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Evaluation of Antimicrobial Regimens for Treatment of Experimental Penicillin- and Cephalosporin-Resistant Pneumococcal Meningitis

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The most appropriate therapy for meningitis caused by *Streptococcus pneumoniae* strains resistant to the extended-spectrum cephalosporins is unknown. We evaluated ceftriaxone, vancomycin, and rifampin alone and in different combinations and meropenem, cefpirome, and clinafloxacin alone in the rabbit meningitis model. Meningitis was induced in rabbits by intracisternal inoculation of one of two pneumococcal strains isolated from infants with meningitis (ceftriaxone MICs, 4 and 1 μg/ml, respectively). Two doses, 5 h apart, of each antibiotic were given intravenously (except that ceftriaxone was given as one dose). Cerebrospinal fluid bacterial concentrations were measured at 0, 5, 10, and 24 h after therapy was started. Clinafloxacin was the most active single agent against both strains. Against the more resistant strain, ceftriaxone or meropenem alone was ineffective. The combination of vancomycin and ceftriaxone was synergistic, suggesting that this combination might be effective for initial empiric therapy of pneumococcal meningitis until results of susceptibility studies are available.

Recently, cases of β-lactam-resistant pneumococcal meningitis that failed therapy with cefotaxime or ceftriaxone have been reported (5, 10, 20). In many developed countries an extended-spectrum cephalosporin is the most commonly prescribed empiric therapy for bacterial meningitis. An increase in the prevalence of penicillin- and cephalosporin-resistant strains of *Streptococcus pneumoniae* has been noted in Texas (10, 13), but the prevalence in other areas of the United States is unknown. Because of the emergence of cephalosporin-resistant *S. pneumoniae*, new strategies will have to be considered for initial empiric management of meningitis.

Since comparative clinical therapeutic trials in patients with pneumococcal meningitis are unlikely to be conducted because of the relative infrequency of these highly resistant strains, we assessed different antimicrobial regimens in a conventional animal model of meningitis caused by either of two penicillin-resistant *S. pneumoniae* strains isolated from children with meningitis treated at our institution. In addition to agents that have been used to treat penicillin-resistant pneumococcal infections (ceftriaxone, vancomycin, and rifampin) we assessed the therapeutic response to new agents which have favorable in vitro activity against penicillin-resistant pneumococci: meropenem, cefpirome, and clinafloxacin. In vitro time-kill studies were performed to evaluate interactions between ceftriaxone and vancomycin.

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MATERIALS AND METHODS

Source and preparation of *S. pneumoniae* strains. Strain 1 was isolated from a 9-month-old infant whose cerebrospinal fluid (CSF) failed to sterilize after 6 days of conventional ceftriaxone therapy (10). Strain 2 was isolated from an 11-month-old infant with meningitis who failed to improve clinically while receiving ceftriaxone therapy. Although CSF was not reexamined after starting therapy and bacteriologic failure was not documented, the child improved clinically after vancomycin was added to ceftriaxone 6 days after the start of therapy.

The two strains were grown overnight on blood agar. The plates were flooded with phosphate-buffered saline, and aliquots of the resultant suspension were frozen at −70°C. Initial freezing resulted in approximately 60% bacterial loss, but the bacterial concentrations of each aliquot, once frozen, remained constant during the study period. Aliquots were thawed and diluted to a concentration of 5×10^4 CFU/ml, and 0.25 ml was injected intracisternally into each rabbit.

The MICs of different antibiotics were determined for each strain by broth microdilution with Mueller-Hinton broth supplemented with 3 to 5% lysed horse blood and an inoculum of 10^5 CFU/ml. Microtiter plates were incubated in room air at 35°C for 20 h. MBCs (99.9% kill) were determined by plating 10-μl aliquots from clear microtiter wells onto blood agar and incubating in 5% CO_2 for 24 h (16).

Antimicrobial therapy. The following agents and dosages were evaluated in the rabbit model: ceftriaxone (125 mg/kg) (Roche, Nutley, N.J.), vancomycin (20 mg/kg) (Lederle, Pearl River, N.Y.), rifampin (15 mg/kg) (Merrel Dow, Ontario, Canada), meropenem (125 mg/kg) (ICI, Wilmington, Del.), cefpirome (100 mg/kg) (Hoechst-Roussel, Somerville, N.J.), and clinafloxacin (20 mg/kg) (previously CI-960; Parke-Davis, Morris Plains, N.J.). Antibiotic dosages were chosen to achieve peak and trough concentrations in CSF similar to those observed in humans. Limited data are available on achievable concentrations of meropenem, cefpirome, and clinafloxacin in serum and CSF, and dosages were based on data observed with other agents of the same class.

Rabbit meningitis model. The rabbit model has been used previously for the evaluation of antimicrobial therapy in pneumococcal meningitis (14, 21). Young male New Zealand

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White rabbits were anesthetized with ketamine (40 mg/kg) and acepromazine (1 mg/kg), given intramuscularly, and were immobilized in stereotactic frames. A spinal needle was introduced into the cisterna magna of each rabbit for inoculation of bacteria and periodic removal of CSF. Sixteen hours after the intracisternal injection of the pneumococcal inoculum, CSF was withdrawn and antimicrobial agents were injected intravenously for several minutes. A second dose of each agent, except ceftriaxone, was given 5 h later. Untreated and treated animals were euthanized 26 and 40 h, respectively, after bacterial inoculation. CSF samples heavily contaminated with blood were not analyzed.

Measurement of bacterial and antibiotic concentrations. Bacterial concentrations in CSF were measured 0, 5, 10, and 24 h after therapy was started by plating undiluted and serial 10-fold dilutions of CSF (100 μl) on sheep blood agar and incubating in 5% CO_2 at 35°C for 24 h. The lowest bacterial concentration detectable was 10 CFU/ml. For purposes of analysis, specimens with <10 CFU/ml were assigned a value of 1 (0 $\log_{10}$) CFU/ml. In vivo synergism between two drugs at any time point was considered when combination therapy reduced the bacterial concentration from the start of therapy by more than 1 $\log_{10}$ CFU/ml compared with the sum of the reductions with each agent alone.

CSF was sampled in treated rabbits 60 to 90 min and 5 h after each intravenous antibiotic dose for the measurement of peak and trough antibiotic concentrations, respectively. Serum peak and trough concentrations (30 min and 5 h after an intravenous dose) were also measured. All specimens were immediately frozen at −70°C until they could be analyzed. Rifampin and clinafloxacin concentrations were determined by disk diffusion microbioassay using *Micrococcus lutea* (ATCC 9341) and *Klebsiella pneumoniae* (ATCC 10872), respectively (19). All other antibiotic concentrations were measured by reverse-phase high-performance liquid chromatography using standards provided by the manufacturers. Standards were stored according to the manufacturers' specifications and were prepared in 10% and whole rabbit serum for assays of concentrations in CSF and serum, respectively. The lower limits of detection of the antibiotic (in micrograms per milliliter) were as follows: ceftriaxone, meropenem, and cefpirome, 0.2; vancomycin, 0.4; clinafloxacin, 0.05; and rifampin, 0.03.

In vitro time-kill studies. Kill kinetics over an 8-h period were studied with strains 1 and 2 in Mueller-Hinton broth with 3% lysed horse blood. Synergy was defined as a ≥2 $\log_{10}$ decrease in CFU/ml between the combination and the most active single agent. Because cultures frequently autolyzed before 24 h, synergy was assessed at 8 h. Bacteria from overnight broth culture were diluted to ~10^6 CFU/ml in fresh broth. After the addition of antibiotics, 10 ml of the broth antibiotic mixtures were placed in 50-ml flasks, sealed with foam stoppers, and incubated on a shaker in ambient air at 35°C. Bacterial concentrations were measured every 2 to 4 h by plating serial dilutions on blood agar, as described above.

Statistical analysis. Mean changes in bacterial concentrations at 5 and 10 h in each treatment group were compared by one-way analysis of variance using the Newman Keuls multiple comparisons test.

RESULTS

The antimicrobial MICs and MBCs for the two pneumococcal strains are shown in Table 1, and the therapeutic regimens that were evaluated are shown in Table 2. Peak and trough antibiotic concentrations in CSF and serum are shown in Table 3. Antibiotic measurements in the single agent and combination treatment groups were similar and have been pooled. The penetration into CSF was <10% for all antibiotics except clinafloxacin, which had a mean ± standard deviation (SD) CSF-peak-to-serum-peak ratio of 0.18 ± 0.015. Antibiotic concentrations in CSF 24 h after the start of therapy were below the limit of detection in all animals except those that received ceftriaxone or cefpirome (mean ± SD = 0.5 ± 0.4 μg/ml for both). The serum half-life of meropenem determined in 5 rabbits was 1.4 ± 0.3 h.

TABLE 1. MICs and MBCs (in micrograms per milliliter) of antimicrobial agents for two pneumococcal strains used to induce meningitis in rabbits

Agent	Strain 1		Strain 2	
	MIC	MBC	MIC	MBC
Penicillin	2	2	1	1
Ceftriaxone	4	4	1	1
Cefpirome	2	2	0.5	1
Meropenem	1	2	0.25	0.5
Vancomycin	0.25	0.5	0.25	0.5
Rifampin	0.008	0.03	0.016	0.03
Clinafloxacin	0.06	0.12	0.03	0.06

Antibiotic efficacy in meningitis with strain 2. Changes in bacterial concentrations of strain 2 are shown in Fig. 1, and the numbers of sterile CSF cultures at 10 and 24 h after treatment are shown in Table 2. Clinafloxacin was the most effective agent, and all CSF specimens but one (with only 1 $\log_{10}$ CFU/ml at 5 h) were sterile after starting treatment. Ceftriaxone was more active against strain 2 than against strain 1 (Fig. 2a) but only sterilized the CSF of two of five rabbits by 10 h and the CSF of none of five at 24 h. Meropenem had limited efficacy against this strain despite peak CSF meropenem concentrations well above the MIC of 0.25 μg/ml. However, only one rabbit had a CSF trough meropenem concentration above 0.25 μg/ml, and in this rabbit the CSF bacterial concentration decreased by 3.1 $\log_{10}$ CFU/ml in 10 h. In the other rabbits it is not known how long the CSF meropenem concentrations were above the MIC.

Antibiotic efficacy in meningitis with strain 1. CSF bacterial concentrations in each rabbit treatment group infected with strain 1 are shown in Fig. 2. Clinafloxacin was the most effective therapy evaluated, whereas ceftriaxone and meropenem were the least effective. Vancomycin therapy resulted in a mean 3.0 $\log_{10}$ CFU/ml reduction in bacterial concentration within 10 h, but regrowth occurred 14 h later. Rifampin was less rapidly bactericidal than vancomycin, but 13 of 15 rabbits that received rifampin alone or in combination had sterile CSF cultures at 24 h (Table 2).

The combination of rifampin with either ceftriaxone or vancomycin was not more effective than single-agent therapy. By contrast, vancomycin and ceftriaxone were synergistic; $\Delta\log_{10}$ CFU/ml at 10 h was −3.99 for the sum of single agent therapies versus −5.12 for combination therapy. At 24 h the $\Delta\log_{10}$ CFU/ml was −4.67 for the combination versus −3.41 for the sum of the agents alone.

In vitro time-kill curves. The kill curves are shown in Fig. 3. Antibiotic concentrations used in these studies are reported as multiples of the respective MIC for each strain. Synergy between vancomycin (both 1× and 0.5× MIC) and ceftriaxone (0.5× MIC) was observed with both strains.

TABLE 2. Antibiotics and dosages administered to rabbits with pneumococcal meningitis and numbers of rabbits with sterile CSF 10 and 24 h after start of therapy

Pneumococcal strain and antibiotic(s)	Dose (mg/kg)[a]	No. of rabbits treated	No. of rabbits with sterile CSF at time (h)[b]	
			10	24
Strain 1				
Untreated		4	0	Not done[c]
Ceftriaxone	125	5	0	0
Cefpirome	100	5	0	3
Meropenem	125	5	0	0
Vancomycin	20	6	2	0
Rifampin	15	5	0	4
Ceftriaxone + vancomycin	125			
	20	7	4	3/5[d]
Ceftriaxone + rifampin	125			
	15	7	0	4/5[d]
Vancomycin + rifampin	20			
	15	5	0	5
Strain 2				
Untreated		4	0	Not done[c]
Ceftriaxone	125	5	2	0
Cefpirome	100	5	5	4
Vancomycin	20	5	3	1
Meropenem	125	5	0	0
Clinafloxacin	15	5	5	5

[a] Two doses of each antibiotic (except ceftriaxone [one dose]) were given at 0 and 5 h.
[b] Specimens with ≤10 CFU/ml were considered sterile.
[c] Animals were agonal before this time and were euthanized.
[d] CSF could not be obtained from two animals.

DISCUSSION

The increasing resistance of *S. pneumoniae* strains to β-lactam antibiotics poses therapeutic problems, especially when such strains cause meningitis. Clinical experience with cephalosporin-resistant strains is limited, and various agents alone or in combination have been used for therapy only in individual cases (1, 3, 5, 10, 20).

In the rabbit model, ceftriaxone therapy lacked bactericidal activity in meningitis induced with the more resistant strain 1 (ceftriaxone MBC, 4 μg/ml), and although bacterial concentrations were reduced by more than 3 $\log_{10}$ CFU/ml with strain 2 (ceftriaxone MBC, 1 μg/ml) within 10 h, regrowth occurred by 24 h. These data support previous studies in experimental meningitis that found that CSF antibiotic concentrations that were at least eightfold greater than the MBC for the infecting organism were necessary for therapeutic efficacy (14, 21). The mean peak CSF ceftriaxone concentration in the animals (4.9 μg/ml) was in the mid-range of concentrations that have been measured in humans (6), and it can therefore be anticipated that ceftriaxone therapy alone would be ineffective in most patients with meningitis caused by similarly resistant strains.

The MICs of cefpirome for 50 and 90% of the penicillin-resistant pneumococci are generally twofold lower than the respective values of cefotaxime or ceftriaxone (13). Although small, such differences may critically affect the therapeutic response in meningitis when the CSF cephalosporin concentrations are close to the MICs. This was highlighted in this study; the cefpirome MICs for the two test strains were twofold lower than the ceftriaxone MICs, whereas CSF antibiotic concentrations were similar. The resultant greater ratio of CSF antibiotic concentration to

TABLE 3. Mean (SD) peak and trough antibiotic concentrations (in micrograms per milliliter) in serum and CSF of rabbits with pneumococcal meningitis

Agent	Concn with dose 1[a]				Concn with dose 2[a]		
	Blood		CSF		Blood peak	CSF	
	Peak	Trough	Peak	Trough		Peak	Trough
Ceftriaxone	195 (54)	56 (19)[b]	4.9 (1.7)	2.0 (1.4)			1.6 (0.4)[c]
Cefpirome	100 (18)	12 (8)	3.9 (1.2)	0.9 (0.3)	124 (10)	7.8 (1.3)	2.8 (1.5)
Meropenem	31 (15)	4.4 (3.3)	2.0 (1.3)	0.3 (0.3)	38 (11)	2.3 (0.7)	0.2 (0.2)
Vancomycin	35 (4)	6.0 (2.3)	2.3 (0.8)	0.9 (0.4)	37 (5)	3.0 (0.7)	0.5 (0.5)
Rifampin	19 (5)	5.5 (1.7)	0.4 (0.3)	0.2 (0.1)	27 (6)	0.8 (0.3)	0.3 (0.2)
Clinafloxacin	4.8 (0.8)	0.4 (0.3)	1.0 (0.2)	0.3 (0.1)	6.4 (2.1)	1.3 (0.2)	0.4 (0.1)

[a] Peak concentrations in blood and CSF (5 to 10 rabbits per group) were measured 30 and 60 to 90 min after a dose, respectively, and trough concentrations in blood and CSF were measured after 5 h.
[b] Trough at 6 h after initial dose was 29 ± 7 μg/ml.
[c] 10 h after initial dose.

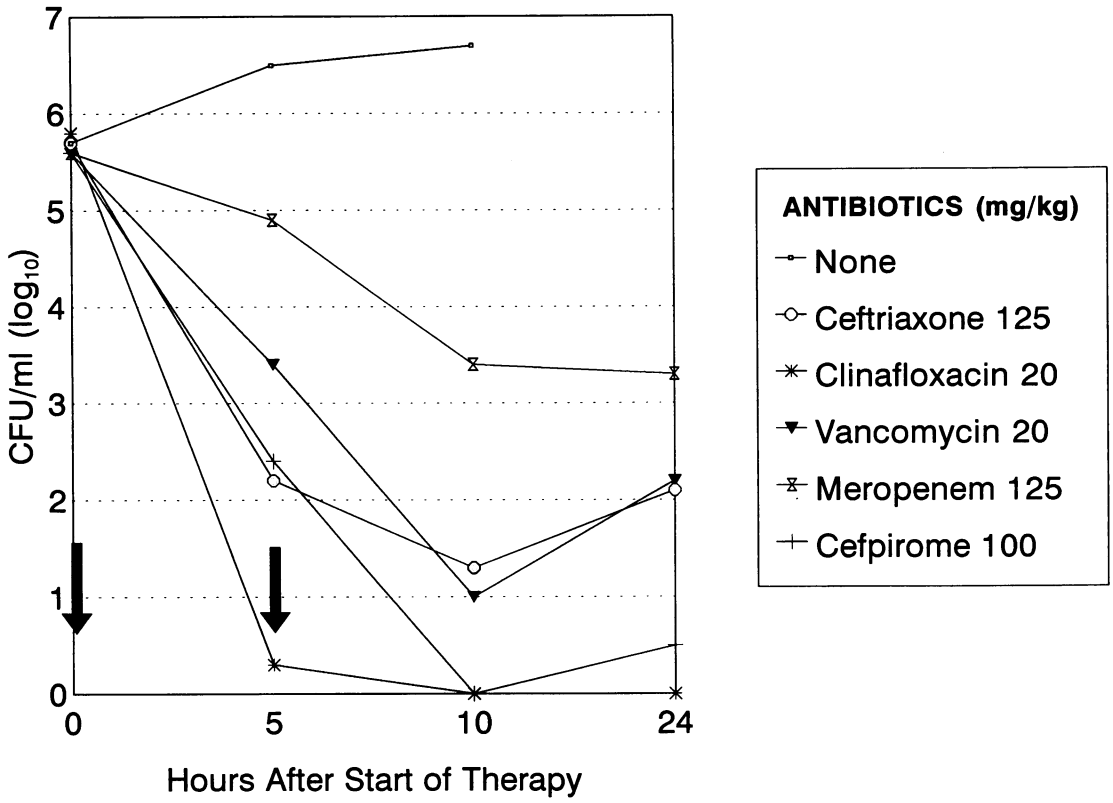

FIG. 1. Mean CSF bacterial concentrations after antibiotic therapy in experimental meningitis induced with pneumococcal strain 2 (ceftriaxone MIC, 1 μg/ml). Arrows indicate time points at which intravenous antibiotic doses were given. Ceftriaxone was given only once at zero hour. Clinafloxacin reduced bacterial concentrations to a greater extent within 5 h than did other antibiotics ($P < 0.05$), whereas meropenem was less bactericidal than other antibiotics within 5 or 10 h ($P < 0.05$).

MIC for cefpirome versus ceftriaxone was sufficient to increase bacterial killing after the first dose in animals infected with the more resistant strain, strain 1 (Fig. 2). The continued bacterial killing with cefpirome therapy was probably a result of the high CSF concentrations achieved after the second dose (~4× MIC for strain 1).

Older quinolones such as ciprofloxacin have borderline activity against *S. pneumoniae* (2), whereas some newer quinolones such as clinafloxacin have excellent in vitro activity (12). Data from the present study confirmed the good activity of clinafloxacin, which was the most rapidly bactericidal agent evaluated in this model. In addition, CSF penetration of clinafloxacin was greater than that of the other agents. Clinical experience with this agent is lacking.

Data obtained 24 h after the start of therapy have been included to give some indication of the duration of action of the respective agents but should, however, be interpreted with caution because vancomycin and the β-lactam antibiotics would be given more frequently during a 24-h period in clinical use than was the case in this model. Of currently available agents, vancomycin was the most rapidly bactericidal but regrowth occurred once vancomycin concentrations declined, suggesting a short postantibiotic effect. This is contrary to the observation in vitro of a prolonged postantibiotic effect with sub-MIC concentrations of vancomycin against a penicillin-resistant pneumococcus (17). The rapid elimination of vancomycin in rabbits may explain the apparent short postantibiotic effect in this model.

Meropenem was relatively ineffective even against strain 2 despite peak concentrations in CSF that were eightfold greater than the MIC. The activity of renal dehydropeptidase differs among mammal species (11), and the reason for the poor efficacy of meropenem may be related to its rapid metabolism in rabbits, resulting in only short periods of supra-MIC concentrations in CSF. Because of this possibility, we determined the serum half-life of meropenem in the rabbits, and the mean value obtained (1.4 h) was similar to that reported in adults with normal renal function (1.5 h) (7). Moreover, even in the one rabbit with CSF meropenem concentrations above the MIC (of strain 2) for 10 h, the bactericidal rate was lower than that observed with other antibiotics. Only limited data are available on the pharmacokinetics of meropenem in CSF of humans, and we are, thus, unable to conclude whether the results obtained in the rabbit model are an accurate prediction of the therapeutic response that can be expected in humans. Until efficacy has been demonstrated in humans, caution should be exercised in the use of this agent for cephalosporin-resistant pneumococcal meningitis.

In vivo synergism has been defined as "a bactericidal effect of the drug combination significantly more pronounced than the sum of the bactericidal effect of each agent alone in comparison with the effect in untreated animals" (8). In the absence of a more specific definition, we defined synergism as a greater than 1 log_{10} CFU/ml reduction in bacterial concentration with combination therapy compared with sum of the reductions with each agent alone. By this definition, vancomycin and ceftriaxone were synergistic for strain 1 in

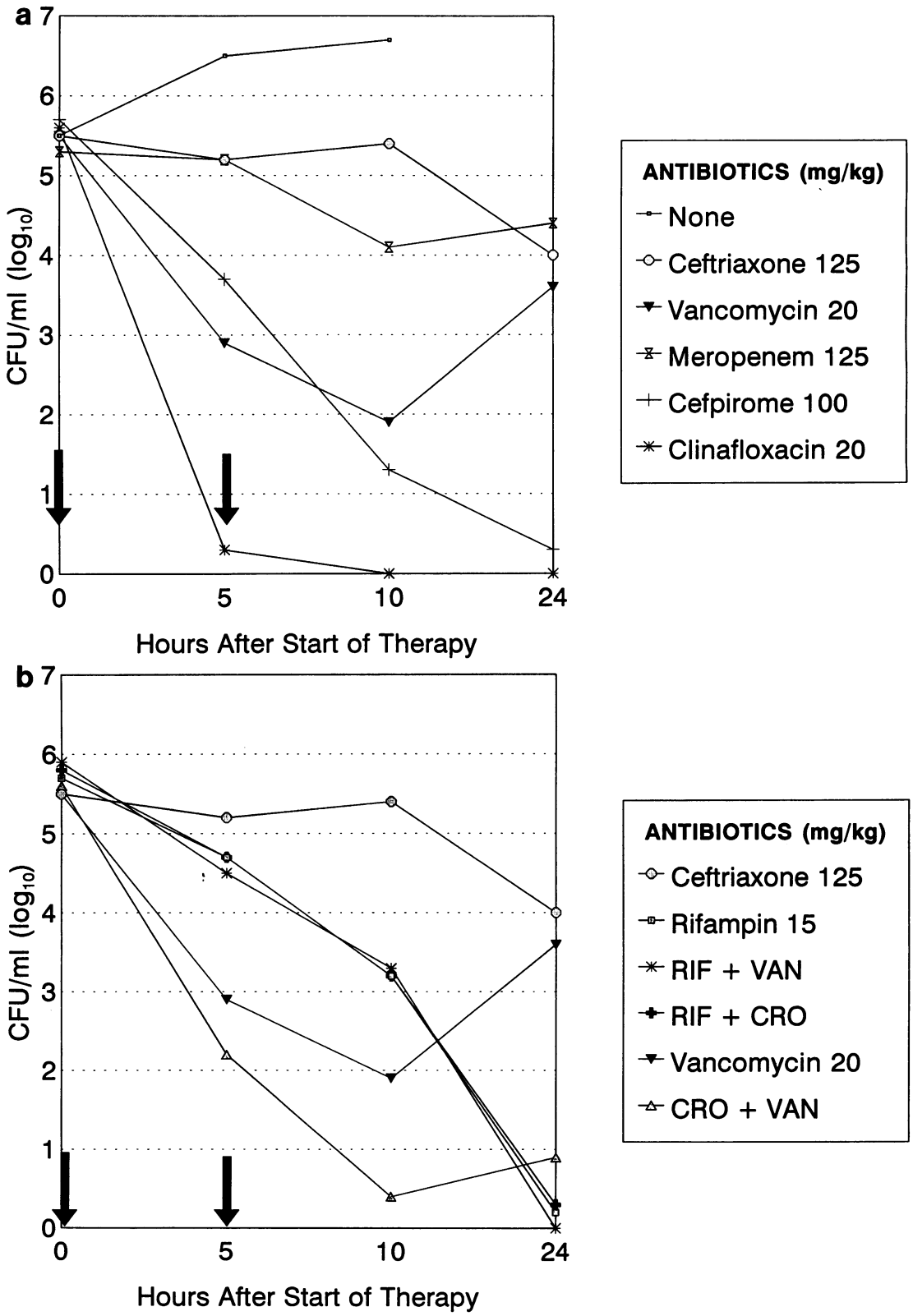

FIG. 2. Mean CSF bacterial concentrations after antibiotic therapy in experimental meningitis induced with pneumococcal strain 1 (ceftriaxone MIC, 4 μg/ml). Arrows indicate time points at which intravenous antibiotic doses were given. Ceftriaxone was given only once at zero hour. Clinafloxacin was more rapidly bactericidal within 5 h than were other treatments ($P < 0.01$). Clinafloxacin, cefpirome, and vancomycin reduced bacterial concentrations to a greater extent within 10 h than the other three antibiotics given alone ($P < 0.05$). The combination of ceftriaxone and vancomycin was superior to vancomycin or ceftriaxone alone ($P < 0.05$). Abbreviations: CRO, ceftriaxone; RIF, rifampin; VAN, vancomycin.

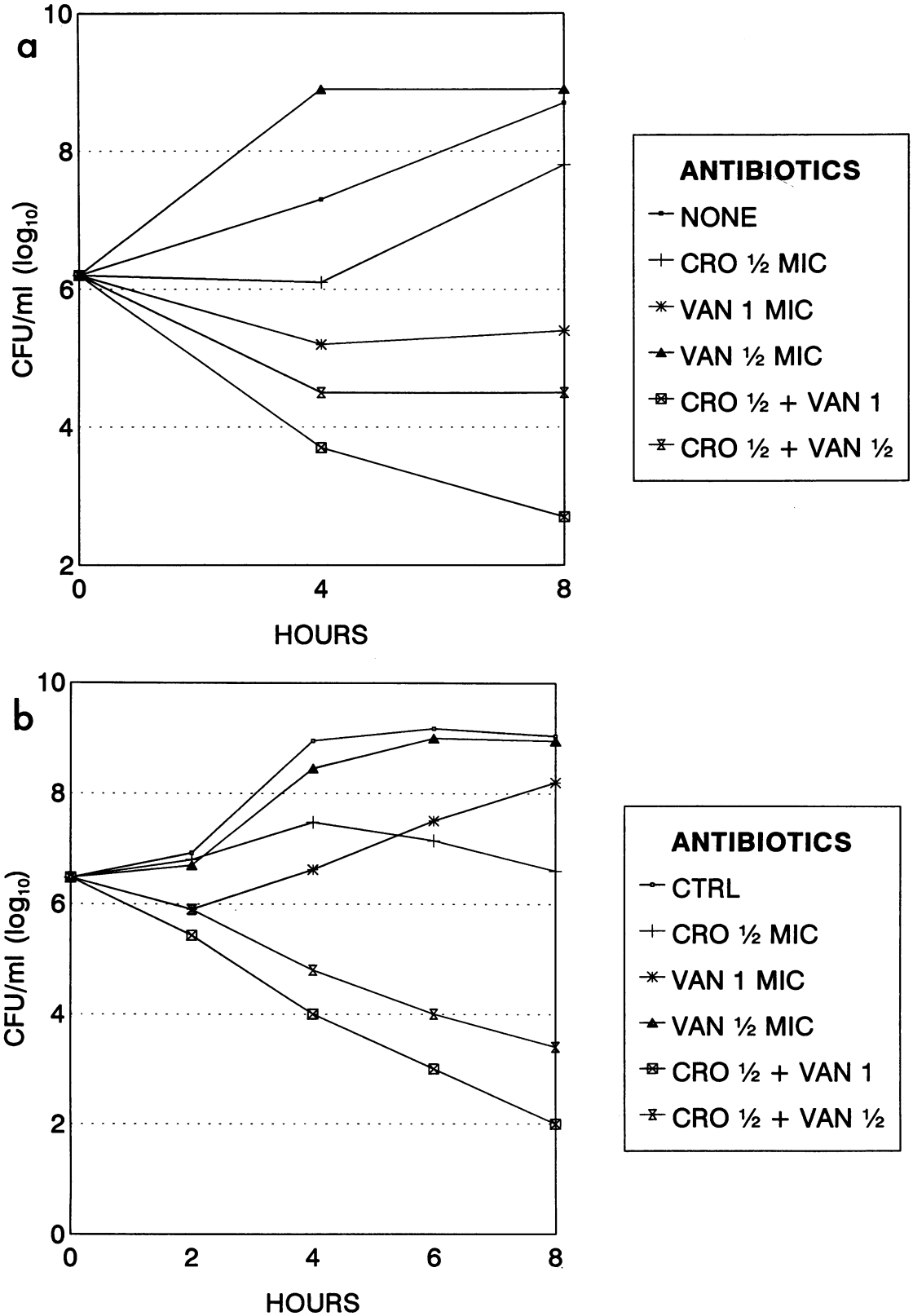

FIG. 3. In vitro time-kill curves with strain 2 (a) and strain 1 (b). Antibiotic concentrations are shown as multiples of the MIC for the respective strains. Abbreviations are as in Fig. 2.

our animal model. By contrast, combinations with rifampin were neither additive nor synergistic. The synergy of vancomycin and cephalosporin combinations was confirmed in vitro for both strains by time-kill studies. Synergism was noted with vancomycin concentrations equal to half the MIC. Even though clinical studies have shown unreliable penetration of vancomycin into CSF (15), concentrations close to the vancomycin MIC for pneumococci (usually ≤0.5 μg/ml) should be readily achievable in humans.

Numerous studies of synergism between β-lactams and aminoglycosides have been conducted, but information on synergy between two cell wall-active antibiotics is limited. A recent in vitro study found synergism with cephalosporins and fosfomycin (a peptidoglycan synthesis inhibitor) against penicillin-resistant pneumococci (4). Studies of combination therapy with penicillin and vancomycin against enterococci have found additive or synergistic effects in some experiments, particularly when vancomycin concentrations were close to the MIC for the organism tested (9, 18). Vancomycin–β-lactam combination therapy for gram-positive infections deserves further investigation.

None of the antimicrobial agents currently available for clinical use is ideal as single-agent therapy for β-lactam-resistant pneumococcal meningitis. Although caution must be exercised in applying results from our animal model to the management of patients, we believe that the combination of an extended-spectrum cephalosporin and vancomycin would be appropriate for the initial treatment of pneumococcal meningitis, especially if a resistant strain has been isolated. In vitro penicillin and cephalosporin susceptibilities should be determined for all meningeal pneumococcal isolates, and we recommend that combination therapy be continued if the cefotaxime or ceftriaxone MIC for a strain is ≥1 μg/ml.

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