168 (4)	9 (7–11)	<0.0001
Piperacillin-tazobactam	979 (20)	156 (23)	863 (20)	1.2 (1–1.5)	0.04
Antipseudomonal carbapenem	761 (16)	185 (27)	576 (14)	2.4 (2–3)	<0.0001

[a] In 350 episodes, more than one β-lactam was administered (ampicillin plus a cephalosporin in 76% of these cases).

propriateness of empirical therapy, and survival status at 30 days of the onset of bacteremia.

Definitions. Infections were defined according to the CDC criteria (4) with slight modifications. Empirical therapy refers to any antibiotic administered before microbiological data (identification and drug susceptibility) were available. Empirical therapy was considered appropriate if at least one of the antibiotics had *in vitro* activity against the blood isolate and was administered at an adequate dosage by an appropriate route. Specific dosages of antibiotics were not registered. However, local guidelines during the study period recommended the administration of aminoglycosides in a single daily dose of 5 to 7 mg/kg of body weight for gentamicin and tobramycin and 15 mg/kg for amikacin in patients with normal renal function.

Statistical analysis. Proportions were compared by using the χ^2 or exact Fisher tests. Patients' characteristics or exposures with a univariate P value of ≤0.25 were subjected to logistic regression modeling (stepwise forward approach) to assess the independent predictors of 30-day mortality. Since the appropriateness of empirical therapy is a plausible intermediate variable by which combination therapy can affect prognosis, models predicting mortality also were constructed without including that variable. For similar reasons, the etiologic microorganisms were not included as potential confounders of the association of therapeutic variables with mortality. Finally, logistic models also were constructed introducing the appropriateness of empirical therapy as a four-strata variable on the basis of the *in vitro* activity of each component, designated as follows: inappropriate therapy (no active antibiotics given), appropriate β-lactam monotherapy (only the β-lactam was active either as a single agent or part of a combination), appropriate aminoglycoside monotherapy (only the aminoglycoside part of the combination was active), and appropriate dual therapy (appropriate β-lactam plus appropriate aminoglycoside). Calculations were done by using the BMDP statistical software (Cork Technology Park, Cork, Ireland).

RESULTS

Antibiotic use and factors associated with combination therapy. During the 12-year study period, 13,710 episodes of bacteremia were evaluated, of which 6,216 involved a single aerobic or facultative Gram-negative organism. From these, a total of 4,863 episodes were empirically treated exclusively with a regimen containing β-lactams alone (n = 4,185; 86%) or β-lactams plus an aminoglycoside (n = 678; 14%). The prevalence of the use of combination therapy was the highest during the first 3 years of the study (234/1,018; 23%), was halved during the second quarter (144/1,184; 12%), and remained stable thereafter (136/1,307 [10%] and 164/1,354 [12%] during the third and fourth quarters, respectively). Classes of β-lactams used are shown in Table 1, and the etiologic agents involved are shown in Table 2. Among aminoglycosides, amikacin was the agent most commonly prescribed (591 episodes; 87%), followed by gentamicin (56 episodes; 8%) and tobramycin (31 episodes; 5%). There were no appreciable shifts in the choice of the different aminoglycosides during the study period. Significant changes in the use of β-lactams were noted over time, particularly in the proportions of patients receiving monotherapy with amoxicillin-clavulanate (from 1% in the first quarter to 7% in the fourth; $P < 0.0001$ for a linear trend), piperacillin-tazobactam (from 5% to 28%; $P < 0.0001$), and antipseudomonal carbapenems (from 8 to 17%; $P < 0.0001$), at the expense of ampicillin (from 12% in the first quarter to 2% in the fourth; $P < 0.0001$) and non-antipseudomonal cephalosporins (from 58 to 36%; $P < 0.0001$). Aminoglycosides were preferentially combined (78% of the time) with antipseudomonal β-lactams.

Patients receiving empirical combination therapy differed

TABLE 2. Etiologic microorganisms in patients receiving and not receiving aminoglycosides as empirical therapy

Microorganism	No. (%; n = 4,863)	No. (%) receiving:		OR (95% CI)	P
		Combination therapy (n = 678)	β-Lactams only (n = 4,185)		
Non-ESBL *Escherichia coli*	2,737 (56)	248 (37)	2,489 (60)	0.4 (0.3–0.5)	<0.0001
ESBL *E. coli*	150 (3)	28 (4)	122 (3)	1.4 (0.9–2)	0.09
Non-ESBL *Klebsiella pneumoniae*	483 (10)	63 (9)	420 (10)	0.9 (0.7–1.2)	0.5
ESBL *K. pneumoniae*	83 (2)	20 (3)	63 (2)	2 (1.2–3)	0.007
Proteus mirabilis	128 (3)	10 (2)	118 (3)	0.5 (0.3–1)	0.04
Salmonella spp.	124 (3)	15 (2)	109 (3)	0.9 (0.5–2)	0.5
AmpC *Enterobacteriaceae*[a]	408 (8)	82 (12)	326 (8)	1.6 (1.3–2)	0.0002
P. aeruginosa	462 (10)	143 (21)	319 (8)	3 (2.6–4)	<0.0001
Other nonfermenters[b]	156 (3)	51 (8)	105 (3)	3 (2–5)	<0.0001
Miscellaneous[c]	132 (3)	18 (3)	114 (3)	0.9 (0.6–1.6)	0.8

[a] Includes *Enterobacter* (n = 230), *S. marcescens* (n = 68), *Citrobacter* (n = 58), and *Proteeae* (n = 52) isolates.
[b] Includes *Acinetobacter baumannii* (n = 57), *Strenotrophomonas maltophilia* (n = 50), *Burkholderia cepacia* (n = 8), and *Pseudomonas* (n = 41) isolates.
[c] Includes *Haemophilus* (n = 37), *Neisseria* (n = 25), *Aeromonas* (n = 20), and other (n = 50).

TABLE 3. Clinical characteristics of patients receiving and not receiving aminoglycosides as empirical therapy

Characteristic[a]	No. (%; n = 4,863)	No. (%) receiving:		OR (95% CI)	P
		Combination therapy (n = 678)	β-Lactam only (n = 4,185)		
Study period					
1997–1999	1,018	234 (35)	784 (19)	1	
2000–2002	1,184	144 (21)	1,040 (25)	0.5 (0.4–0.6)	
2003–2005	1,307	136 (20)	1,171 (29)	0.4 (0.3–0.5)	
2006–2008	1,354	164 (24)	1,190 (28)	0.5 (0.4–0.6)	<0.0001
Age >65 yr	2,771 (57)	300 (44)	2,471 (59)	0.6 (0.5–0.7)	<0.0001
Male gender	2,464 (51)	375 (55)	2,089 (50)	1.2 (1.1–1.5)	0.01
Place of acquisition					
Community	2,973	191 (28)	2,782 (67)	1	
Hospital	1,358	306 (45)	1,052 (25)	4.2 (3.5–5)	
Health care related	532	181 (27)	351 (8)	7.5 (6–9)	<0.0001
Ultimately/finally fatal underlying disease	1,991 (41)	421 (62)	1,570 (38)	3 (2–3.2)	<0.0001
Hematological cancer	609 (13)	261 (39)	348 (8)	7 (6–8)	<0.0001
Solid organ cancer	992 (20)	144 (21)	848 (20)	1 (0.9–1.3)	0.6
BMT	103 (2)	48 (7)	55 (1)	6 (4–9)	<0.0001
Solid-organ transplant	312 (6)	21 (3)	291 (7)	0.4 (0.3–0.7)	0.0001
Neutropenia	374 (8)	190 (28)	184 (4)	9 (7–11)	<0.0001
Heart failure	546 (11)	58 (9)	488 (12)	0.7 (0.5–0.95)	0.02
COPD	358 (7)	49 (7)	309 (7)	1 (0.7–1.3)	0.9
Renal insufficiency	324 (7)	47 (7)	227 (7)	1 (0.8–1.5)	0.8
Diabetes mellitus	916 (19)	82 (12)	834 (20)	0.6 (0.4–0.7)	<0.0001
Cirrhosis	490 (10)	22 (3)	468 (11)	0.3 (0.2–0.4)	<0.0001
HIV infection	169 (4)	22 (3)	147 (4)	0.9 (0.6–2)	0.7
Prior corticosteroids	870 (18)	202 (30)	468 (11)	2.3 (1.9–2.7)	<0.0001
Prior antibiotics	1,807 (37)	434 (64)	1,373 (33)	3.6 (3–4.3)	<0.0001
Prior surgery	539 (11)	118 (17)	421 (10)	1.9 (1.5–2.3)	<0.0001
Bladder catheter	855 (18)	191 (28)	664 (16)	2 (1.9–2.5)	<0.0001
Shock on presentation	694 (14)	168 (25)	664 (16)	2.3 (1.9–2.8)	<0.0001
Source of infection					
Unknown	870 (18)	219 (32)	651 (16)	1	
Urinary tract	2,235 (46)	124 (18)	2,111 (50)	0.17 (0.1–0.2)	
i.v. catheter	419 (9)	128 (19)	291 (7)	1.3 (1.01–1.7)	
Pneumonia	249 (5)	82 (12)	167 (4)	1.5 (1.1–2)	
Intraabdominal	276 (6)	30 (4)	246 (6)	0.4 (0.2–0.5)	
Biliary tract	551 (11)	47 (7)	504 (12)	0.3 (0.02–0.4)	
Skin/soft tissues	132 (3)	29 (4)	103 (3)	0.8 (0.5–1.3)	
Other	131 (3)	19 (3)	112 (3)	0.5 (0.3–0.8)	<0.0001
Inappropriate empirical therapy	454 (9)	57 (8)	397 (9)	1.1 (0.9–1.5)	0.4

[a] BMT, bone marrow transplantation; COPD, chronic obstructive pulmonary disease.

from those treated with β-lactams alone in many clinical aspects (Table 3). They were younger; more frequently had an infection acquired in the hospital or health-care-related setting, from an intravenous (i.v.) catheter, or from lung, skin soft tissues, or unknown sources; had an ultimately or rapidly fatal underlying disease; had hematological cancer, bone marrow transplantation, neutropenia, an indwelling bladder catheter, a surgical procedure within the last month, or shock on presentation; and had been exposed to corticosteroids and antibiotics within the previous month. On the other hand, patients receiving combination therapy were less likely to have diabetes, cirrhosis, solid-organ transplantation, and a urinary or biliary tract source of bacteremia.

Multivariate analysis revealed that the following variables were independently associated with the administration of empirical combination therapy: first quarter of the study (odds ratio [OR], 3.3; 95% confidence interval [CI], 2.7 to 4.2), age < 65 years (OR, 1.3; 95% CI, 1.03 to 1.5), hospital-acquired (OR, 1.5; 95% CI, 1.2 to 2) or health care-related (OR, 2.2; 95% CI, 1.6 to 3) infection, an ultimately or rapidly fatal underlying disease (OR, 1.3; 95% CI, 1.01 to 1.6), hematological cancer (OR, 2; 95% CI, 1.5 to 2.6), neutropenia (OR, 2.8; 95% CI, 2.1 to 3.9), solid-organ transplantation (OR, 0.5; 95% CI, 0.3 to 0.8), cirrhosis (OR, 0.2; 95% CI, 0.1 to 0.4), indwelling bladder catheter (OR, 2; 95% CI, 1.6 to 2.6), prior antibiotic therapy (OR, 1.6; 95% CI, 1.3 to 2), shock on presentation (OR, 1.9; 95% CI, 1.5 to 2.5), and a urinary tract (OR, 0.4; 95% CI, 0.3 to 0.6), i.v. catheter (OR, 1.4; 95% CI, 1.02 to 1.9), or lung (OR, 1.9; 95% CI, 1.3 to 2.8) source of bacteremia.

As shown in Table 4, combination therapy increased the chances of providing appropriate empirical therapy to episodes due to extended-spectrum β-lactamase (ESBL)- and AmpC-producing *Enterobacteriaceae* and *P. aeruginosa*.

Prognostic factors. A total of 467 (10%) episodes of Gram-negative bacteremia had a fatal outcome. Thirty-day mortality remained unchanged during the study period. Univariate and

TABLE 4. Appropriateness of antibiotic therapy in patients receiving or not receiving aminoglycosides as empirical therapy

Microorganism	No./total no. (%) receiving:		OR (95% CI)	*P*
	Combination	β-Lactam		
Non-ESBL *E. coli*	242/248 (98)	2,454/2,489 (99)	0.6 (0.2–1.7)	0.3
ESBL *E. coli*	21/28 (75)	62/122 (51)	2.9 (1.07–8.2)	0.02
Non-ESBL *K. pneumoniae*	62/63 (98)	393/420 (94)	4 (0.7–177)	0.2
ESBL *K. pneumoniae*	18/20 (90)	38/63 (60)	2 (1.2–4.2)	0.01
P. mirabilis	10/10 (100)	116/118 (98)		1
Salmonella spp.	15/15 (100)	108/109 (99)		1
AmpC organisms	78/82 (95)	258/326 (79)	5.1 (1.8–20)	0.001
P. aeruginosa	133/143 (93)	201/319 (63)	7.8 (3.8–16)	<0.0001
Other nonfermenters	24/51 (47)	53/105 (51)	0.9 (0.4–1.8)	0.7
Miscellaneous	18/18 (100)	105/114 (92)		0.4

multivariate analysis of factors associated with 30-day mortality are shown in Tables 5 and 6, respectively. The only therapeutic variable independently associated with mortality was the inappropriateness of empirical therapy. After adjusting for the predictors of mortality selected by multivariate analysis (Table 6), combination therapy had an OR of 0.91 (95% CI, 0.7 to 1.2; $P = 0.6$). Not including the appropriateness of empirical therapy in the analysis produced a model containing exactly the same other variables as those shown in Table 6 with similar measures of association. In this case, the estimated OR for combination therapy after adjusting for the best predictors was 0.87 (95% CI, 0.6 to 1.2; $P = 0.4$).

Logistic models also were constructed by introducing the appropriateness of empirical therapy stratified as inappropriate therapy ($n = 454$), appropriate β-lactam monotherapy ($n = 3807$), appropriate aminoglycoside monotherapy ($n = 86$), and appropriate dual therapy ($n = 516$). The best model consisted of exactly the same set of variables as those shown in Table 6 and, again, only inappropriate therapy was significantly associated with mortality (OR, 1.8; 95% CI, 1.3 to 2.5). In this regard, neither appropriate aminoglycoside monotherapy (OR, 1.2; 95% CI, 0.6 to 2.5) nor appropriate dual therapy (OR, 0.8; 95% CI, 0.6 to 1.2) was significantly different from appropriate β-lactam monotherapy.

Subgroup analysis. A total of 4,302 episodes were empirically treated with an appropriate single β-lactam ($n = 3,786$) or appropriate dual therapy ($n = 516$). In this subgroup, 372 (9%) patients had died by day 30. As in the whole series, multivariate analysis did not select combination therapy as a significant predictor of mortality. The best model included the following variables: age > 65 years (OR, 2.2; 95% CI, 1.7 to 3), an ultimately or rapidly fatal underlying disease (OR, 2.3; 95% CI, 1.8 to 3.1), bone marrow transplantation (OR, 2.4; 95% CI, 1.1 to 4.8), cirrhosis (OR, 1.9; 95% CI, 1.4 to 2.7), indwelling bladder catheter (OR, 1.5; 95% CI, 1.1 to 2), shock on presentation (OR, 9.6; 95% CI, 7.4 to 12), and urinary tract (OR, 0.3; 95% CI, 0.2 to 0.4), i.v. catheter (OR, 0.4; 95% CI, 0.2 to 0.8), lung (OR, 2.4; 95% CI, 1.6 to 3.7), and biliary tract (OR, 0.5; 95% CI, 0.3 to 0.8) sources of bacteremia. The estimated OR for combination therapy after adjusting for these predictors was 0.8 (95% CI, 0.6 to 1.2; $P = 0.2$).

Risk factors for 30-day mortality also were specifically analyzed in episodes originating in sources other than the urinary tract and i.v. catheter ($n = 2,209$; 349 [16%] died), episodes associated with neutropenia ($n = 374$; 67 [18%] died), and

TABLE 5. Univariate analysis of the association of clinical, microbiological, and therapeutic characteristics with 30-day mortality

Characteristic[a]	Patient outcome		OR (95% CI)	*P*
	Died ($n = 467$)	Survived ($n = 4,396$)		
Age >65 yr	287 (62)	2,484 (57)	1.2 (1–1.5)	0.04
Male gender	267 (57)	2,197 (50)	1.3 (1.1–1.6)	0.003
Place of acquisition				
Community	206 (44)	2,767 (63)	1	
Nosocomial	206 (44)	1,152 (26)	2.4 (1.9–3)	
Health care related	55 (12)	477 (11)	1.6 (1.1–2)	<0.0001
Ultimately fatal underlying disease	328 (70)	1,663 (39)	4 (3–5)	<0.0001
Hematological cancer	77 (17)	532 (12)	1.4 (1.1–2)	0.006
Solid-organ cancer	129 (28)	863 (20)	1.6 (1.3–2)	<0.0001
BMT	15 (3)	88 (2)	1.6 (0.9–3)	0.08
Solid-organ transplant	25 (5)	287 (7)	0.8 (0.5–1.3)	0.3
Neutropenia	67 (14)	307 (7)	2 (1.7–3)	<0.0001
Heart failure	48 (10)	498 (11)	0.9 (0.7–1.2)	0.5
COPD	46 (10)	312 (7)	1.4 (1–2)	0.03
Renal insufficiency	43 (9)	281 (6)	1.5 (1–2)	0.02
Diabetes mellitus	82 (18)	834 (19)	0.9 (0.7–1.2)	0.5
Cirrhosis	106 (23)	384 (9)	3 (2.4–4)	<0.0001
HIV infection	19 (4)	150 (3)	1.2 (0.7–2)	0.5
Prior corticosteroids	127 (27)	743 (17)	1.8 (1.5–2)	<0.0001
Prior antibiotics	221 (47)	1,586 (36)	1.6 (1.3–1.9)	<0.0001
Prior surgery	50 (11)	489 (11)	1 (0.7–1.3)	0.8
Bladder catheter	135 (29)	720 (16)	2 (1.9–2.5)	<0.0001
Shock on presentation	250 (54)	444 (10)	10 (8–13)	<0.0001
Source of infection				
Unknown	109 (23)	761 (17)	1	
Urinary tract	86 (18)	2,149 (49)	0.3 (0.2–0.4)	
i.v. catheter	32 (7)	387 (9)	0.6 (0.4–0.9)	
Pneumonia	89 (19)	160 (4)	3.9 (2.8–5.4)	
Intraabdominal	75 (16)	201 (5)	2.6 (1.9–3.6)	
Biliary tract	36 (8)	515 (12)	0.5 (0.3–0.7)	
Skin/soft tissues	26 (6)	106 (2)	1.7 (1.1–2.8)	
Other	14 (3)	117 (3)	0.8 (0.5–1.5)	<0.0001
Etiologic microorganism				
Non-ESBL *E. coli*	199 (43)	2,538 (58)	1	
ESBL *E. coli*	17 (4)	133 (3)	1.6 (1–2.8)	
Non-ESBL *K. pneumoniae*	47 (10)	436 (10)	1.4 (1–1.9)	
ESBL *K. pneumoniae*	22 (5)	61 (1)	4.6 (2.8–7.7)	
P. mirabilis	10 (2)	118 (3)	1.1 (0.6–2.1)	
Salmonella spp.	11 (2)	133 (3)	1.2 (0.7–2.3)	
AmpC *Enterobacteriaceae*	46 (10)	362 (8)	1.6 (1.2–2.3)	
P. aeruginosa	79 (17)	383 (9)	2.6 (2–3.5)	
Other nonfermenters	26 (6)	130 (3)	2.6 (1.6–4)	
Miscellaneous	10 (2)	122 (3)	1.1 (0.5–2)	<0.0001
Combination therapy	101 (22)	577 (13)	1.8 (1.4–2.3)	<0.0001
Inappropriate empirical therapy	79 (17)	375 (9)	2.2 (1.7–2.9)	<0.0001

[a] BMT, bone marrow transplantation; COPD, chronic obstructive pulmonary disease.

TABLE 6. Multivariate analysis of factors associated with 30-day mortality in the whole series

Characteristic	OR (95% CI)
Age >65 yr	2 (1.6–2.6)
Place of acquisition	
Community	1
Hospital	1.5 (1.2–1.9)
Health care related	0.9 (0.6–1.4)
Ultimately or rapidly fatal underlying disease	2.5 (1.9–3.2)
Liver cirrhosis	1.9 (1.4–2.6)
Prior corticosteroids	1.5 (1.1–2)
Shock	8.8 (7–11)
Source of infection	
Unknown	1
Urinary tract	0.4 (0.3–0.6)
i.v. catheter	0.6 (0.4–0.9)
Pneumonia	2.8 (1.9–4.1)
Intraabdominal	1.4 (1–2.1)
Biliary	0.6 (0.4–0.9)
Skin/soft tissues	1.4 (0.8–2.5)
Other	1.2 (0.6–2.3)
Inappropriate empirical therapy	1.8 (1.3–2.5)

episodes associated with shock on presentation (n = 694; 250 [36%] died), as well as in those due to *Enterobacteriaceae* organisms resistant or potentially resistant to expanded-spectrum cephalosporins (ESBL or AmpC producers; n = 641; 85 [13%] died) and *P. aeruginosa* (n = 462; 79 [17%] died). The best predictors of mortality for these subgroups selected by models not including the appropriateness of empirical therapy as an explanatory variable are shown in Table 7. Only in shock and neutropenic episodes was combination therapy independently associated with 30-day mortality (as a protective factor). After forcing combination therapy into the models containing the best predictors, its OR for episodes originating in sources other than the urinary tract or venous catheter, episodes due to ESBL or AmpC *Enterobacteriaceae*, and those due to *P. aeruginosa* were 0.8 (95% CI, 0.6 to 1.1, P = 0.2), 0.85 (95% CI, 0.4 to 1.6, P = 0.6), and 0.8 (95% CI, 0.4 to 1.4, P = 0.4), respectively. When the appropriateness of empirical therapy was allowed to step into the multivariate models, it was significantly associated with mortality (or showed a trend toward significance) as a protective factor in episodes originating from the urinary tract and catheters (OR, 0.6; 95% CI, 0.4 to 0.9), episodes with shock on presentation (OR, 0.6; 95% CI, 0.3 to 1), episodes due to *P. aeruginosa* (OR, 0.5; 95% CI, 0.3 to 0.9), and those due to ESBL- or AmpC-producing *Enterobacteriaceae* (OR, 0.6; 95% CI, 0.3 to 1.07). Only in patients with neutropenia was the appropriateness of empirical therapy by itself not predictive of survival, whereas combination therapy was associated with a 50% relative reduction in 30-day mortality. This was because neutropenic episodes treated with a single appropriate β-lactam had a fatality rate (36 out of 158; 23%) similar to the rate of those treated with inappropriate therapy (9 out of 32; 21%), which was higher than the fatality of the episodes managed with combination therapy in which at least one component was appropriate (22 out of 174; 13%).

DISCUSSION

The present analysis of a relatively large series of patients with Gram-negative bacteremia empirically treated with either a combination of ß-lactam-aminoglycoside or ß-lactam alone suggests that in some subgroups, namely, those presenting shock or neutropenia, empirical treatment with combination therapy still conveys a survival advantage.

TABLE 7. Multivariate analysis of factors associated with 30-day mortality in selected subgroups

Characteristic	OR (95% CI) for mortality subgroup:				
	Non-UTI, non-i.v. catheter sources	Neutropenia	Shock	ESBL or AmpC	*P. aeruginosa*
Age >65 yr	1.8 (1.4–2.4)		2.1 (1.4–3.1)		2.6 (1.4–5)
Place of acquisition					
Community	1			1	
Hospital	1.6 (1.1–2.2)			1.7 (1–3.2)	
Health care situation	0.9 (0.6–1.4)			0.5 (0.2–1.4)	
Ultimately or rapidly fatal disease	2.6 (1.9–3.4)		2.3 (1.6–3.4)	4.8 (2.5–9.1)	2.1 (1.1–4)
Hematological cancer		0.5 (0.3–1)			
Cirrhosis			1.7 (1–2.9)		
Renal insufficiency	1.6 (1.01–2.6)	5.5 (1.3–23)			
Prior surgery	0.3 (0.2–0.5)				0.4 (0.2–1)
Bladder catheter	1.5 (1.02–2.2)				
Shock	7.9 (6–11)	10 (5.5–19)		8 (5–14)	6.4 (3.5–12)
Source of infection					
Unknown	1		1	1	1
Urinary tract			0.3 (0.2–0.6)	1.3 (0.5–2.4)	0.2 (0.1–0.9)
i.v. catheter			0.3 (0.1–0.7)	0.8 (0.3–1.8)	0.7 (0.3–1.8)
Pneumonia	2.9 (2–4.3)		2.3 (1.3–4.2)	5 (1.6–13)	3.3 (1.5–7)
Intraabdominal	2 (1.3–3)		1 (0.5–1.6)	1.2 (0.5–3.2)	2.8 (0.7–12)
Biliary	0.5 (0.3–0.8)		0.3 (0.2–0.7)	0.4 (0.1–1.4)	0.6 (0.1–2.4)
Skin/soft tissues	1.6 (0.9–2.7)		1.4 (0.5–3.6)	0.8 (0.2–3.8)	1 (0.3–3.6)
Other	1.3 (0.7–2.4)		0.9 (0.3–2.4)	2 (0.4–9)	2.8 (0.7–12)
Combination therapy		0.5 (0.3–0.9)	0.6 (0.4–0.9)		

When trying to evaluate the possible influence of therapy variables on outcomes, one of the most important drawbacks of observational studies lies in the fact that the therapeutic regimen is not selected by chance. Many patients' characteristics that by themselves are expected to have an impact on prognosis can, at the same time, influence the decision-making process leading to the prescription of single or combination therapy. At the outset, it is quite probable that different populations are treated with different regimens, and there is never certainty that some relevant prognostic factors are not missed on the way. Adjusting for confounding is necessary, but even after doing so, inferring causality is always hazardous. In this regard, the present study is not an exception. Our data suggest that combination therapy was preferentially administered to patients with more severe underlying disease or clinical condition on presentation or suspected of being infected by more resistant pathogens, particularly *P. aeruginosa*. On the other hand, the concern about nephrotoxicity probably underlies the sparing of aminoglycosides in patients who were older or had diabetes, cirrhosis, or solid-organ transplantation. The bias toward administering combination therapy to patients with more severe disease probably explains that, in the whole series, the 30-day mortality rate was almost double for episodes treated with aminoglycosides (OR, 1.8; $P < 0.0001$), and that it was not until adjusting for confounding that this association vanished. As a matter of fact, although neither in the entire series nor in the episodes due to ESBL or AmpC *Enterobacteriaceae* and *P. aeruginosa* combination therapy was a variable independently associated with mortality, its adjusted OR always laid on the protective side (ranging from 0.87 in the whole series to 0.8 in the subgroups above mentioned).

Contrary to what was observed in the whole series or other subgroups, combination therapy was a strong predictor of survival for episodes with shock or neutropenia. It is of note that in patients with shock, combination therapy remained significant after adjusting for the appropriateness of empirical therapy. This suggests that, in the presence of shock, combination therapy still could be associated with a survival advantage when the microorganism was resistant to both the β-lactam and aminoglycoside. In patients with neutropenia, the major association of combination therapy with survival was the result of the high mortality rate observed in episodes treated with appropriate single-β-lactam monotherapy. Although we cannot provide an adequate explanation for these findings, it still is plausible that certain antibacterial properties of combination therapy, such as synergy (9) or lower endotoxin release (13), really matter when dealing with Gram-negative bacteremia in some clinical scenarios.

On the basis of a systematic review of 64 randomized trials performed in nonneutropenic patients (14) (43 of which qualified for the analysis of mortality and included 5,527 patients), the authors discouraged the addition of an aminoglycoside to a β-lactam, because fatality remained unchanged while the risk for adverse events increased. Although the number of patients with Gram-negative bacteremia included in this analysis was small (about 100 per arm), the combination therapy OR estimate for this subset of patients fell on the protective side (0.7; 95% CI, 0.4 to 1.4). Therefore, the results of this systematic review were very similar to those obtained from the analysis of our whole series concerning patients with Gram-negative bacteremia. However, specific data on the subset of patients with septic shock were not provided by the systematic review.

In another review of 47 randomized trials, which included 7,807 cancer patients with febrile neutropenia (16), no significant differences in mortality were found between patients empirically treated with β-lactam monotherapy and those treated with β-lactam-aminoglycoside combination therapy. In this instance, however, the trend favored β-lactam monotherapy and was consistent with a 13% relative reduction in mortality. Although the same result was obtained from the subgroups of patients with bacteremia ($n = 583$), documented Gram-negative infections (328), and *P. aeruginosa* infections ($n = 58$), no specific data on patients with Gram-negative bacteremia were reported.

Since randomized trials have included small numbers of patients with Gram-negative bacteremia, some attempts have been done to evaluate the issue by applying meta-analytic techniques on observational studies focused on bacteremia (17). Overall no differences were found, but in patients with *P. aeruginosa* bacteremia a significant 50% relative reduction in mortality was estimated (OR, 0.5; 95% CI, 0.3 to 0.8). It is of note that in the instance of *P. aeruginosa*, when the OR for mortality after combination therapy was recalculated after excluding aminoglycoside monotherapy from the monotherapy arm, the strength of the association decreased to a nonsignificant value of 0.8 (95% CI, 0.5 to 1.4) (9, 15), a figure almost identical to our adjusted estimation. A more recent retrospective study of bacteremic episodes also was unable to demonstrate a survival advantage for combination therapy, although the specific subgroup analysis of patients with neutropenia or shock was not performed (2).

The decisive role of the appropriateness of empirical therapy on prognosis was first described in the 1960s (12), confirmed through the 1970s until the 1990s (6, 7), and widely brought to medical attention during the last decade (1). In this regard, the present study just fulfilled what was already expected. Two observations are, however, of note. First of all, we did not find that appropriate aminoglycoside monotherapy (the nonsusceptibility of the blood isolate to the β-lactam component) was associated with a worse outcome than that of appropriate β-lactam monotherapy (appropriate single β-lactam or resistance of the isolate to the aminoglycoside component). The issue of the efficacy of aminoglycoside monotherapy in patients with Gram-negative bacteremia remains unsettled (9, 18), but in at least one observational study, aminoglycoside monotherapy clearly was inferior to single β-lactam treatment, except for that of patients with urinary tract infections (UTI) (8). Although we can speculate about the importance of systematically administering aminoglycosides in a single daily dose or the possibility of synergy with the β-lactam despite *in vitro* resistance, it has to be acknowledged that our observation was based on just 86 episodes in which the aminoglycoside was the sole active drug. Second, it was clear that combination therapy increased the chances of administering appropriate therapy when organisms resistant or potentially resistant to β-lactams were involved. Thus, for bacteremic episodes due to these pathogens, it is expected that combination therapy with an aminoglycoside will exert a beneficial effect on patient outcome.

In conclusion, we have been unable to demonstrate an over-

all significant association between β-lactam-aminoglycoside combination therapy and survival in patients with Gram-negative bacteremia. However, a survival advantage cannot be discarded for episodes presenting shock or neutropenia, and therefore, in patients with these conditions the empirical use of combination therapy may still be justified. Combination therapy also should be considered for patients at risk of being infected with resistant organisms, if only to increase the appropriateness of empirical therapy. In regard to these issues it is of note that a retrospective study with multiple subgroup analysis cannot generate firm conclusions, hence further studies would be needed to definitively support these contentions.

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