Evaluation of Ceftaroline Activity versus Ceftriaxone against Clinical Isolates of *Streptococcus pneumoniae* with Various Susceptibilities to Cephalosporins in an *In Vitro* Pharmacokinetic/Pharmacodynamic Model

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Drug resistance in *Streptococcus pneumoniae*, a frequent pathogen in community-acquired pneumonia, is increasing. Ceftaroline (active metabolite of ceftaroline fosamil) is a broad-spectrum intravenous cephalosporin with activity *in vitro* against drug-resistant Gram-positive organisms. We investigated ceftaroline at 600 mg every 12 h (q12h) (maximum concentration of the free, unbound drug in serum [fC_{max}] is 15.2 μg/ml, and half-life [$T_{1/2}$] is 2.5 h) versus ceftriaxone at 1 g q24h ($fC_{max} = 23$ μg/ml, $T_{1/2} = 8$ h) against six clinical *S. pneumoniae* isolates in a one-compartment *in vitro* pharmacokinetic/pharmacodynamic 96-h model (starting inoculum of 10^7 CFU/ml). Differences in CFU/ml (at 24 to 96 h) were evaluated by analysis of variance with a Tukey's *post hoc* test. Bactericidal activity was defined as a $\geq$3 $\log_{10}$ CFU/ml decrease from the initial inoculum. Ceftaroline MICs were 0.06, 0.015, $\leq$0.008, 0.25, 0.25, and 0.5 μg/ml, and ceftriaxone MICs were 0.5, 0.25, 0.25, 4, 4, and 8 μg/ml for SP 1477, SP 669, SP 132, SP 211, SP 90, and SP 1466, respectively. Against the ceftaroline- and ceftriaxone-susceptible strain SP 1477, ceftaroline displayed sustained bactericidal activity (3 to 96 h, -5.49 $\log_{10}$ CFU/ml) and was significantly ($P \leq 0.012$) better than ceftriaxone (72 to 96 h, -2.03 $\log_{10}$ CFU/ml). Against the ceftriaxone-resistant strains, ceftaroline displayed sustained bactericidal activity at 96 h and was significantly better than ceftriaxone (SP211 [-5.91 $\log_{10}$ CFU/ml, $P \leq 0.002$], SP 90 [-5.26 $\log_{10}$ CFU/ml, $P \leq 0.008$], and SP1466 [-5.14 $\log_{10}$ CFU/ml, $P \leq 0.042$]). Ceftaroline was the more effective drug and displayed sustained bactericidal activity. Ceftaroline fosamil may provide a therapeutic option to treat ceftriaxone-resistant *S. pneumoniae* infections.

Community-acquired pneumonia (CAP) represents a serious health care issue, with mortality rates ranging from <1% in mild disease stages (pneumonia severity index risk classes I and II) to more than 30% in patients with severe CAP (pneumonia severity index risk class V) (21). CAP is the 6th leading cause of death in the United States and the leading cause of death from infectious disease (22).

Streptococcus pneumoniae is the most frequent pathogen isolated in CAP (15, 26). Although a recent study found a decrease in invasive pneumococcal disease during 2002 to 2008 compared to the incidence from 1999 to 2000, a significant increase in penicillin and cefotaxime resistance has been reported during the 10-year period (25). It has recently been estimated that more than 40% of strains are penicillin resistant in some regions of the United States (14). Similarly, in some European countries, strains of *S. pneumoniae* recovered from invasive disease in adults also demonstrated an increased antimicrobial resistance profile, with more than 15% of the isolates being resistant to cefotaxime in France and more than 20% being resistant to cefotaxime/ceftriaxone (CRO) in Spain (7, 23). In addition, the introduction of the heptavalent pneumococcal conjugate vaccine (PCV7) has been associated with the emergence of multidrug-resistant (MDR) serotypes, such as serotype 19A (13, 24). Therefore, in addition to the high mortality rate of pneumococcal infections, the emergence of MDR *S. pneumoniae* highlights the need for newer compounds exhibiting higher activity against MDR isolates.

Ceftaroline (CPT), the active metabolite of the prodrug ceftaroline fosamil, is a new and broad-spectrum cephalosporin that displays *in vitro* activity against methicillin-resistant *Staphylococcus aureus* (MRSA) and cephalosporin and penicillin-resistant *S. pneumoniae* (12, 18). Ceftaroline has demonstrated potent *in vitro* activity against bacteremia isolates of MRSA and penicillin-resistant *S. pneumoniae* recovered from patients with CAP (MIC$_{90}$s of 2 and 0.25 mg/liter, respectively) (20).

Resistance to β-lactam agents is mediated by successive alterations in essential penicillin binding proteins (PBPs). Unlike other β-lactams, ceftaroline displays *in vitro* activity against penicillin- and cephalosporin-resistant *S. pneumoniae*, as it maintains high affinity for PBP 2X mutants (8, 18, 19). Ceftaroline fosamil is approved for the treatment of acute bacterial skin and skin structure infections and community-acquired bacterial pneumonia caused by susceptible bacteria. Ceftaroline fosamil represents a potential option for treatment of pneumococcal infections caused by MDR *S. pneumoniae* isolates, although further study is needed.

The objective of the study was to investigate the *in vitro* activity of ceftaroline at a dosage of 600 mg every 12 h (q12h) against clinical isolates of *S. pneumoniae* using a well-established one-

compartment *in vitro* pharmacokinetic and pharmacodynamic (PK/PD) model.

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MATERIALS AND METHODS

Bacterial strains. Six clinical strains of *S. pneumoniae* (3 ceftriaxone susceptible [CRO-S] and 3 ceftriaxone resistant [CRO-R]) were evaluated (obtained from JMI Laboratories, North Liberty, IA). The *S. pneumoniae* isolate ATCC 49619 (quality control [QC] MIC range of 0.03 to 0.125 mg/liter for ceftriaxone and 0.008 to 0.03 mg/liter for ceftaroline) was used for quality control in all susceptibility testing.

Antimicrobial agents. Microbiologically active ceftaroline (CPT) (lot number FMD-CEF-035) was supplied by Forest Laboratories (New York, NY). Ceftriaxone was commercially purchased from Sigma-Aldrich (St. Louis, MO). Stock solutions of each antibiotic were prepared fresh daily.

Media. All susceptibility testing and *in vitro* PK/PD models were performed using Todd Hewitt broth (Difco Laboratories, Detroit, MI) with 0.5% yeast as previously described for experiments evaluating *S. pneumoniae* isolates (4). Colony counts and emergence of resistance were determined using Mueller-Hinton agar with 5% sheep blood without and with drug at 3× the baseline MIC, respectively.

Susceptibility testing. MICs were determined by a broth microdilution technique, using Todd-Hewitt broth supplemented with 0.5% yeast extract (medium used in PK/PD model) and an inoculum of 5×10^6 CFU/ml. MIC trays were incubated for 24 h at 37°C in 5% CO_2.

One-compartment *in vitro* PK/PD model. An *in vitro* PK/PD 96-h model consisting of a 210-ml 1-compartment glass chamber with multiple ports for the addition and removal of growth medium, delivery of antibiotics, and collection of samples was utilized to assess ceftaroline and ceftriaxone activities. The apparatus was prefilled with fresh medium, antibiotics were administered as boluses, and all experiments were performed in duplicate to ensure reproducibility. Prior to each experiment, lawns of overnight growth from three Mueller-Hinton agar plates supplemented with 5% lysed sheep blood were introduced into the one-compartment model system (yielding 10^7 CFU/ml) 30 min prior to each simulation to allow the microorganism to adapt to the medium. The model was placed in a room incubator at 37°C for the duration of the experiments. Peristaltic pumps (Masterflex; Cole-Parmer Instrument Company, Chicago, IL) were used to continually replace antibiotic-containing medium with fresh, antibiotic-free medium (at a rate simulating the plasma clearance and half-lives of the antibiotics). To maintain similar growth conditions for all tested regimens, the pump rate was set to the rate for the antibiotic with the fastest clearance (ceftaroline in this study). A second chamber was utilized for all experiments with ceftriaxone, and ceftriaxone was supplemented into this chamber to maintain the longer half-life (3). Simulated regimens included 600 mg intravenous (i.v.) ceftaroline every 12 h (maximum concentration of the free, unbound drug in serum [fC_{max}], 15.2 µg/ml [i.e., 80% of 19 µg/ml, based on 20% protein binding]; average half-life, 2.5 h) and 1 g i.v. ceftriaxone every 24 h (fc_{max}, 23 µg/ml [85% protein binding]; average half-life, 8 h) (1, 11).

Pharmacokinetic analysis. Antibiotic concentrations were determined from samples drawn from each model system at 0, 1, 2, 3, 6, 24, 27, 30, 48, 54, 72, and 96 h in duplicate. Samples were stored at −70°C until analysis. Ceftaroline and ceftriaxone concentrations were determined by bioassay using *Bacillus subtilis* ATCC 6633 and *Escherichia coli* ATCC 25922. Blank 1/4-in. disks were spotted with 10 µl of the standards (2.5, 10, and 40 µg/ml of ceftaroline or 5, 10, and 20 µg/ml of ceftriaxone) or samples. Each standard was tested in duplicate by placing the disk on Mueller-Hinton agar plates, which were preswabbed with a 0.5 McFarland suspension of the test organism. Plates were incubated at 37°C for 18 to 24 h, at which time the zone sizes were measured. This assay was linear over the range tested ($r^2 = 0.95$; between-day and intraday coefficient of vari-

ation for low, medium, and high standards, ≤12.8%). Similar to other cephalosporins, the PK/PD index that best correlates with efficacy for ceftaroline is free-drug percentage of time above the MIC ($r^2 = 83$ to 88%) (2). Ceftaroline and ceftriaxone free-drug peak and trough concentrations, times above the MIC (or multiples of the MIC), and half-lives were calculated using concentration-time plots of the model samples. The area under the concentration-time curve from 0 to 24 h was calculated by using the linear trapezoid method and the PKANALYST program (version 1.10; MicroMath Scientific Software, Salt Lake City, UT).

Pharmacodynamic analysis. Samples (approximately 1.5 ml each) from each model were collected at 0, 3, 6, 24, 27, 30, 48, 54, 72, and 96 h. Samples were then serially diluted in 0.9% sodium chloride. Bacterial counts were determined by drop plating 10-µl amounts of each diluted sample on Mueller-Hinton agar supplemented with 5% blood. In order to minimize antibiotic carryover, all samples were diluted at least 10-fold before plating or plated following vacuum filtration (direct sample of 1 ml washed through a 0.45-µm-pore-size filter with normal saline) for dilutions with predicted concentrations close to or greater than the MIC for the tested organism. Plated samples were incubated at 37°C with 5% CO_2 for 24 h, at which point colony counts were determined. The limit of detection for this method of colony count determination is 1 $\log_{10}$ CFU/ml. *In vitro* time-kill curves were determined by plotting mean colony counts ($\log_{10}$ CFU/ml) versus time. Bactericidal activity (99.9% kill) was defined as a ≥3 $\log_{10}$ CFU/ml reduction in colony count from the starting inoculum using linear regression if the r^2 was ≥0.95 or by visual inspection.

Detection of resistance. Samples (100 µl each) from the 96-h time point were plated on the day of collection onto Mueller-Hinton agar supplemented with 5% blood containing an antibiotic concentration (of the respective model run) of 3 times the MIC for each organism. Plates were incubated for up to 48 h at 37°C with 5% CO_2 in order to monitor the development of resistance and visually inspected for the growth of resistant subpopulations after 24 and 48 h of incubation. The MIC for each colony recovered onto drug-containing plates was determined by the broth microdilution method as described above.

Statistical analysis. Differences in outcome ($\log_{10}$ CFU/ml) between regimens (including growth control) at 24, 48, 72, and 96 h were determined using one-way analysis of variance with Tukey's *post hoc* test. For all experiments, a P value of ≤0.05 was considered indicative of statistical significance. All statistical analyses were performed using SPSS (version 18.0; SPSS, Inc., Chicago, IL).

RESULTS

MICs and serotypes for the six *S. pneumoniae* isolates studied are displayed in Table 1. The pharmacokinetic parameters achieved (average ± standard deviation) for ceftaroline (half-life [$T_{1/2}$], 2.38 ± 0.3 h; maximum concentration of the free, unbound drug in serum [fC_{max}], 15.2 ± 2 µg/ml; fC_{min}, 0.46 ± 0.08 µg/ml) and for ceftriaxone ($T_{1/2} = 8.2 ± 1.2$ h, $fC_{max} = 19.6 ± 1.5$ µg/ml, $fC_{min} = 2.54 ± 0.34$ µg/ml) were well matched with the targeted values. The pharmacodynamic parameters achieved are also displayed in Table 1. As can be seen, ceftaroline free time above the MIC ($fT >$ MIC) ranged from 97.7 to 100% and $fT > 4×$ MIC ranged from 59 to 100%. For the CRO-S strains SP 1477, SP 669, and SP 132, ceftriaxone $fT >$ MIC and $fT > 4×$ MIC were 100%. In contrast, the ceftriaxone $fT >$ MIC and $fT > 4×$ MIC achieved for CRO-R SP 1466 (CRO MIC, 8 µg/ml) were 44% and 0%, respectively. For CRO-R SP 211 and SP 90 (CRO MIC 4 µg/ml), the ceftriaxone $fT >$ MIC and $fT > 4×$ MIC achieved were 78.4% and 10%.

The activity of ceftaroline and ceftriaxone against the six isolates tested is displayed in Fig. 1. Against the CRO-R strains SP 1466, SP 211, and SP 90, ceftriaxone failed to maintain bactericidal activity at 96 h (Fig. 1A to C). In contrast, ceftaroline displayed

TABLE 1 MICs for *Streptococcus pneumoniae* isolates and analysis of pharmacokinetic parameters achieved

Drug and isolate (serotype)	MIC (μg/ml)	ΔLog$_{10}$ CFU/ml[a]	Time to 99.9% reduction in CFU/ml[b]	% of dosing interval at $fT >$:		
				MIC	2× MIC	4× MIC
Ceftaroline						
SP 1466 (19F)	0.5	−5.14	1.99	97.7	77.9	59
SP 211 (19A)	0.25	−5.91	4.28	100	97.7	77.9
SP 90 (35B)	0.25	−5.26	2.15	100	97.7	77.9
SP 1477 (6C)	0.06	−5.49	2.15	100	100	100
SP 669 (7F)	0.015	−6.09	1.57	100	100	100
SP132 (3)	≤0.008	−5.94	1.44	100	100	100
Ceftriaxone						
SP 1466 (19F)	8	−2.25	NA	44	10	0
SP 211 (19A)	4	0.36	NA	78.4	44	10
SP 90 (35B)	4	−2.35	NA	78.4	44	10
SP 1477 (6C)	0.5	−2.03	NA	100	100	100
SP 669 (7F)	0.25	−6.00	1.86	100	100	100
SP132 (3)	0.25	−5.79	1.86	100	100	100

[a] ΔLog$_{10}$ CFU/ml is the change in log$_{10}$ CFU/ml from the starting inoculum as assessed at 96 h.
[b] Times to 99.9% reduction in CFU/ml counts relative to starting inoculum are indicated for those isolates showing sustained bactericidal activity (i.e., ≥99.9% reduction in CFU/ml as assessed at 96 h). NA, not applicable as sustained bactericidal activity was not observed by 96 h.

rapid (Table 1) and sustained bactericidal activity against the three CRO-R strains (Fig. 1). Against CRO-S SP 1477 (CPT MIC = 0.06 μg/ml, CRO MIC = 0.5 μg/ml) ceftaroline displayed rapid and sustained bactericidal activity, while regrowth occurred periodically with ceftriaxone between 24 h and 96 h (Fig. 1D). Ceftaroline was significantly more active and sustained than ceftriaxone in decreasing colony counts from 72 to 96 h against CRO-R SP 1466 ($P \leq 0.042$), SP 211 ($P \leq 0.002$), and SP 90 ($P \leq 0.008$) and against CRO-S SP 1477 ($P \leq 0.012$). As for SP 1477, ceftriaxone treatment of SP 211, SP 90, and SP 1466 resulted in periodic regrowth and killing over the 24- to 96-h dosing period, unlike the sustained bactericidal activity observed for ceftaroline. Against the 2 CRO-S strains, SP 669 and SP 132, both ceftaroline and ceftriaxone displayed rapid (Table 1) and sustained bactericidal activity (Fig. 1E and F). No mutant was recovered for either ceftaroline or ceftriaxone at 3× MIC at 96 h.

DISCUSSION

In this study, we evaluated the *in vitro* activity of ceftaroline versus that of ceftriaxone against six clinical isolates of *S. pneumoniae* of various serotypes and degrees of susceptibility to ceftriaxone. As would be expected, ceftaroline and ceftriaxone both displayed rapid bactericidal activity against two of the CRO-S strains, SP 669 and SP 132. A 3-log$_{10}$ reduction in CFU/ml was achieved at 3 h, and a maximal effect of a 6-log$_{10}$ reduction in CFU/ml was achieved by the end of the experiment. This is consistent with both ceftaroline and ceftriaxone exhibiting time above the MIC, 2× MIC, and 4× MIC of 100% of the dosing interval for both organisms. The activities of ceftaroline and ceftriaxone against the third cephalosporin-susceptible strain (SP 1477) are interesting, as this organism has slightly higher MIC values and both antibiotics were above 4× the MIC for 100% of the dosing interval. The ceftaroline kill kinetics were slightly slower for this strain than for SP 669 and SP 132 but were still bactericidal at 3 h and at detection limits by 6 h. The decrease in CFU counts was maintained for the 96 h of the experiment. Ceftriaxone also reduced counts to detection limits; interestingly, this was followed by a bactericidal regrowth pattern over the duration of the 96 h. This pattern was also observed with

CRO for the 3 CRO-R strains. For the two isolates with CRO MICs of 4 μg/ml, the times above the 2× and 4× MIC were approximately 44 and 10% of the dosing interval. For these two isolates (SP 90 and SP 211), ceftriaxone decreased the inoculum counts but failed to reach detection limits, unlike with SP 1477, and regrowth occurred to a greater extent than with SP 1477. The largest bactericidal regrowth pattern with ceftriaxone was observed against SP 1466 (CRO MIC = 8 μg/ml) and corresponded to free times above the 2× and 4× MIC of 10% and 0%. Against the CRO-R strains, ceftaroline also displayed rapid and sustained bactericidal activity, with times above the MIC of 97 to 100% of the dosing interval.

The results from this *in vitro* study support the results of a previous *in vivo* study that examined the efficacy of both ceftaroline and ceftriaxone in an immunocompetent pneumococcal pneumonia rabbit model against three strains: penicillin susceptible and CRO-S, penicillin intermediate and CRO-S, and penicillin resistant and CRO-R (6). In that study, the inoculum decreases in the lungs at 48 h for the two CRO-S strains were over 6 log$_{10}$ CFU/g for both ceftaroline and ceftriaxone. For the CRO-R strain, ceftaroline retained substantial bactericidal activity in the lung while ceftriaxone produced only a small decrease in log$_{10}$ CFU/g that was not statistically different from the results for controls. Ceftaroline total-drug and free-drug times above the MIC of 40% and 25% were associated with complete eradication. Total drug time above the MIC for ceftriaxone did not appear to predict activity, with 100% $fT >$ MIC failing to achieve eradication in the majority of animals. The findings by Croisier-Bertin et al. (4) appear similar to those of our current study in which ceftriaxone time above the MIC or multiples of the MIC did not appear to fully explain the activity in the CRO-R strains and in SP 1477.

The limitations of this study include the short study duration of 4 days as opposed to 5 to 7 days for clinical treatment of community-acquired pneumonia. Additionally, the growth conditions for *S. pneumoniae* in the *in vitro* PK/PD model are different from those in the human lung and therefore give both tested antibiotics an artificial advantage. As the *in vitro* PK/PD model uti-
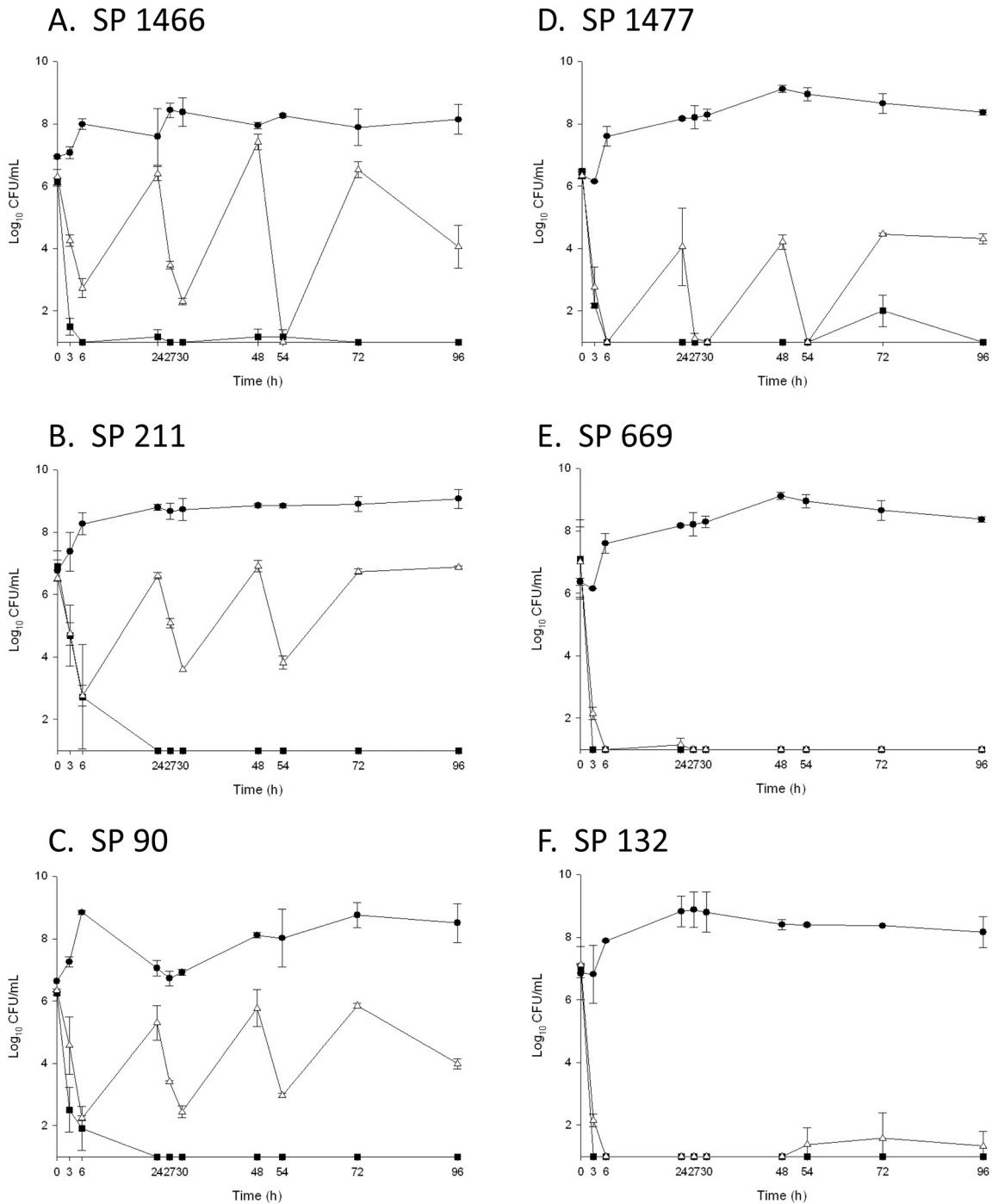
FIG 1 *In vitro* killing in the one-compartment pharmacokinetic/pharmacodynamic model. Filled circles, growth control; filled squares, 600 mg i.v. ceftaroline q12h; open triangles, 1 g i.v. ceftriaxone q24h.

lized in this study was a one-compartment model, the target concentrations were those of the serum and did not take into account time or extent of penetration into the lung tissue. Additionally, only three CRO-R strains were tested in this study (such strains are relatively rare clinically).

The treatment of community-acquired pneumonia will continue to represent a clinical challenge as drug resistance is continuing to increase. Recent analysis of amoxicillin-clavulanate, peni-

cillin, and ceftriaxone susceptibilities in *S. pneumoniae* isolates from 1998 to 2009 revealed increasing resistance against all three antibiotics to more than 10% of isolates (16). Ceftaroline fosamil has been shown to be effective and well tolerated in the treatment of community-acquired pneumonia in two large, randomized trials, FOCUS I and FOCUS II (NCT00621504 and NCT00509106) (9, 10, 17). Ceftaroline had higher clinical cure rates than ceftriaxone for CAP caused by *S. pneumoniae* in FOCUS I (88.9% ver-

sus 66.7%) and FOCUS II (83.3% versus 70.0%) (10, 17). In these two trials, however, only one isolate with intermediate susceptibility to penicillin was recovered (5). There may, therefore, be some clinical relevance associated with ceftriaxone-susceptible strains, such as SP 1477, in which ceftriaxone fails to maintain bactericidal activity and is significantly worse than ceftaroline. At this time, therefore, there is limited clinical data on the utility of ceftaroline fosamil to treat community-acquired pneumonia caused by these β-lactam-resistant pneumococcal strains. The combination of the *in vitro* data from this study, the *in vivo* data from the rabbit pneumonia model, and the overall safety and efficacy in clinical trials on community-acquired pneumonia support the clinical use of ceftaroline fosamil and its potential to treat pneumonia infections caused by CRO-resistant *S. pneumoniae.*

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