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Prospective Observational Study of *Klebsiella* Bacteremia in 230 Patients: Outcome for Antibiotic Combinations versus Monotherapy

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Combination antimicrobial agent therapy has been advocated for treatment of gram-negative bacteremia, including that caused by *Klebsiella* spp. We performed a prospective, observational, 10-hospital collaborative study to evaluate the efficacy of antibiotic combination therapy versus that of monotherapy for 230 consecutive patients with *Klebsiella* bacteremia. The species involved were *K. pneumoniae* (82%), *K. oxytoca* (15%), and *K. ozaenae* (0.4%). Of the bacteremias, 26% were polymicrobial in nature. A total of 53% of cases were nosocomial infections. The most common portals were the urinary tract (28%), biliary tract (12%), lung (10%), and abdomen (9%). Some 49 and 51% of the patients had received monotherapy and antibiotic combination therapy (beta-lactam plus aminoglycoside), respectively; 14-day mortalities in the two groups were 20 and 18%, respectively. However, for the subgroup of patients who experienced hypotension within 72 h prior to or on the day of the positive blood culture, those patients who received combination therapy experienced significantly lower mortality (24%) than did those who received monotherapy (50%). We conclude that monotherapy with an antibiotic that is active in vitro against *Klebsiella* (beta-lactam or aminoglycoside) is sufficient therapy for less severely ill patients (immunocompetent, urinary tract portal, mentally alert, normal vital signs). On the other hand, for severely ill patients who experience hypotension, antibiotic combination therapy with a beta-lactam and an aminoglycoside agent is preferred.

Klebsiella spp. are the second most frequent cause of gram-negative bacteremia (3, 5, 12, 14). Combination therapy with a beta-lactam and an aminoglycoside has been advocated for treatment of *Klebsiella* bacteremia because of its notable mortality (1, 11, 15).

Most studies of bacteremia have focused on *Klebsiella* spp. not as a single entity but, rather, have included it in the category of gram-negative bacteremias. This is problematic, given the inherent differences in antibiotic susceptibility and virulence among the aerobic gram-negative rods. Young (15) has also pointed out that failure to stratify patients by underlying disease category in most studies of therapy for gram-negative bacteremia has resulted in invalid comparisons of antibiotic efficacy.

We performed a prospective, observational, multicenter collaborative study to evaluate the efficacy of antibiotic combination therapy versus monotherapy on the outcome of *Klebsiella* infections. We made a concerted effort to address those areas of weakness that have characterized previous studies, including a prospective rather than retrospective study design, adequate sample size for statistical evaluation, assessment for severity of illness, and requirement for bacteremia as an eligibility criterion. Furthermore, given the large sample size of 230 patients, analysis by subgroups including underlying disease was feasible.

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MATERIALS AND METHODS

Study design. From 1986 to 1987, 230 consecutive patients from whose blood *Klebsiella* spp. were isolated were followed prospectively in 10 hospitals. The study was observational in that treatment decisions were made by the attending physicians. The hospitals were classified as university hospitals (with bed sizes ranging from 536 to 644; Presbyterian University Hospital, Pittsburgh, Pa.; North Shore University Hospital, Manhasset, N.Y.; Richland Memorial Hospital, Columbia, S.C.); Veterans Affairs (VA) medical centers (with bed sizes ranging from 550 to 715; Pittsburgh, Pa.; Buffalo, N.Y.; Minneapolis, Minn.), and community (with bed sizes ranging from 363 to 500; Conemaugh Valley Memorial Hospital, Johnstown, Pa.; Mercy Hospital, Pittsburgh, Pa.; Western Pennsylvania Hospital, Pittsburgh, Pa.; St. Clair Hospital, Pittsburgh, Pa.).

Definitions. Onset of bacteremia was defined as the date when the first positive blood culture was obtained.

Antimicrobial agent susceptibilities were determined by the individual hospital microbiology laboratories using standard criteria set forth by the National Committee for Clinical Laboratory Standards (12). Organisms were isolated and

identified at the microbiology laboratory of each hospital and were then transported to a central laboratory (Pittsburgh). These organisms are available to other investigators. Monotherapy was defined as treatment with a single antibiotic that was active in vitro against the *Klebsiella* strain that was isolated from the blood for at least 2 days within the first 3 days from the date that the positive blood culture was drawn.

Combination therapy was defined as treatment with two antibiotics that were active in vitro against the organism for at least 2 days within the first 4 days from the date that the positive blood culture was drawn. All other patients who received an antibiotic that was active in vitro against *Klebsiella* spp. were considered to have received monotherapy. Treatment with one antibiotic that was active in vitro against *Klebsiella* spp. and another antibiotic that was inactive in vitro was also considered monotherapy (only 4 of 230 patients were in this category).

Immunosuppression was defined as present if there was at least one of the following: leukopenia (leukocyte count, <2,700 cells per mm^3), neutropenia (neutrophils, <1,000 cells per mm^3), hematologic malignancy, corticosteroid therapy, or cancer chemotherapy.

Bacteremia was defined as being of nosocomial origin if the blood culture yielding a *Klebsiella* sp. was obtained after 3 days from the time the patient was admitted to the hospital. Otherwise, the case was considered community acquired.

Severity of illness was scored by using the following clinical criteria: mental status, presence of fever, hypotension, requirement for respiratory support, and cardiac arrest within 3 days of positive blood culture. Hypotension was defined as a systolic blood pressure of less than 90 mm Hg within 3 days prior to or on the day of the positive blood culture. Severity of illness was quantified as follows: temperature of >38°C, (1 point), temperature of >39°C (2 points), mental status (alert, 0 points; disoriented, 1 point; stupor, 2 points; coma, 4 points), hypotension (2 points), mechanical respiratory support (2 points), and cardiac arrest (4 points). Patients were considered ill at a level of 4+ if they accumulated four or more points. This scoring system has proven to be highly predictive of survival in previous studies of gram-negative bacteremia (4, 9, 10).

The portal of organism entry into the patient was determined by the investigator using clinical criteria and isolation of the bacteremic organism from sources other than blood.

Study endpoint. The clinical endpoint was survival or death at 14 days from the date the positive blood culture was obtained.

Data management and analysis. Clinical data were entered into a computer data base (Prophet Systems; National Institutes of Health) specifically designed for analysis of biomedical research data. Categorical data were analyzed by the chi-square test or the Fisher exact test. Continuous variables were compared by using the t test or the Mann-Whitney test. Survival analysis was done by using the Gehan-Breslow test to compare differences between two Kaplan-Meier curves. A stepwise regression model was used to examine the effects of multiple risk factors on mortality. The factors used in the regression model included those found to be significant by univariate analysis and for monotherapy versus antibiotic combination therapy.

RESULTS

Patients. A total of 230 consecutive patients with *Klebsiella* bacteremia were enrolled in the study. Patient ages ranged between 1 day and 95 years, with a median of 65 years. Underlying disease, clinical features, severity of illness, and portal of entry are summarized in Table 1.

Hospitals. The following patient risk factors occurred significantly more often in patients hospitalized in VA medical centers than in those in university or community hospitals: history of chronic alcoholism (38% in VA medical centers versus 14% in community and university hospitals; $P < 0.0005$; chi-square) and chronic obstructive pulmonary disease (28% in VA medical centers versus 4% in community and university hospitals; $P < 0.0001$; chi-square). The following risk factors occurred significantly more frequently in patients in university hospitals than in those in VA medical centers or community hospitals: hematologic malignancy (17% in university hospitals versus 7% in VA medical centers and community hospitals; $P < 0.01$; chi-square), onset of bacteremia in an intensive care unit stay (29% versus 15%, $P < 0.02$; chi-square), surgery (22% versus 8%; $P < 0.002$), and immunosuppression (41% versus 23%; $P < 0.003$; chi-square). Diabetes mellitus occurred significantly more frequently in patients in community hospitals (27%) than in patients in VA medical centers and university hospitals (13%; $P < 0.01$; chi-square).

Organisms. The following *Klebsiella* spp. were isolated: *K. pneumoniae*, 82% (188 of 230 patients); *K. oxytoca*, 15% (34 of 230 patients); *K. ozaenae*, 0.4% (1 of 230 patients); and unknown (but not *K. pneumoniae*), 3% (7 of 230 patients). The mortality rates were similar for all species, as follows: *K. pneumoniae*, 19% (35 of 188 patients); *K. oxytoca*, 21% (7 of 34 patients); and *K. ozaenae*, 0% (0 of 1 patient). No significant difference was seen between *K. pneumoniae* and *K. oxytoca* for aminoglycoside resistance (7 versus 12%), immunosuppression (32 versus 29%), malignancy (40 versus 29%), or portal of entry.

The most common portals of entry assessed by the investigators were urinary tract (28%; 65 of 230 patients), biliary tract (12%; 28 of 230 patients), lung (10%; 22 of 230 patients), and abdomen (9%; 21 of 230 patients) (Table 1). Microbiologic confirmation by isolation of the *Klebsiella* sp. from the presumed portal was obtained for 70% of the patients.

Resistance to gentamicin was documented in 5% of isolates that caused bacteremia. Gentamicin resistance was significantly more likely in patients with nosocomial infections ($P < 0.05$). There was no significant association for gentamicin resistance and site of infection (data not shown). Likewise, gentamicin resistance was not associated with higher mortality (data not shown).

Polymicrobial bacteremias. A total of 26% of the patients (60 of 230) had polymicrobial bacteremias. Organisms isolated in conjunction with *Klebsiella* were *Escherichia coli* ($n = 24$), *Enterococcus faecalis* ($n = 12$), *Pseudomonas aeruginosa* ($n = 10$), *Staphylococcus epidermidis* ($n = 6$), *Proteus mirabilis* ($n = 4$), *Enterobacter cloacae* ($n = 3$), and *Staphylococcus aureus* ($n = 3$). Other organisms isolated from only a single patient each were *Streptococcus pneumoniae*, *Citrobacter* sp., *Candida tropicalis*, *Morganella morganii*, *Micrococcus* sp., *Serratia marcescens*, and *Streptococcus* sp. The primary portals of entry for polymicrobial bacteremia were urinary tract, 30% (18 of 60 patients), abdomen or biliary tract, 20% (12 of 60 patients), and lung, 10% (6 of 60 patients). Patient mortality caused by polymicrobial bacteremia (20%; 12 of 60 patients) was similar to that caused by *Klebsiella* spp. alone (19%; 32 of 170 patients).

Nosocomial versus community-acquired infections. A total of 53% (121 of 230 patients) of the infections were nosocomial, and 47% (109 of 230 patients) were community

TABLE 1. Patient groups receiving monotherapy and combination antibiotic therapy

Patient characteristic	% of patients[a]		*P* value[b]
	Monotherapy (*n* = 118)	Combination therapy (*n* = 112)	
Underlying disease			
Chronic obstructive pulmonary disease	7 (8/118)	14 (16/112)	NS (0.06)
Lung cancer	3 (3/118)	6 (7/112)	NS
Hematologic malignancy	8 (10/118)	14 (16/112)	NS
Solid organ cancer	31 (36/118)	18 (21/112)	0.04
Diabetes mellitus	17 (20/118)	17 (19/112)	NS
Immunosuppressed	26 (31/118)	37 (41/112)	NS (0.08)
Corticosteroid	18 (21/118)	23 (26/112)	NS
Chemotherapy	14 (17/118)	25 (28/112)	0.04
Radiation therapy	5 (6/118)	75 (8/112)	NS
Risk factor			
Chronic alcoholism	17 (20/118)	24 (27/112)	NS
Nosocomial	53 (62/118)	53 (59/112)	NS
Community acquired	47 (56/118)	47 (53/112)	NS
Prosthesis	3 (4/118)	8 (9/112)	NS
Hemodialysis	2 (2/118)	2 (2/112)	NS
Neutropenia[c]	4 (5/118)	14 (16/112)	0.01
Surgery	19 (22/118)	11 (12/112)	NS (0.09)
Prior antibiotics	15 (18/118)	20 (22/112)	NS
Hypotension	22 (26/118)	26 (29/112)	NS
Severity of illness			
+1–+2	60 (71/118)	65 (73/112)	NS
+3	13 (15/118)	15 (17/112)	NS
+4	27 (32/118)	20 (22/112)	NS
Portal of entry			
Urinary tract	30 (36/118)	16 (29/112)	NS
Biliary	12 (14/118)	13 (14/112)	NS
Lung	9 (11/118)	10 (11/112)	NS
Abdomen	12 (14/118)	6 (7/112)	NS
Intravenous line associated	3 (4/118)	8 (9/112)	NS
Wound or skin	4 (5/118)	4 (5/112)	NS
Unknown	23 (27/118)	29 (33/112)	NS
Other	6 (7/118)	4 (4/112)	NS

[a] Values in parentheses indicate number of patients with the indicated characteristic/total number of patients receiving monotherapy or combination therapy.
[b] NS, not significant; $P > 0.05$, chi-square test, two-tailed.
[c] Neutropenia was <1,000 cells per mm^3.

acquired. Not surprisingly, nosocomial *Klebsiella* bacteremia was associated with the presence of a urinary catheter and receipt of prior antibiotics significantly more often than community-acquired disease was ($P < 0.01$) (data not shown). Nosocomial infections were also significantly more likely to occur in VA medical centers (62%) and university hospitals (54%) than in community hospitals (40%) ($P < 0.05$, chi-square). Mortality was significantly higher for nosocomial bacteremias (see below).

Mortality. The overall mortality at 14 days was 19% (44 of 230 patients); by 28 days the mortality had increased to 28% (65 of 230 patients). Mortality subclassified by antibiotic therapy is discussed below. The following factors were significantly associated with mortality by univariate analysis: nosocomial origin (24% mortality; 29 of 121 patients) versus community-acquired bacteremia (14% mortality; 15 of 109 patients) ($P < 0.05$) and increasing severity of illness ($P = 0.0001$). Bacteremic patients with pneumonia had significantly higher rates of mortality (36%; 8 of 22 patients) than did patients without pneumonia (17%; 36 of 208 patients) ($P = 0.04$). Patients with urinary tract infections had a lower rate of mortality (12%; 8 of 65 patients) than did patients with infections other than those of the urinary tract (22%; 36 of 165 patients), but statistical significance was not attained ($P = 0.10$). A total of 24% (55 of 230) of the patients experienced hypotension, and 36% (20 of 55) of those who experienced hypotension died. The mortality rates among patients in the three different types of hospitals were not significantly different. Surprisingly, increasing age was not associated with increasing mortality, even when 12 pediatric patients less than age 18 years were excluded from the analysis (data not shown). Severity of illness, nosocomial origin, antibiotic therapy (i.e., combination therapy versus monotherapy), and presence of pneumonia were assessed in a stepwise logistic regression model; nosocomial origin ($P < 0.04$) and severity of illness ($P < 0.001$) proved to be significant factors in affecting mortality.

Antibiotics. A total of 51% (118 of 230) of the patients received monotherapy, usually an aminoglycoside or a beta-lactam (Table 2). Some 49% (112 of 230) of the patients received combination therapy usually consisting of a beta-lactam agent plus an aminoglycoside (Table 3). A total of 109 patients received two active antibiotics for at least a 2-day duration the first 3 days from the date of the first positive blood culture, and 3 patients received two active antibiotics for at least a 2-day duration starting on the third day

TABLE 2. Patients who received monotherapy subclassified by individual agents and the associated mortality[a]

Therapy	No. of patients	% Mortality[b]
Beta-lactam	56	
Cephalosporin[c]		
First generation	17	6 (1/17)
Second generation	9	11 (1/9)
Third generation	21	19 (4/21)
Imipenem	5	0 (0/5)
Penicillin		
Piperacillin	3	67 (2/3)
Ticarcillin-clavulanate	1	0 (0/1)
Aminoglycoside	60	
Gentamicin	46	22 (10/46)
Tobramycin	8	50 (4/8)
Amikacin	6	0 (0/6)
Trimethoprim-sulfamethoxazole	2	100 (2/2)

[a] A total of 118 patients received monotherapy.
[b] Values in parentheses are number of patients who died/total number of patients in subgroup.
[c] First generation, cefazolin (n = 17); second generation, cefamandole (n = 2), cefoxitin (n = 5), and cefuroxime (n = 2); third generation, cefotaxime (n = 7), ceftriaxone (n = 6), ceftazidime (n = 4), ceftizoxime (n = 2), cefoperazone (n = 1), and moxalactam (n = 1).

following the positive blood culture. There was no significant difference in mortality between patients in the two treatment groups (Table 4). Patients in the monotherapy and combination therapy groups who experienced polymicrobial bacteremia versus those who had bacteremia caused by *Klebsiella* spp. only had similar mortality rates (Table 4).

The two therapy groups were generally comparable except for immunosuppressed patients, surgical patients, and patients with chronic obstructive pulmonary disease or solid organ cancer (Table 1); however, when patients were stratified by various risk factors, including surgery and immunosuppression, no significant difference in mortality could be found for those who received combination therapy versus those who received monotherapy (Table 4).

It should be noted that in the subgroup of most severely ill patients (4+ ill), patients who received combination therapy had lower mortality rates (32%; 7 of 22 patients) than those who received monotherapy (50%; 16 of 32 patients). This difference was not statistically significant (P = 0.12; chi-square). On the other hand, for the subgroup of patients who experienced hypotension within 72 h prior to or on the day of the first positive blood culture, mortality was significantly lower for those patients who received combination therapy (24%; 7 of 29 patients) than it was for those who received monotherapy only (50%; 13 of 26 patients) ($P < 0.05$; chi-square [Table 4]; $P < 0.03$; Gehan-Breslow [Fig. 1]).

Although patients were few, when mortalities were analyzed by individual beta-lactam antibiotic or aminoglycoside

TABLE 3. Patients who received combination therapy subclassified by specific antibiotics and the associated mortality[a]

Therapy	No. of patients	Mortality[b]
Beta-lactam plus aminoglycoside[c]		
Cephalosporin[d]		
First generation	26	12 (3/26)
Second generation	21	14 (3/21)
Third generation	17	29 (5/17)
Imipenem	4	25 (1/4)
Penicillin[e]	42	19 (8/42)
Other		
Rifampin plus gentamicin	1	0 (0/1)
Piperacillin plus ceftazidime	1	0 (0/1)

[a] A total of 112 patients received combination therapy.
[b] Values in parentheses are number of patients who died/total number of patients in subgroup.
[c] Aminoglycosides, amikacin (n = 9), tobramycin (n = 16), gentamicin (n = 84), and kanamycin (n = 1).
[d] First generation, cefazolin (n = 25) and cephapirin (n = 1); second generation, cefoxitin (n = 18), cefuroxime (n = 1), and cefamandole (n = 2); third generation, ceftriaxone (n = 3), ceftazidime (n = 4), ceftizoxime (n = 3), cefotaxime (n = 5), and cefoperazone (n = 2).
[e] Penicillins, piperacillin (n = 36), mezlocillin (n = 4), ticarcillin (n = 1), and ticarcillin-clavulanate (n = 1).

TABLE 4. Mortality in patients who received monotherapy versus mortality in patients who received combination antibiotic therapy

Group	% Mortality[a]		P value
	Mono-therapy	Combination therapy	
All patients	20 (24/118)	18 (20/112)	NS[b]
Urinary tract portal	11 (4/36)	14 (4/29)	NS
Pulmonary portal	45 (5/11)	27 (3/11)	NS
Immunosuppressed[c]	26 (8/31)	22 (9/41)	NS
Immunocompetent	18 (16/87)	16 (11/70)	NS
Severity of illness			
0–3+	9 (8/86)	14 (13/90)	NS
4+	50 (16/32)	32 (7/22)	
Hypotension[d]	50 (13/26)	24 (7/29)	0.047
Diabetes mellitus	10 (2/20)	16 (3/19)	NS
Alcohol abuse	15 (3/20)	30 (8/27)	NS
Surgery[e]	18 (4/22)	0 (0/12)	NS
Neutropenia[f]	20 (1/5)	19 (3/16)	NS
Polymicrobial	18 (6/34)	23 (6/26)	NS
Klebsiella spp. only	21 (18/84)	16 (14/86)	NS
Nosocomial	24 (15/62)	24 (14/59)	NS
Community-acquired	16 (9/56)	11 (6/53)	NS

[a] Values in parentheses are number of patients who died/total number of patients in subgroup.
[b] NS, not significant ($P > 0.05$).
[c] Immunosuppressed was defined as receipt of corticosteroids, cancer chemotherapy, or radiation therapy; presence of hematologic malignancy; or neutropenia.
[d] Hypotension was defined as a systolic pressure of 90 mm Hg occurring within 72 h prior to or on the day of the first positive blood culture.
[e] Surgery that required general anesthesia within 10 days of *Klebsiella* bacteremia.
[f] Neutropenia was defined as a neutrophil count of <1,000 cells per mm^3. No significant difference was seen if the other definitions used including neutrophil counts of <100 cells per mm^3.

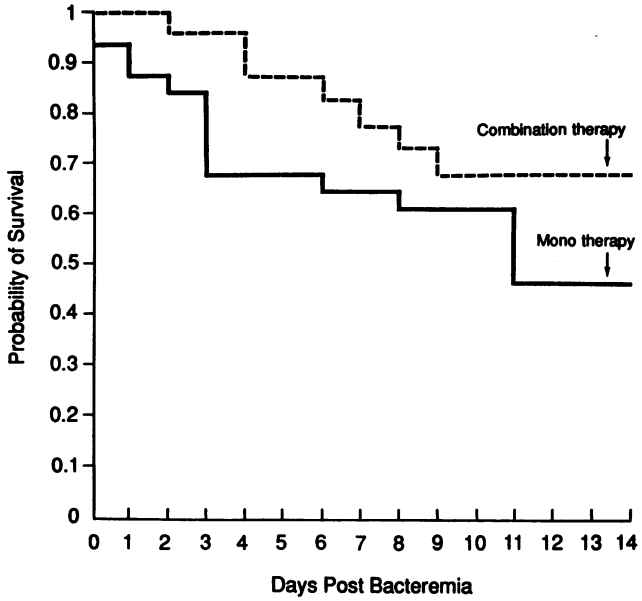

FIG. 1. Mortality rates in the first 14 days for 55 patients experiencing hypotension who received antibiotic combination therapy versus mortality rates in patients who received monotherapy. Mortality rates were significantly lower for those patients who received the combination antibiotic therapy ($P < 0.03$; Gehan-Breslow).

(Tables 2 and 3), the mortalities were similar. For the patients who received monotherapy, mortality was 24% (14 of 58 patients) for those who received an aminoglycoside alone, whereas it was 14% (8 of 56 patients) for those who received a beta-lactam agent alone (Table 2); this difference was not statistically significant. When the patient population was stratified by severity of illness, statistical analysis of mortality for individual antibiotics was not meaningful, given the small number of patients in each antibiotic subgroup. Thus, if the antibiotics were active in vitro, there was no clear trend for improved outcome with more potent antibiotics (as defined by the ratio of serum drug concentrations to MIC) and lower mortality.

DISCUSSION

There have been few studies of *Klebsiella* bacteremia (Table 5). Previous studies were generally retrospective (2, 5, 7, 11, 14), had relatively small sample sizes (27 to 57 patients), and were conducted over a 5- to 10-year period (1, 5, 14) or were conducted at a single institution and reflected the types of disease specific to that hospital (e.g., cancer hospitals or children's hospitals) (1, 2). Our study is the largest prospective study of *Klebsiella* bacteremia reported to date; 10 hospitals, a mix of university hospitals, community hospitals, and VA medical centers, contributed to the study.

The demographics of patients with *Klebsiella* bacteremia varied by hospital type (university, community, VA medical center). Patients with chronic alcoholism and chronic obstructive pulmonary disease were significantly more likely to be hospitalized in VA medical centers, while immunosuppressed patients were more likely to be hospitalized in university hospitals.

K. pneumoniae and *K. oxytoca* constituted 82 and 15% of the *Klebsiella* bacteremias, respectively. The mortalities from infections with the different species were similar. The most common portal for *Klebsiella* spp. was the urinary tract (28%); this was followed by the biliary tract (12%), lung (10%), and abdomen (9%) (Table 1).

In our study, polymicrobial bacteremia with *Klebsiella* spp. occurred in 26% (60 of 230) of the cases, with aerobic, gram-negative rods being the most common organisms isolated concomitantly with *Klebsiella* spp. Unlike studies by Umsawasdi et al. (14) and Montgomerie and Ota (11) (Table 5), mortality from polymicrobial *Klebsiella* bacteremia (20%) was not higher than that from *Klebsiella* bacteremia alone (19%).

Interestingly, early reports of *Klebsiella* bacteremia reported a nosocomial predominance (11, 13); however, in recent years a greater percentage of community-acquired cases have been reported (6, 7) (Table 5). In our study, the incidences of community-acquired bacteremias were 60, 46, and 38% in community hospitals, university hospitals, and VA medical centers, respectively; this difference was statistically significant.

The overall mortality 14 days after obtaining a positive blood culture was 19% (44 of 230 patients). Pneumonia

TABLE 5. Literature review of *Klebsiella* bacteremia

Reference (year, study years)	No. of patients	Age (yr)	% of patients[a]				% Mortality (1 versus 2 drugs)
			With nosocomial infection	With polymicrobial infection	Who received prior antibiotics	Overall mortality	
13 (1972, 1968–1971)	27	NR[b]	100 (27/27)	NR	85 (23/27)	33 (9/27)	NR
14 (1973, 1968–1971)	137	46[c]	NR	12 (17/137)	75 (102/137)	37 (50/137)	NR
11 (1980, 1972–1973)	41	0–70	98 (40/41)	NR	66 (27/41)	37 (15/41)	NR
5 (1985, 1977–1982)	100	58.7	77 (77/100)	12 (12/100)	44 (44/100)	25 (25/100)	22% (9/41) versus 20% (9/45)
7 (1989, 1982–1985)	46	66[c]	59 (27/46)	7 (3/46)	NR	22 (10/46)	NR
2 (1989, 1979–1988)	57	Ped[e]	75 (43/57)	26 (15/57)	25 (14/57)	20 (11/57)	NR
1 (1989, 1972–1981)	330	44	88 (290/330)	NR	58 (191/330)	31 (114/368)	43 (91/212) versus 21 (16/76)[d]
6 (1990, 1987–1988)	47	46	53 (25/47)	0 (0/47)	NR	55 (26/47)	47 (7/15) versus 0 (0/9)
Present study (1985–1987)	230	65[c]	53 (121/230)	26 (60/230)	17 (39/230)	19 (44/230)	21 (24/114) versus 18 (20/116)

[a] Values in parentheses are number of patients with the indicated characteristic/total number of patients.
[b] NR, not reported.
[c] Median.
[d] Clinical response, not mortality, was used as the endpoint. Number of episodes, not number of patients, was used as the denominator.
[e] Ped, 38 patients were less than 12 months of age; the remainder were pediatric.

carried a significantly poorer prognosis than urinary tract infection (36%, [8 of 22 patients] versus 12% [8 of 65 patients]), a finding that is in agreement with the results of other studies (1, 5, 6, 11). Not surprisingly, increasing severity of illness (see Materials and Methods) at the onset of bacteremia was associated with increasing mortality.

Klebsiella spp. may be less virulent than *Pseudomonas aeruginosa* as a human pathogen. Some 23% of the patients were classified as critically ill (4+ ill) at the onset of *Klebsiella* bacteremia, whereas 37% of patients with *P. aeruginosa* bacteremia (9) were critically ill as determined by using an identical severity-of-illness scale. The corresponding mortality for *P. aeruginosa* bacteremia at 14 days was 39% (78 of 200 patients [8]).

Antibiotic combination therapy has been advocated for gram-negative bacteremia, although few studies have focused on *Klebsiella* bacteremia. de la Torre et al. (5) reported similar mortalities in a series of 100 patients who received combination therapy (20%) and monotherapy (22%). Feldman et al. (6) reported a lower overall mortality in patients treated with beta-lactam plus aminoglycoside agents, but statistical significance was not achieved. However, when Feldman et al. (6) confined the analysis to patients who survived for 48 h, antibiotic combination therapy was significantly superior to monotherapy. It should be noted that the sample size was only 28 patients, with only 9 patients receiving combination therapy (Table 5). Bodey et al. (1) found a significant improvement in clinical response (not mortality) for cephalosporin plus aminoglycoside therapy versus that for monotherapy in a cancer hospital.

In our study, 118 patients received monotherapy with a single active antibiotic (Table 2). Antibiotic combination therapy usually consisting of a beta-lactam and an aminoglycoside was received by the remaining 112 patients (Table 3). A statistically significant difference in mortality was not observed for the total patient study group; the mortality was 18% (20 of 112) for patients who received antibiotic combination therapy, whereas it was 20% (24 of 118) for patients who received monotherapy. However, for the subgroup of patients who experienced hypotension within 72 h prior to or on the day of the positive blood culture, those patients who received combination therapy experienced significantly lower mortality (24%; 7 of 29 patients) than did those patients who received monotherapy (50%; 13 of 26 patients) ($P < 0.05$) (Table 4 and Fig. 1).

What are the weaknesses of this study? It should be acknowledged that the allocation of patients to monotherapy versus antibiotic combination therapy was not controlled. Thus, verification of our findings would ideally require large-scale, prospective, randomized studies of monotherapy versus combination therapy; however, such studies are logistically difficult to perform. It may be argued that combining the various agents under the single headings of beta-lactam agents or aminoglycosides is invalid, because in vitro, *Klebsiella* spp. have greater susceptibilities to the newer antibiotics. We subclassified the mortality rates for patients who received the individual antibiotics (Tables 2 and 3). It appears that if the antibiotics are active in vitro, increased potency is not necessarily equated with improved outcome. This analysis is hardly definitive, given the small sample size of patients who received the individual antibiotics and the fact that stratification for severity of illness was not depicted.

Results of our study show that monotherapy with an antibiotic that is active against *Klebsiella* spp. in vitro is sufficient therapy for less severely ill patients (for example, patients who are immunocompetent, have urinary tract portal, have normal mental status, and who do not experience hypotension). Combination antibiotic therapy is preferred for severely ill patients, especially if hypotension has occurred.

Given the fact that the type of beta-lactam or aminoglycoside used was not a clear-cut factor in patient outcome, it appears that as long as these agents are active in vitro, it may be rational to select antibiotics for the treatment of *Klebsiella* sepsis on the basis of toxicity, cost, improved pharmacokinetics, or convenience of dosing.

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