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Clindamycin Therapy of Experimental Meningitis Caused by Penicillin- and Cephalosporin-Resistant *Streptococcus pneumoniae*

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Although penicillin resistance among *Streptococcus pneumoniae* strains is increasing in many areas, resistance to clindamycin remains low. In our well-characterized rabbit meningitis model, we conducted experiments to evaluate the bacteriologic efficacy of clindamycin after a penicillin- and cephalosporin-resistant *S. pneumoniae* strain was intracisternally inoculated. Animals received a loading intravenous dose of 30 mg of clindamycin per kg of body weight and then two doses of 20 mg/kg given 5 h apart. In addition to clindamycin, some animals received dexamethasone (DXM) with or without ceftriaxone. The concentrations of clindamycin in cerebrospinal fluid were from 8.9 to 12.8% of the concomitant concentrations in serum and were unaffected by DXM administration. Mean changes in CFU ($\log_{10}$ per milliliter) at 10 and 24 h were −3.7 and −6.1, respectively, for clindamycin-treated rabbits, −3.6 and −6.3 for clindamycin-DXM-treated rabbits, −3.9 and −5.8, respectively, for clindamycin-ceftriaxone-treated rabbits, and −5.0 and −6.7, respectively, for clindamycin-ceftriaxone-DXM-treated rabbits. By 24 h all but one of the cultures of cerebrospinal fluid (that from a clindamycin-DXM-treated rabbit) were sterile. Because of the potential risk for clindamycin-treated rabbits to develop macrolide-licosamide resistance, we attempted, unsuccessfully, to induce clindamycin resistance in vitro in two *S. pneumoniae* strains. Although clindamycin therapy might be effective in selected patients with multiple-drug-resistant pneumococcal meningitis who have failed conventional treatments, clinical experience is necessary before it can be recommended.

Rates of penicillin- and cephalosporin-resistant *Streptococcus pneumoniae* isolates of more than 20% have been reported worldwide (11, 16), whereas those of clindamycin resistance have generally been less than 6% (15, 24, 31, 33, 39). Although it has been available for many years, clindamycin use for central nervous system infections has not been recommended because of poor blood-brain barrier penetration (10). More recently, however, clindamycin has been successfully used to treat AIDS patients with *Toxoplasma* encephalitis (8, 9, 23, 34, 40).

Because new alternatives for the treatment of infections caused by resistant *S. pneumoniae* strains are necessary and because of the low incidence of clindamycin resistance among these organisms, we performed experiments to determine the penetration into cerebrospinal fluid (CSF) and bacteriologic effectiveness of clindamycin in a rabbit pneumococcal meningitis model and whether clindamycin resistance in two penicillin-resistant *S. pneumoniae* strains could be induced in vitro.

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MATERIALS AND METHODS

In vivo experiments. (i) Pathogen. The strain used in the experiments described here was recovered from a culture CSF from a child with meningitis (17). After overnight culture on sheep blood agar the organism was washed with phosphate-buffered saline (PBS)–pyrogen-free solution, and aliquots of this suspension were frozen at −70°C. The inoculum was prepared by diluting the aliquots in PBS to ~10^5 CFU/ml, and 250 μl was intracisternally inoculated. From 7.5×10^4 to 1.2×10^5 CFU was inoculated.

(ii) Treatment. Clindamycin (Cleocin; The Upjohn Company, Kalamazoo, Mich.) was given intravenously as a loading dose of 30 mg/kg of body weight; this was followed by the administration of two doses of 20 mg/kg 5 h apart. This regimen was chosen because the concentrations achieved in serum were similar to those obtained in children given routine dosages. In addition to clindamycin, some animals received dexamethasone (1 mg/kg; Luitpold Pharmaceutical Inc., Shirley, N.Y.), with or without ceftriaxone (75 mg/kg; Roche Laboratories, Nutley, N.J.), at 0 and 10 h intravenously.

(iii) Meningitis experiments. We used our well-characterized meningitis model in male New Zealand White rabbits weighing 2 to 2.5 kg (18, 26, 38) as modified originally by Dacey and Sande (7). Before each procedure, the animals were intramuscularly anesthetized with ketamine (40 mg/kg) and acepromazine (3 mg/kg). Treatment was initiated 12 to 14 h after the inoculation of the organism. CSF samples were withdrawn at 0, 5, 10, 24, and 36 h. Bacterial concentrations were quantified by plating serial dilutions of CSF on sheep blood agar and incubating the plates at 35°C for 24 h in 5% CO_2. The remaining CSF was stored at −70°C for the determination of antibiotic concentrations. Serum samples (0.5, 1, 5, 5.5, and 10 h) and additional CSF samples (1 and 6 h) were obtained and stored as described above for the determination of clindamycin concentrations.

(iv) Clindamycin measurement. Clindamycin concentrations were determined by a disk diffusion microbioassay with *Micrococcus luteus* ATCC 9341 (36). The lower limit of detection was 0.3 μg/ml. The interassay and intraassay coefficients of variation for CSF samples were 3 and 4.4%, respectively, and for serum they were 4.3 and 3.8%, respectively.

In vitro studies. (i) Susceptibility testing. The MICs and MBCs of penicillin, ceftriaxone, clindamycin, and erythromycin were determined for JG and HAN strains by a microdilution method with Mueller-Hinton broth supplemented with 2.5% lysed horse blood. The inoculum contained approximately 5×10^5 CFU/ml. The plates were immediately sealed with an adhesive tape to avoid evaporation and were incubated for 20 h at 35 to 37°C in ambient air. The MICs of clindamycin and erythromycin were also determined by the E-test (AB Biodisk, Solna, Sweden) on Mueller-Hinton agar supplemented with 5% sheep blood incubated at 35 to 37°C for 20 h in 5% CO_2 or ambient air.

(ii) Time-kill experiments. Time-kill experiments were done to evaluate *S. pneumoniae* strains for macrolide-lincosamide resistance by a method modified from that of Fernandes et al. (14). A 100-μl aliquot of an overnight culture of pneumococci was added to 10 ml of Mueller-Hinton broth supplemented with 2.5% lysed horse blood. The flasks were rotated at 35 to 37°C in ambient air. At 0 h, erythromycin (0.1 μg/ml) or clindamycin (0.001 μg/ml) was added to some bottles. After 2 h of incubation, the organisms were challenged with antibiotic at concentrations onefold lower and up to threefold greater than the MBC of clindamycin or erythromycin. Bacterial concentrations were quantified every 2 h by making 10-fold dilutions of an aliquot that were inoculated onto blood agar plates and incubated for 24 to 36 h in 5% CO_2 at 35°C. Two penicillin- and cephalosporin-resistant (JG and HAN) strains were used in these time-kill experiments.

(iii) Spontaneous mutation. The mutation rates for three pneumococcal

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TABLE 1. MICs and MBCs for the strains used in the present experiments

Antibiotic	JG		HAN		ATCC 49619	
	MIC (μg/ml)[a]	MBC (μg/ml)	MIC (μg/ml)[a]	MBC (μg/ml)	MIC (μg/ml)	MBC (μg/ml)
Penicillin	2	2	4	4	0.25	0.25
Ceftriaxone	4	4	2	4	0.03	0.03
Clindamycin	0.016	0.03	0.03	0.03	0.03	0.03
Erythromycin	2	2	1	2	0.03	0.03

[a] The erythromycin and clindamycin MICs determined by the E-test after 20 h of incubation in 5% CO_2 and ambient air were 8 and 0.064 μg/ml and 2 and 0.016 μg/ml, respectively, for strain JG and 8 and 0.047 μg/ml and 2 and <0.016 μg/ml, respectively, for strain HAN. The erythromycin MICs for strains JG and HAN under the two incubation conditions are considered by Fasola et al. (12a) to indicate intermediate resistance.

strains (two penicillin- and cephalosporin-resistant strains [JG and HAN] and one penicillin-resistant but cephalosporin-susceptible strain [ATCC 49619]) were determined as described previously (25). Briefly, from an overnight culture in Mueller-Hinton broth supplemented with 2.5% lysed horse blood, 100 μl (~10^8 CFU) was inoculated onto Mueller-Hinton agar supplemented with 2.5% lysed horse blood containing concentrations equal to and 2 and 10 times the MBC of clindamycin, and the plates were incubated at 35 to 37°C in ambient air for 72 h. Some of the studies were conducted with strains that were preexposed overnight to subinhibitory concentrations of erythromycin. Bacterial counts were done daily for 3 consecutive days.

Statistical analysis. One-way analysis of variance (Newman-Keuls multiple comparisons test) or Student's t test was used for parametric data. For comparison of positive and negative cultures, the two-tailed Fisher exact test was used. A P value of <0.05 was considered significant. There were six to eight rabbits per group.

RESULTS

The MICs and MBCs of penicillin, ceftriaxone, clindamycin, and erythromycin for the strains used in the present experiments are provided in Table 1.

Meningitis experiments. The concentrations of clindamycin in CSF were from 8.9 to 12.8% of the concomitant values in serum, and the amount of drug in CSF did not significantly change when dexamethasone was given (Fig. 1). When clindamycin was given to noninfected rabbits, the mean CSF drug concentrations at 6 and 10 h were significantly lower ($P < 0.05$) than those in infected animals. The penetration in the noninfected animals was 7%.

Figure 2 shows the bacterial counts in CSF at five time

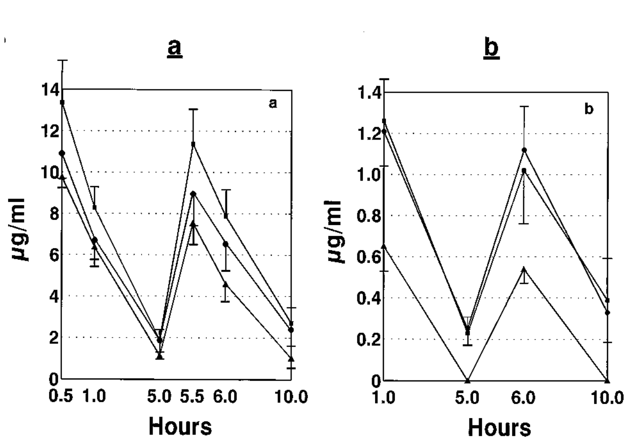

FIG. 1. Mean ± standard deviation concentrations of clindamycin in serum (a) and CSF (b) of rabbits that were intracisternally inoculated with the JG strain of pneumococcus (penicillin MIC, 2 μg/ml; penicillin MBC, 2 μg/ml) and treated with clindamycin alone (■) or with dexamethasone (●). Also shown are clindamycin MICs and MBCs for noninfected rabbits treated with clindamycin (▲).

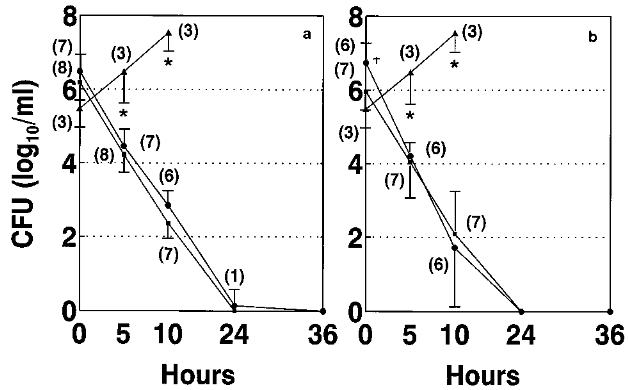

FIG. 2. Mean ± standard deviation bacterial concentrations and number of positive cultures (in parentheses) after intracisternal inoculation of the JG strain of pneumococcus. *, $P < 0.05$ between treated and nontreated rabbits; †, $P < 0.05$ between dexamethasone- and non-dexamethasone-treated rabbits. (a) ■, clindamycin; ●, clindamycin plus dexamethasone; ▲, control. (b) ■, clindamycin plus ceftriaxone; ●, clindamycin plus ceftriaxone plus dexamethasone; ▲, control.

points after the animals were intracisternally inoculated with the JG strain and treated with clindamycin or the combination of clindamycin and ceftriaxone with or without dexamethasone. All CSF cultures but one were sterile at 24 h. The positive culture was from a dexamethasone- and clindamycin-treated rabbit. By 36 h, 12 h after the administration of the last dose of antibiotic(s), all CSF cultures were sterile. When the rabbits were inoculated with the penicillin- and cephalosporin-resistant strain, ceftriaxone therapy was ineffective, with the colony counts being similar to those for untreated rabbits, regardless of whether dexamethasone was used (data not shown).

One additional experiment was performed with nine rabbits to determine whether CSF cultures remained sterile for 5 days after the start of clindamycin therapy. By 24 h after the initiation of therapy, all CSF cultures were sterile and all but one culture (that of CSF from a clindamycin- and dexamethasone-treated rabbit) remained sterile at the completion of the study, more than 96 h after the administration of the last dose of clindamycin. The MIC and MBC of clindamycin for the organism isolated from one rabbit had on day 5 were the same as those for the original strain.

Time-kill experiments. When the JG strain was preincubated (induced) with erythromycin or clindamycin, inhibition of growth was similar for concentrations that were one- to twofold the MBCs of clindamycin and erythromycin, regardless of the preincubation states (Fig. 3a versus b and Fig. 3c versus d). However, when the HAN strain was preincubated (induced) with erythromycin and challenged with onefold the MBC of this drug (1 μg/ml), there was no inhibition of the organism compared with the inhibition under the nonpreincubated (noninduced) conditions (Fig. 4a versus b). Preincubation with clindamycin had no effect on the bacteriologic results with four times the MIC of erythromycin or two times the MIC of clindamycin (Fig. 4c versus d).

Spontaneous mutation rate experiments. When the three strains of pneumococci were incubated with clindamycin, the spontaneous mutation rates were less than 10^{-9} colonies, regardless of whether these organisms were exposed overnight to subinhibitory concentrations of erythromycin (Table 2).

DISCUSSION

Clindamycin therapy has been used for almost 30 years. In an extensive review of clindamycin in 1981 (10), clindamycin

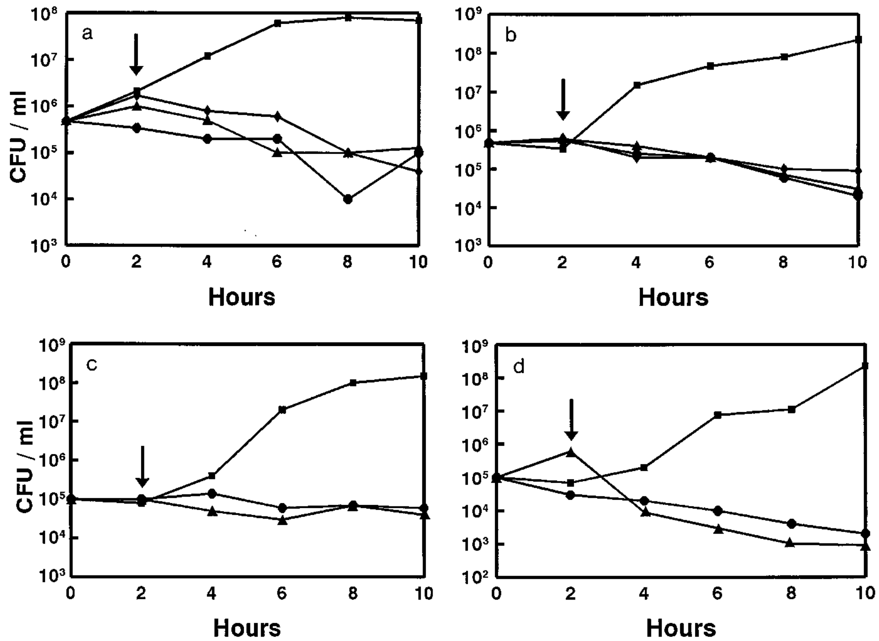

FIG. 3. Results of time-kill studies after the JG strain was nonpreincubated (noninduced) and challenged (chall) (a), preincubated (induced) and challenged with erythromycin (0.1 μg/ml) (b), noninduced and challenged (c), and induced and challenged with clindamycin (0.001 μg/ml) (d). Erythromycin or clindamycin for challenge (arrow) was added after 2 h of initial inoculation. (a) ■, unchallenged; ◆, challenged with erythromycin (4 μg/ml); ▲, challenged with erythromycin (8 μg/ml); ●, challenged with clindamycin (0.06 μg/ml). (b) ■, induced, unchallenged; ◆, induced, challenged with erythromycin (4 μg/ml); ▲, induced, challenged with erythromycin (8 μg/ml); ●, induced, challenged with clindamycin (0.06 μg/ml). (c) ■, unchallenged; ▲, challenged with erythromycin (8 μg/ml); ●, challenged with clindamycin (0.06 μg/ml). (d) ■, induced, unchallenged; ▲, induced, challenged with erythromycin (8 μg/ml); ●, induced, challenged with clindamycin (0.06 μg/ml).

was not recommended for the treatment of central nervous system infection because it was believed that it did not penetrate the blood-brain barrier well. Clindamycin was used to treat three patients with central nervous system infections caused by *Bacteroides fragilis*, two of whom had ventriculitis and meningitis and one of whom had a brain abscess (13, 20). Only the patient with the brain abscess improved during clindamycin therapy, although this child received other antibiotics

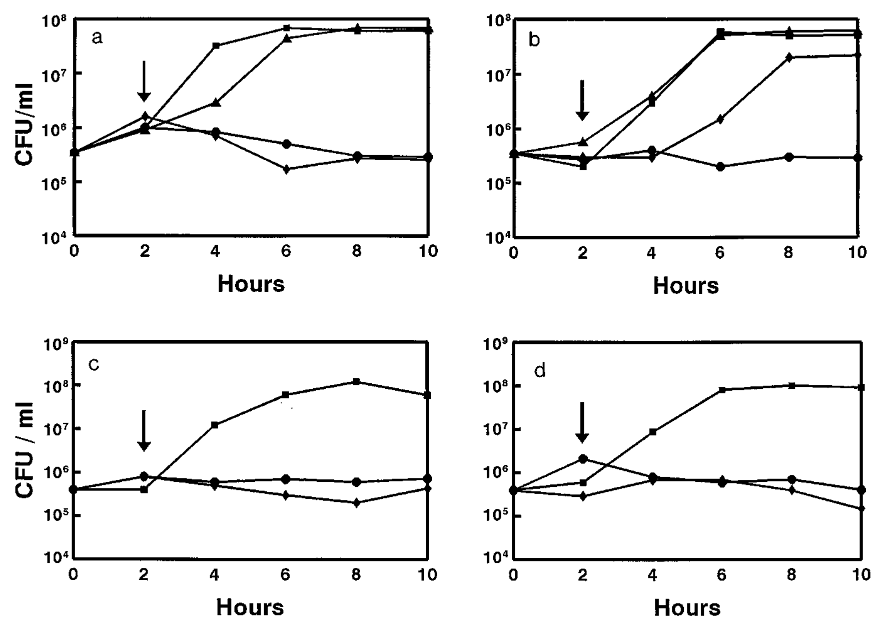

FIG. 4. Time-kill results after HAN strain of pneumococcus was nonincubated (noninduced) and challenged (a), preincubated (induced) and challenged with erythromycin (0.1 μg/ml) (b), noninduced and challenged (c), and induced and challenged with clindamycin (0.001 μg/ml) (d). Erythromycin or clindamycin for challenge (arrow) was added after 2 h of the initial inoculation. (a) ■, unchallenged; ◆, challenged with erythromycin (4 μg/ml); ▲, challenged with erythromycin (1 μg/ml); ●, challenged with clindamycin (0.06 μg/ml). (b) ■, induced, unchallenged; ◆, induced, challenged with erythromycin (4 μg/ml); ▲, induced, challenged with erythromycin (1 μg/ml); ●, induced, challenged with clindamycin (0.06 μg/ml). (c) ■, unchallenged; ◆, challenged with erythromycin (4 μg/ml); ●, challenged with clindamycin (0.06 μg/ml). (d) ■, induced, unchallenged; ◆, induced, challenged with erythromycin (4 μg/ml); ●, induced, challenged with clarithromycin (0.06 μg/ml).

TABLE 2. Spontaneous mutation rates of pneumococcal strains that were exposed or not exposed to erythromycin

Organism	Inoculum (CFU/plate)	Spontaneous mutation rate (10^{-9})	No. of colonies growing on plates to which clindamycin was added at:		
			0.03 μg/ml	0.06 μg/ml	0.3 μg/ml
JG	8.4×10^8	<1.2	No growth	No growth	No growth
JG (exposed)[a]	5.9×10^8	<1.7	No growth	No growth	No growth
HAN	8.9×10^8	<1.1	No growth	No growth	No growth
HAN (exposed)[a]	1.0×10^9	<1.0	No growth	No growth	No growth
ATCC 49619	5.7×10^8	<1.8	No growth	No growth	No growth
ATCC 49619 (exposed)[b]	3.7×10^8	<2.7	6	No growth	No growth

[a] The organisms were exposed to 0.1 μg of erythromycin per ml for 12 to 14 h before the experiments were performed.
[b] The organisms were exposed to 0.003 μg of erythromycin per ml for 12 to 14 h before the experiments were performed.

both before and concomitantly with clindamycin. The inhibitory and bactericidal titers against the pathogen in CSF were 1:32 5 h after the administration of the clindamycin dose (20). The other two patients had clindamycin concentrations in ventricular fluid of 0.9 to 2.8 μg/ml after the administration of a dose of 20 mg/kg and 0.5 to 1.5 μg/ml after the administration of a dose of 10 mg/kg. These concentrations were 3 and 12.5 times higher than the MICs, but were lower than the MBCs for the organisms (13). By contrast, when clindamycin was used in combination with pyrimethamine to treat patients with encephalitis caused by *Toxoplasma gondii* (9, 23, 34, 40), the clinical effectiveness of the combination was comparable to that of pyrimethamine plus sulfadiazine (8). In the present experiments the concentrations of clindamycin in CSF ranged from 9 to 13% of the simultaneous concentrations in serum. These values are lower than those reported by Picardi et al. (32), who showed concentrations of approximately 20% in the CSF of animals before and after head trauma. The concentrations achieved in the CSF of our animals exceeded by more than eightfold the MBC for the penicillin-resistant pneumococcal strain used and resulted in the prompt eradication of the organism.

The bacteriologic results with clindamycin therapy in the present model compared favorably with those obtained by using other therapeutic regimens that have been previously tested by us in this same model (28, 29). This is displayed in Table 3, in which the bacteriologic results of therapy with clindamycin, vancomycin, and trovafloxacin (CP-99,219) with or without dexamethasone are compared. Although trovafloxacin therapy appeared to be associated with more rapid killing 5 h after the initial therapy, the bacteriologic efficacy of clindamycin in sterilizing CSF cultures at 10 and 24 h was comparable to those with this investigational fluoroquinolone and with vancomycin.

Of 18 animals that received clindamycin and dexamethasone therapy, the CSF from 2 animals was positive on cultures after three doses of clindamycin. For one animal there was a 99% reduction in the CSF colony count at 24 h and the CSF culture was sterile at 36 h. The CSF from the other animal was positive on culture on day 5 of the experiment, more than 96 h after the administration of the last dose of clindamycin; cultures of CSF from this animal were sterile at 24 and 48 h.

Time-kill studies were performed to evaluate the potential for the induction of macrolide-lincosamide resistance resulting from the methylation of adenine residues in the 23S rRNA that has been described in streptococci, staphylococci, enterococci, and members of the family *Enterobacteriaceae*. Although this resistance can be plasmid or chromosomally mediated, the macrolide-lincosamide resistance of *S. pneumoniae* is mainly chromosomal (27). The transfer of resistance between pneumococci and other organisms has been described previously (6, 12, 35). We were able to induce resistance to erythromycin in one strain, but inhibition of the growth of this strain by clindamycin was not altered, regardless of whether the organisms were preexposed to erythromycin or clindamycin. Furthermore, preexposure of these organisms to erythromycin did not change the mutation rates for clindamycin resistance, with the rate remaining less than 1 in 10^9 colonies for the three strains tested.

Treatment failures have been reported in patients with penicillin-resistant pneumococcal meningitis treated with various antibiotics such as cefotaxime, ceftriaxone, vancomycin, erythromycin, rifampin, chloramphenicol, penicillin, and imipenem given alone or in combination (1–5, 17, 19, 21, 22, 37). The current recommendation is to treat patients with suspected pneumococcal meningitis initially with ceftriaxone or cefotaxime and vancomycin until the susceptibilities of the isolates are available (30). Although we demonstrated good penetration into CSF and a good bacteriologic response with clindamycin in rabbits with experimental pneumococcal meningitis, more clinical information is necessary before clindamycin can be recommended for use in the treatment of patients with

TABLE 3. Comparison of bacterial concentrations in CSF of rabbits inoculated with JG strain of pneumococcus[a] and treated with vancomycin, trovafloxacin, or clindamycin with or without dexamethasone or given no therapy (control group)

Treatment groups (MIC [μg/ml])[b]	Bacteriologic response (mean change in $\log_{10}$ CFU/ml) at the following times after the start of therapy[c]:		
	0–5 h	0–10 h	0–24 h
1. Control	+1.0	+2.1	ND[d]
2. Van (0.25)	−2.9	−4.6	−5.8
3. Van + DXM	−2.4	−3.9	−5.1
4. Trovafloxacin (0.06)	−4.2	−5.9	−6.1
5. Trovafloxacin + DXM	−5.2	−6.3	−6.3
6. Clin (0.016)	−2.0	−3.7	−6.1
7. Clin + DXM	−2.0	−3.6	−6.3

[a] Penicillin and ceftriaxone MICs of 2 and 4 μg/ml, respectively.
[b] Van, vancomycin; DXM, dexamethasone; Clin, clindamycin. There were 6 to 10 animals per group. Data for treatment groups 2 to 5 are from references 28 and 29.
[c] Significant differences ($P < 0.05$) were found for treatment groups 2 to 7 versus treatment group 1, for treatment groups 4 and 5 versus treatment groups 2 and 3 and treatment groups 6 and 7 for the bacteriologic response at 0 to 5 h, and no differences were found for the bacteriologic response at 0 to 24 h.
[d] ND, not done; death occurred in most animals at between 10 and 24 h.

pneumococcal meningitis who have failed therapy with other antimicrobial regimens.

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