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Effect of Quinolones and Other Antimicrobial Agents on Cell-Associated *Legionella pneumophila*

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We evaluated the in vitro susceptibility of *Legionella pneumophila* ATCC 33152 (serogroup I) to 13 antibiotics alone and in combination with rifampin (0.1 mg/liter) by three methods. Extracellular susceptibility was determined by MIC determinations and time kill curves in buffered yeast extract broth, while intracellular susceptibility was determined by peripheral human monocytes in RPMI 1640 culture medium. Antibiotic concentrations equal to or greater than the broth dilution MIC inhibited or killed *L. pneumophila* by the time kill method, except this was not the case for trimethoprim-sulfamethoxazole. Antibiotic concentrations below the broth dilution MIC did not inhibit *Legionella* growth. The only antibiotic-rifampin combinations which produced improved killing of *L. pneumophila* by the time kill method were those in which the logarithmic growth of *L. pneumophila* occurred during the experiment (rosoxacin, amifloxacin, cinoxacin, trimethoprim-sulfamethoxazole, clindamycin, and doxycycline). Neither direct MICs nor time kill curve assays accurately predicted intracellular *L. pneumophila* susceptibility. Rifampin, erythromycin, ciprofloxacin, rosoxacin, enoxacin, amifloxacin, gentamicin, clindamycin, and doxycycline all inhibited intracellular *L. pneumophila* growth at readily achievable concentrations in serum. Cefoxitin and thienamycin showed no inhibition of growth, although they were present extracellularly at concentrations that were 20 to 1,000 times their broth dilution MICs. Clindamycin was the only antibiotic that was able to inhibit intracellular *L. pneumophila* growth at an extracellular concentration below its MIC. The gentamicin (5 mg/liter)-rifampin combination was the only antibiotic-rifampin combination which demonstrated decreased cell-associated *Legionella* survival in this model of in vitro susceptibility.

Legionella pneumophila was first described in 1976 after an outbreak of acute respiratory illness in Philadelphia (10). In early reports, treatment of this illness with beta-lactam antibiotics was generally unsuccessful, while treatment with erythromycin or rifampin was associated with a good clinical response (11). Since the first defined outbreak, several investigators (17–19, 24) have shown that *L. pneumophila* survives intracellularly within human monocytes and macrophages, and it is currently believed that this ability protects it from antibiotics which remain predominantly in the extracellular space. In vitro susceptibility systems should include an evaluation of the intracellular activity of antimicrobial agents against *L. pneumophila* to be clinically useful. In this experiment we examined the ability of 13 antibiotics alone and in combination with rifampin to inhibit intracellular multiplication of *L. pneumophila* in peripheral human monocytes, and compared this procedure with susceptibility testing, including time kill curve techniques.

MATERIALS AND METHODS

Preparation of infectious inocula. Virulent *L. pneumophila* ATCC 33152 (serogroup I) was obtained from the Centers for Disease Control, Atlanta, Ga., was used in all experiments, and was frozen at −70°C until needed. At that time a sample of the strain was plated onto buffered charcoal yeast extract agar (GIBCO Diagnostics, Madison, Wis.) and grown for 48 h at 35°C in room air. After this time, pure colonies of *L. pneumophila* were placed in buffered yeast extract (BYE) broth (6) and incubated overnight on a gyratory shaker at 35°C. The inoculum was then standardized to a 0.5 McFarland standard and diluted to a final concentration of 5×10^5 organisms per ml for each experiment.

MIC determination. Broth dilution MICs were ascertained by adding 0.05 ml of a BYE broth solution containing 1×10^6 *L. pneumophila* per ml to 0.05 ml of BYE broth containing standard antibiotic concentrations (final concentration, 5×10^5 CFU/ml) in microtiter wells. After 48 h on a gyratory shaker at 35°C, the last well in which no visible growth appeared was accepted as the MIC for the organism. Each MBC was determined by using the 1986 National Committee for Clinical Laboratory Standards proposed guidelines. Plates were incubated at 35°C in room air for 72 h, and the lowest concentration which showed 99.9% killing (12 colonies or less) was accepted as the MBC for the organism.

Time kill curves. *L. pneumophila* was inoculated into BYE broth at a final concentration of 5×10^5 CFU/ml in spinner flasks containing no antibiotic, rifampin (0.1 mg/liter), experimental drug, or experimental drug-rifampin (0.1 mg/liter). Flasks were incubated at 35°C in room air. At 1, 24, 48, 72, and 96 h, a fraction of broth was removed and the number of CFU of *L. pneumophila* per ml was determined by the methods outlined below. Experimental drug concentrations were run at approximately one-tenth the peak level in serum obtained with that drug.

The following drug concentrations were assessed: ciprofloxacin (Miles Laboratories, Inc., West Haven, Conn.), rosoxacin (Sterling-Winthrop Research Institute, Rensselaer, N.Y.), and cinoxacin and erythromycin (Eli Lilly & Co., Indianapolis, Ind.) at 0.25 mg/liter; cefoxitin (Merck & Co., Inc., Rahway, N.J.) at 1.0 mg/liter; rifampin (Merrell Dow Research Institute, Cincinnati, Ohio) at 0.1 mg/liter;

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TABLE 1. MICs and MBCs at 48 h for *L. pneumophila* as determined in BYE broth

Antimicrobial agent(s)	MIC (mg/liter)	MBC (mg/liter)
Amifloxacin	0.078	0.15
Cefoxitin	0.097	0.39
Cinoxacin	1.25	1.25
Ciprofloxacin	0.019	0.019
Clindamycin	12.5	50.0
Doxycycline	0.39	25.0
Enoxacin	0.15	0.31
Erythromycin	0.195	>50.0
Gentamicin	0.39	1.56
Rifampin	≤0.002	6.25
Rosoxacin	0.009	0.009
Thienamycin	0.097	25.0
Trimethoprim-sulfamethoxazole	0.15/2.9	>1.25/23.7

thienamycin (Merck & Co.) at 5.0 mg/liter; trimethoprim-sulfamethoxazole (Hoffmann-La Roche Inc., Nutley, N.J.) at 0.025/0.5 and 0.15/2.9 mg/liter; gentamicin (Schering Corp., Galloping Hill, N.J.) at 1.56 and 5.0 mg/liter; clindamycin (The Upjohn Co., Kalamazoo, Mich.) at 3.0 mg/liter; and doxycycline (Pfizer Inc., Brookland, N.Y.) at 0.4 mg/liter. Thymidine phosphorylase (0.1 IU/ml) was added to each flask containing trimethoprim-sulfamethoxazole (22).

Leukocyte isolation. Human monocytes were obtained from healthy volunteer donors with no previous history of *L. pneumophila* infection. Samples were collected in heparinized syringes, and the mononuclear cell line was isolated by Ficoll-Hypaque centrifugation by the method described by Horwitz et al. (17). The cells were washed twice in RPMI 1640 buffer containing 15% calf serum and counted in a hemacytometer. Cells were diluted to a final concentration of 10^6 mononuclear cells per ml for each experiment. Mononuclear cells were approximately two-thirds lymphocytes and one-third monocytes. Viability was determined by the trypan blue exclusion technique. Greater than 95% of the monocytes showed viability on day 1 and greater than 90% showed viability on day 4.

Monocyte experiments. A total of 3×10^5 monocytes per ml were incubated with *L. pneumophila* (1×10^5 organisms per ml) in RPMI 1640 medium containing 15% fetal bovine serum. All glassware was siliconized. Each flask contained no antibiotic, rifampin, experimental drug, or experimental drug-rifampin. Flasks were placed on a gyratory shaker for 1 h at 35°C in room air and incubated in 95% oxygen–5% CO_2 at 35°C for the remainder of the experiment. Experimental drug concentrations were run at approximately one-tenth the peak level in serum for each drug.

The following drug concentrations were assessed: rosoxacin, enoxacin, amifloxacin, and erythromycin at 0.25 mg/liter; ciprofloxacin at 0.25 and 3.0 mg/liter; cinoxacin at 0.25, 1.5, and 15.0 mg/liter; cefoxitin at 0.2, 1.0, and 10.0 mg/liter; thienamycin at 5.0 mg/liter; trimethoprim-sulfamethoxazole at 0.025/0.5 and 0.15/2.9 mg/liter; gentamicin at 1.56 and 5.0 mg/ml; clindamycin at 1.56 and 3.0 mg/liter; and doxycycline at 0.4 mg/liter. Antibiotics were present in each flask at the start of each experiment. Thymidine phosphorylase (0.1 IU/ml) was added to each flask containing trimethoprim-sulfamethoxazole (22).

At 1, 24, 48, 72, and 96 h, the flasks were agitated; and a 1.0-ml fraction containing cells and buffer was removed. Each fraction was spun at $70 \times g$ for 5 min, and the supernatant was removed. The cells were washed and centrifuged twice in RPMI 1640 buffer containing fetal bovine serum. A final suspension of the cellular pellet was done in 1.0 ml of normal saline. Cells were then lysed by sonication for 5 s, and the number of CFU of *L. pneumophila* within each pellet was determined by 10-fold serial dilutions. *L. pneumophila* survival was not affected by the sonication procedure (pre- and postsonication CFU/ml were 8×10^4 and 7.8×10^4, respectively).

Determination of *L. pneumophila* concentrations. Final determinations of the number of CFU of *L. pneumophila* per ml were made by serial 10-fold dilutions of each sample. Fractions of each dilution were plated on buffered charcoal yeast extract agar, and the number of CFU/ml was determined after 72 h of incubation at 35°C in room air. By this technique, a lower limit of 10 CFU/ml could be determined.

Statistical analysis. Original data in all experiments were analyzed after logarithmic transformation. Statistical significance for time kill curves was determined by the Mann-Whitney test, and for monocyte experiments statistical significance was determined by the unpaired Student test (26). Adjustments for unequal variances were made whenever appropriate. Confidence intervals of 99% were determined for the population range of organisms in each experiment. Results from single antibiotic trials falling outside this range are reported as being antibiotic related.

RESULTS

MIC and MBC determinations. The 48-h MICs and MBCs for *L. pneumophila* (ATCC 33152), as determined in BYE broth, are shown in Table 1. By this technique, growth of *L. pneumophila* was inhibited by rifampin, erythromycin, cefoxitin, trimethoprim-sulfamethoxazole, thienamycin, ciprofloxacin, rosoxacin, enoxacin, amifloxacin, cinoxacin, gentamicin, and doxycycline at concentrations of these drugs that are achievable in serum. Clindamycin was the only antibiotic tested which was unable to inhibit *Legionella* growth at a concentration of one-half its peak level in serum.

Time kill curves. The number of CFU/ml expressed over time for control organisms and organisms exposed to rifampin, experimental antibiotic, or experimental antibiotic-rifampin is given in Fig. 1A to G. As determined by time kill curves, antibiotic activity against cell-free *L. pneumophila* could be classified into one of three categories.

First, cefoxitin, ciprofloxacin, gentamicin, thienamycin, and erythromycin showed steady decreases in the number of *L. pneumophila* CFU/ml when compared with controls (Fig. 1A, C, E, and F). Each drug was present in concentrations equal to or greater than its MIC, as determined in BYE broth (10 and 100 times the cefoxitin, MIC, 13 times the ciprofloxacin MIC, 4 and 12 times the gentamicin MIC, 50 times the thienamycin MIC, and 1.5 times the erythromycin MIC). The combination of rifampin with these antibiotics produced variable results. For cefoxitin, ciprofloxacin, and gentamicin, the rate of killing of *L. pneumophila* was slightly decreased (Fig. 1A, C, and E). This delayed killing was most apparent for ciprofloxacin and gentamicin (1.56 mg/liter), as 2 additional days were required to achieve comparable reductions of *L. pneumophila* CFU/ml (Fig. 1C and E) when rifampin was present. Erythromycin-rifampin, however, did show a greater than 2 log unit decrease in *L. pneumophila* CFU/ml when compared with erythromycin alone on days 3 and 4 (Fig. 1F).

The second group contained rifampin, amifloxacin, rosoxacin, and doxycycline. These antibiotics showed transient decreases in the number of *L. pneumophila* CFU/ml when

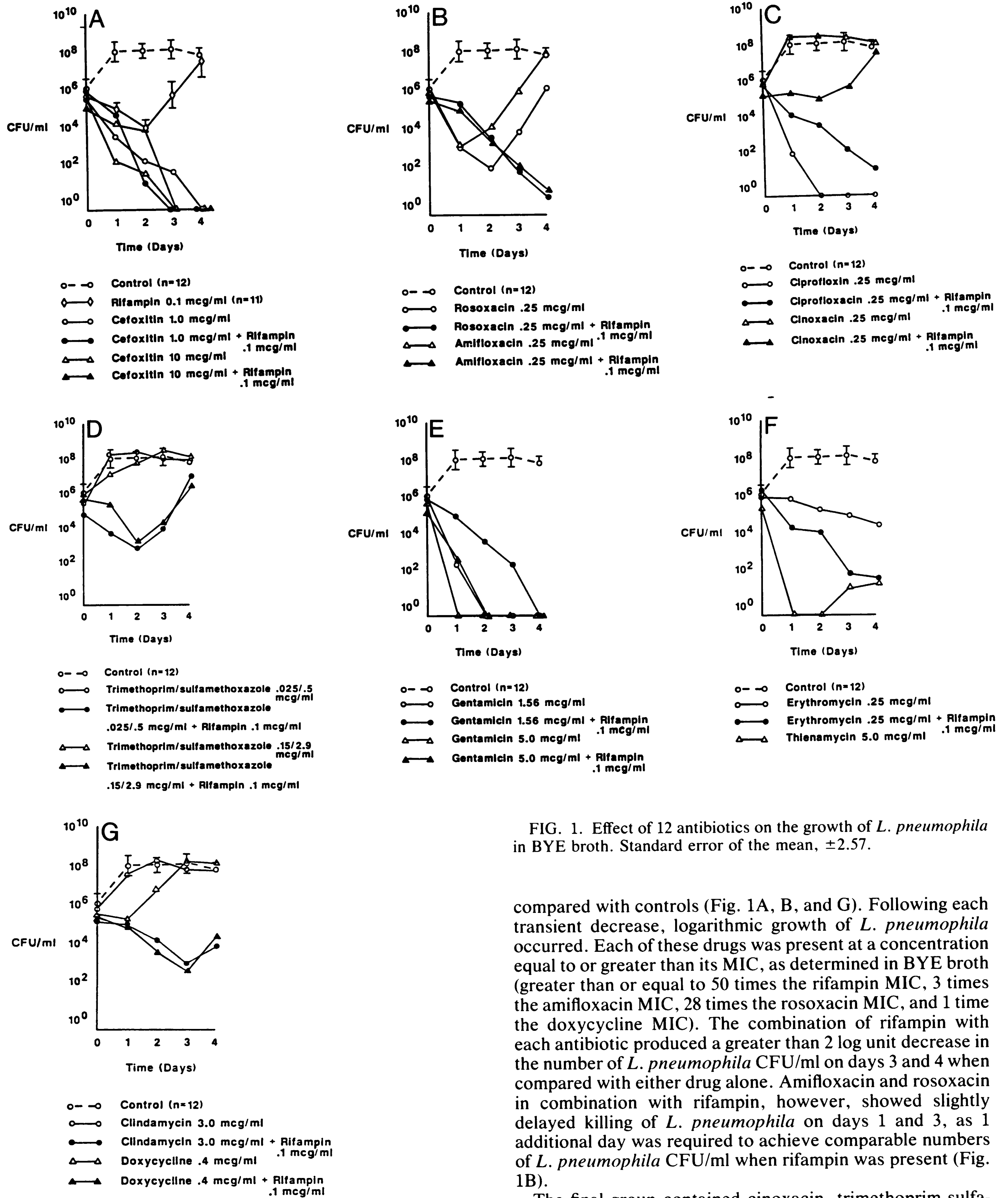

FIG. 1. Effect of 12 antibiotics on the growth of *L. pneumophila* in BYE broth. Standard error of the mean, ±2.57.

compared with controls (Fig. 1A, B, and G). Following each transient decrease, logarithmic growth of *L. pneumophila* occurred. Each of these drugs was present at a concentration equal to or greater than its MIC, as determined in BYE broth (greater than or equal to 50 times the rifampin MIC, 3 times the amifloxacin MIC, 28 times the rosoxacin MIC, and 1 time the doxycycline MIC). The combination of rifampin with each antibiotic produced a greater than 2 log unit decrease in the number of *L. pneumophila* CFU/ml on days 3 and 4 when compared with either drug alone. Amifloxacin and rosoxacin in combination with rifampin, however, showed slightly delayed killing of *L. pneumophila* on days 1 and 3, as 1 additional day was required to achieve comparable numbers of *L. pneumophila* CFU/ml when rifampin was present (Fig. 1B).

The final group contained cinoxacin, trimethoprim-sulfamethoxazole, and clindamycin. These antibiotics had no effect of *L. pneumophila* multiplication (Fig. 1C, D, and G). Each drug was present at a concentration that was less than or equal to its MIC, as determined in BYE broth (0.2 times

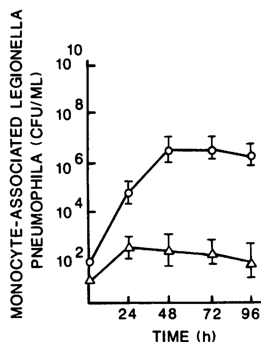

FIG. 2. Growth of cell-associated *L. pneumophila* over 96 h as exemplified by rifampin (△; n = 18) and non-antibiotic-containing controls (○; n = 20). Standard error of the mean, ±2.57.

the cinoxacin MIC, 0.25 times the clindamycin MIC, 0.17 and 1 times the trimethoprim-sulfamethoxazole MIC). The addition of rifampin produced fewer *L. pneumophila* CFU/ml compared with that of each drug alone on days 1 through 4 (Fig. 1C, D, and G). No rifampin combination in this group showed a greater than 2 log unit decrease when compared with rifampin alone.

Monocyte experiments. The numbers of cell-associated *L. pneumophila* organisms in non-antibiotic-containing controls showed logarithmic increases for the first 48 h of incubation (Fig. 2). Between 48 and 72 h a slower increase occurred, and after 72 h no further increases occurred. When present, antibiotic effects occurred after 24 h and persisted for the remainder of each experiment, as was the case with rifampin. *L. pneumophila* was not able to reproduce solely in RPMI 1640 medium with 15% fetal bovine serum.

The number of *L. pneumophila* CFU/ml associated with human mononuclear cells on day 3 is presented in Fig. 3. Rifampin, erythromycin, ciprofloxacin, rosoxacin, enoxacin, amifloxacin, cinoxacin (15 mg/liter), clindamycin (3.0 mg/liter), doxycycline, gentamicin, and trimethoprim-sulfamethoxazole (0.15/2.9 mg/liter) all exhibited a decrease in the number of cell-associated *L. pneumophila* CFU/ml below the lower limit of the 99% confidence interval for the control organisms (2.5 × 10^5 CFU/ml). By contrast, cinoxacin (0.25 and 1.5 mg/liter), clindamycin (1.56 mg/liter), trimethoprim-sulfamethoxazole (0.025/0.5 mg/liter), cefoxitin (0.2, 1.0, and 10.0 mg/liter), and thienamycin (5.0 mg/liter) did not show a decrease outside this limit, although cinoxacin (1.2 times the MIC), cefoxitin (20, 100, and 1,000 times the MIC), and thienamycin (500 times the MIC) were all run at concentrations greater than their MIC, as determined in BYE broth.

Clindamycin at 3.0 mg/liter (0.25 times the MIC) was able to inhibit cell-associated *Legionella* growth below the lower limit of the 99% confidence interval for control organisms (7.0 × 10^3 versus 2.5 × 10^5 CFU/ml). Cinoxacin (0.2 times the MIC) and trimethoprim-sulfamethoxazole (0.17 times the MIC) showed no effect on cell-associated *L. pneumophila* growth at sub-MIC concentrations. Ciprofloxacin at 3.0 mg/liter (<10 CFU/ml) was the only antibiotic to inhibit cell-associated *L. pneumophila* growth below the lower limit of the 99% confidence interval for rifampin (1.9 × 10^1).

The addition of rifampin to each antibiotic (Fig. 4) failed to demonstrate increased activity against cell-associated *L. pneumophila* multiplication unless the single antibiotic did not inhibit *L. pneumophila* growth (i.e., cefoxitin, trimethoprim-sulfamethoxazole, and cinoxacin). This growth inhibition was not different than that for rifampin alone. The only combination regimen which fell below the lower limit of the 99% confidence interval for rifampin alone was gentamicin (5.0 mg/liter)-rifampin (<10 CFU/ml). Overall, ciprofloxacin (3.0 mg/liter) and the combination of gentamicin (5.0 mg/liter)-rifampin were the most effective inhibitors of cell-associated *L. pneumophila* growth. Both of these regimens had fewer than 10 CFU/ml associated with the mononuclear cell pellet on day 3.

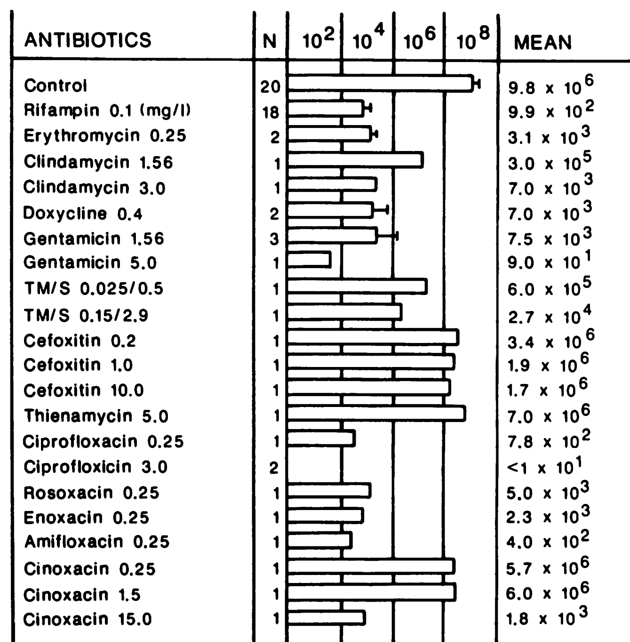

FIG. 3. Representative growth of cell-associated *L. pneumophila* as noted on day 3 of trial runs. The mean is expressed in CFU per milliliter. Bars indicate the standard deviation. TM/S, Trimethoprim-sulfamethoxazole.

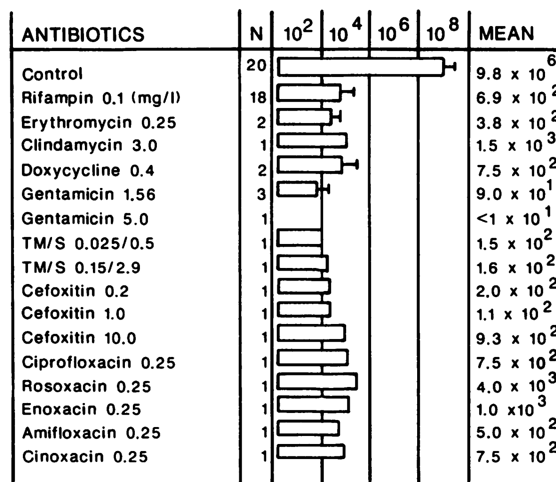

FIG. 4. Effect of 11 antibiotics in combination with rifampin on the cell-associated growth of *L. pneumophila*. The mean is expressed in CFU per milliliter. Bars indicate the standard deviation. TM/S, Trimethoprim-sulfamethoxazole.

DISCUSSION

The results of *L. pneumophila* susceptibility paralleled each other when determined by direct MIC and time kill techniques. Time kill curves which were performed at antibiotic concentrations equal to or greater than the BYE broth dilution MIC generally showed decreases in *L. pneumophila* CFU when compared with that in controls. Only trimethoprim-sulfamethoxazole failed to inhibit *L. pneumophila* growth by the time kill curve method when run at its MIC.

Current recommendations for intravenous trimethoprim-sulfamethoxazole use suggest administration within 2 h of reconstitution to prevent precipitation of drugs at high doses (27). To our knowledge, studies of trimethoprim-sulfamethoxazole stability in BYE broth have not been performed. Other antibiotics might have deteriorated during the 4 days over which our experiments were carried out. This factor could explain the increased *L. pneumophila* growth we observed on days 3 and 4 of the time kill curve experiments when the organisms were incubated with rifampin, amifloxacin, rosoxacin, and doxycycline. No studies on the stability of these antibiotics in BYE broth have been published to date.

The emergence of resistance should also be considered as a possible explanation for the increased *L. pneumophila* growth we observed on days 3 and 4 of the time kill curve experiments. We have seen rifampin resistance develop during time kill curve experiments with a different strain of *L. pneumophila* (unpublished data).

For rifampin in combination with ciprofloxacin, amifloxacin, rosoxacin, cefoxitin, and gentamicin, slightly improved survival of *L. pneumophila* was shown by the time kill curve method, suggesting that there was possible antagonism. DNA transcription may be necessary for these drugs to be most effective. Because rifampin inhibits transcription, it may have decreased the effectiveness of these drugs (29). Drug inactivation by rifampin is also a consideration. Results of a previous study (15) have shown that rifampin is a significant inactivator of antibiotics through the hepatic enzyme system; however, this is an in vivo phenomenon, and we are not aware of evidence for direct chemical inactivation by rifampin.

In 1980, Horwitz et al. (17) first demonstrated that *L. pneumophila* multiplies within human macrophages. Since that time, several different cell types have been used to support intracellular *L. pneumophila* growth (1, 7, 17, 20, 24, 30). In our experiments, human blood mononuclear cells supported logarithmic growth of *L. pneumophila*, although lymphocytes were predominant in the culture. Our monocyte concentration of 3×10^5 cells per ml yielded an *L. pneumophila* CFU/ml that was comparable to that determined by other investigators (17).

Several factors are involved in intracellular *L. pneumophila* growth. Agar-passed strains of *Legionella* have been shown to reproduce less actively in human macrophages (20). While unactivated human macrophages (18) and hydroxyl radical scavengers (20) allow improved intracellular *Legionella* survival and growth. The presence of antibiotics has variable effects on growth. Erythromycin (1, 7, 19, 30), rifampin (7, 30), ciprofloxacin (7), pefloxacin (28), gentamicin (1, 8, 30), nalidixic acid (30), tetracycline (30), and chloramphenicol (30) have each inhibited intracellular *L. pneumophila* growth under a variety of experimental conditions. Beta-lactam antibiotics such as ampicillin (30), cefoxitin (30), cefotaxime (30), and thienamycin (8) have not been shown to inhibit intracellular *L. pneumophila* multiplication.

Results of this study support the theory that *L. pneumophila* can reproduce independently or in association with human monocytes and that antibiotics which remain in the extracellular space are not effective against intracellular pathogens. Rifampin (16, 21), erythromycin (16, 21), clindamycin (16, 21), trimethoprim-sulfamethoxazole (12), and ciprofloxacin (4) have been shown to be concentrated within human leukocytes. The uptake for clindamycin is quite pronounced, with intracellular concentrations being 20 to 50 times greater than extracellular concentrations (16). This uptake may have allowed sub-MIC extracellular drug levels of clindamycin to achieve high enough intracellular concentrations to inhibit *L. pneumophila* growth. Gentamicin was the only antibiotic with a low cellular/extracellular concentration ratio which effectively inhibited cell-associated *Legionella* growth. This could be explained by the fact that gentamicin was present at the time of bacterial inoculation and therefore inhibited phagocytosis (14) or had its effect before phagocytosis occurred. Our results with gentamicin are similar to those of Bacheson et al. (1), who have shown that gentamicin effectively kills cell-associated *L. pneumophila* 2.5 h after bacterial inoculation (28).

Since the quinolones were also present at the time of bacterial inoculation, a possible effect on phagocytosis cannot be completely excluded. In studies in which the effects of quinolones on leukocyte function were measured, increased macrophage phagocytic capacity has been demonstrated by pefloxacin (3). In contrast, lymphocyte studies with quinolones have shown reduced mitogen-induced cell proliferation (difloxacin) and decreased DNA synthesis with norfloxacin and difloxacin (2, 13). The effect of each quinolones on leukocyte function could not be clearly defined in our model.

Ciprofloxacin, rosoxacin, enoxacin, and amifloxacin showed good activity against cell-associated *L. pneumophila*. Cinoxacin showed only moderate effects at 15 mg/liter, which is its approximate peak level in serum. Ciprofloxacin at 3.0 mg/liter showed no detectable *L. pneumophila* associated with leukocytes. This result may be related to the fact that intracellular ciprofloxacin levels are approximately 2.5 times the extracellular levels (4). Pefloxacin (28) and ofloxacin (25) have also been shown to inhibit intracellular *L. pneumophila* growth in similar in vitro models.

Vilde et al. (28) evaluated the extracellular concentration of six antibiotics that was necessary to inhibit intracellular growth of *L. pneumophila* for 24 h. They found at least a 90% decrease in intracellular CFU/ml for erythromycin ($\geq$0.05 mg/liter), rifampin ($\geq$0.005 mg/liter), pefloxacin ($\geq$0.06 mg/liter), trimethoprim-sulfamethoxazole ($\geq$0.1/0.5 mg/liter), and doxycycline ($\geq$0.8 mg/liter). Our model of *L. pneumophila* growth over 72 h gave similar results. Rifampin (0.1 mg/liter) and erythromycin (0.25 mg/liter) produced an approximate 4 log unit decrease in *L. pneumophila* growth. Each of these antibiotics was present at higher concentrations than those determined for 90% growth inhibition at 24 h. Conversely, antibiotics which were run at concentrations closer to those determined by Vilde et al. (28) to be necessary to inhibit growth (doxycycline at 0.4 mg/liter, trimethoprim-sulfamethoxazole at 0.15/2.9 mg/liter) were less effective (2.5 to 3 log unit decreases).

Some investigators have advocated the use of erythromycin-rifampin for serious *Legionella* infections. Based on our results with time kill curves, better killing of *L. pneumophila* should occur with this combination than with either drug alone. Our results with the macrophage model, however, indicated no significant difference between the erythromycin-rifampin combination and either drug alone. Different

results may be obtained if higher or lower concentrations of drugs are examined. In a model similar to ours, lower concentrations of rifampin plus either erythromycin or pefloxacin demonstrated an additive effect (28).

Recently, Edelstein et al. (5) and Fitzgeorge et al. (9) tested a variety of antibiotics in experimentally induced *Legionella* pneumonia in guinea pigs. They found rifampin, erythromycin, doxycycline, trimethoprim-sulfamethoxazole, and ciprofloxacin to be effective agents in treating this infection. When they evaluated beta-lactam antibiotics and gentamicin in their animal models, no improvement in survival occurred. These results closely parallel those obtained with our in vitro macrophage-*Legionella* susceptibility model. Only gentamicin gave a discrepant result.

Our results help to explain the in vitro and in vivo discrepancies of *L. pneumophila* susceptibility to beta-lactam antibiotics (23). Also, our results support the use of the macrophage-*L. pneumophila* model to evaluate antimicrobial susceptibility testing of *L. pneumophila*.

Using this model, we have shown that several antibiotics, including many quinolone derivatives, inhibit monocyte-associated *L. pneumophila* growth. The role of these compounds in the treatment of human *Legionella* infections remains unclear, although their use as alternative agents in carefully selected patients seems possible.

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