Original Article

Pharmacodynamic Evaluation of Oral Amoxicillin, Amoxicillin/Clavulanate, Cefditoren, and Azithromycin Against *Streptococcus pneumoniae*-Caused Respiratory Tract Infections: A Monte Carlo Simulation

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Objective: To estimate the probability of oral amoxicillin, amoxicillin/clavulanate, cefditoren, and azithromycin achieving pharmacokinetic/pharmacodynamics [PK/PD] targets against *Streptococcus pneumoniae* in Thais.

Materials and Methods: A Monte Carlo simulation of 10,000 *S. pneumoniae* infected patients was conducted. Steady-state serum drug concentration-time profiles were created to determine the probability of target attainments at each minimum inhibitory concentration [MIC]. The MICs of 100 *S. pneumoniae* isolates were used. The cumulative fraction of responses [CFRs] were calculated to provide a single estimate of the probability of achieving PK/PD targets for dosage regimens against *S. pneumoniae* populations. A CFR of more than 90% was required.

Results: One third of *S. pneumoniae* isolates were susceptible to penicillin. The $MICs_{90}$ of amoxicillin-based regimens, cefditoren, and azithromycin against *S. pneumoniae* were 2, 0.5, and 128 μg/ml, respectively. The probability of achieving PK/PD targets of all amoxicillin-based regimens and cefditoren 200 mg every eight hours were more than 90% for MIC_{90} values, while that of azithromycin 500 mg daily was 0%. All amoxicillin-based regimens, cefditoren 200 mg every eight hours, and cefditoren 400 mg every 12 hours achieved the CFR target, while azithromycin did not.

Conclusion: Based on the simulations, amoxicillin-based regimens or high-dose cefditoren provided a greater likelihood of achieving optimal PK/PD targets in adults with *S. pneumoniae*-related respiratory tract infections [RTIs].

Keywords: *Streptococcus pneumoniae*, Amoxicillin-based regimens, Cefditoren, Azithromycin, Pharmacokinetics/pharmacodynamics, Monte Carlo simulation

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Streptococcus pneumoniae is Gram positive diplococci causing both invasive pneumococcal diseases [IPDs] (such as bacterial meningitis, primary bacteremia, endocarditis, bone and joint infections, and other invasive infections) and non-invasive pneumococcal diseases [non-IPDs] (such as otitis media infections, sinusitis, bronchitis, and pneumonia). Non-IPDs are very common in community acquired infections. Their clinical presentations are upper and lower respiratory tract infections [RTIs][(1)].

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Beta-lactams, e.g., aminopenicillins and cephalosporins, and macrolides are recommended medications for treating *S. pneumoniae*-related RTIs. However, previous studies across the globe have shown an increase in the resistance rate of these medications. A study from the United States revealed that susceptibility rates of *S. pneumoniae* in non-meningitis diseases to oral penicillin, amoxicillin-based, and erythromycin were 56.3%, 81.1%, and 55.2%, respectively[(2)].

The Asian Network for Surveillance of Resistant Pathogens [ANSORP], a prospective trial that collected 2,184 clinical *S. pneumoniae* isolates from 60 centers in 11 Asian countries between 2008 and 2009, revealed that 4.6% and 0.7% of the collected isolates were

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penicillin non-susceptible *S. pneumoniae* [PNSP] (minimum inhibitory concentration [MIC] ≥4 µg/ml) and penicillin resistant (MIC ≥8 µg/ml), respectively. From the ANSORP 2000-2001 to the ANSORP 2008-2009, the prevalence of *S. pneumoniae* resistance to cefuroxime has increased from 32.4% to 53.9%. The average prevalences of *S. pneumoniae* resistance to erythromycin, azithromycin, and clarithromycin were 72.7%, 69.7%, and 68.9%, respectively[3]. However, the prevalences of PNSP and *S. pneumoniae* resistance to erythromycin in Thailand were 39.3% and 32.3%, respectively[4].

As mentioned above, the prevalence of *S. pneumoniae* resistance has been increasing worldwide, including in Thailand. This could lead to an increased use of other broad-spectrum antimicrobials. It is very important to use the appropriate drug and antimicrobial regimen to prevent *S. pneumoniae* resistance. To predict the pharmacodynamic-based dosage regimens and the clinical effectiveness of a variety of antimicrobials, this study was conducted using a Monte Carlo simulation to estimate the probabilities of attaining the desired percentage of time over MIC [%T>MIC] of oral amoxicillin, amoxicillin/clavulanate, and cefditoren, and the area under the curve per MIC ratio [AUC/MIC] of azithromycin for the treatment of *S. pneumoniae*-related RTIs in Thailand.

Material and Methods

Microbiology

The authors collected a hundred *S. pneumoniae* isolates from respiratory tract infected patients visiting Siriraj Hospital, a university hospital located in Bangkok, Thailand, in 2011. The broth microdilution method was performed to evaluate the MICs of oral antimicrobials against *S. pneumoniae* according to the Clinical and Laboratory Standards Institute [CLSI] 2009 guidelines[5]. Interpretive criteria for susceptibility of *S. pneumoniae* to amoxicillin, amoxicillin/clavulanate and azithromycin were based on the guidelines of CLSI 2011[6], and of the US Food and Drug Administration [FDA] for cefditoren[7].

Antimicrobials and dosage regimens

Dosage regimens for the included antimicrobials were based on RTI guidelines and the labeling recommendations of the Thai FDA. Drug regimens included amoxicillin 500 mg every eight hours, amoxicillin 500 mg every six hours, amoxicillin/clavulanate 500/125 mg every eight hours, amoxicillin/clavulanate 875/125 mg every 12 hours, amoxicillin/clavulanate 875/125 mg every eight hours, cefditoren 200 mg every 12 hours, cefditoren 200 mg every eight hours, cefditoren 400 mg every 12 hours, and azithromycin 500 mg every 24 hours[8-12].

Pharmacokinetic data

Pharmacokinetic data were collected from previous studies[13-16]. Where appropriate, pharmacokinetic parameters for each selected dose and dosing interval were extracted. Specific variables included the absorption rate constant (k_a), the elimination rate constant (k_e), and the apparent volume of distribution corrected for bioavailability (Vd/F), for the first-order, one-compartment model. The oral clearance (CLt/F), volume of distribution of the central compartment (Vc/F), intercompartment clearance (Q/F), volume of distribution of the peripheral compartment (Vt/F), and k_a were included in the first-order, two-compartment model.

Monte Carlo simulation

A Monte Carlo simulation of a cohort of 10,000 infected patients (Oracle Crystal Ball, 2012, Oracle, USA) was conducted to create steady-state drug concentration-time profiles and to estimate the T>MIC for amoxicillin, amoxicillin/clavulanate, and cefditoren, and the AUC/MIC ratio for azithromycin of each regimen. The one-compartment model was used to generate the pharmacokinetic parameters of amoxicillin, amoxicillin/clavulanate, and cefditoren. The two-compartment model was used to generate the pharmacokinetic parameters of azithromycin. The number of patients who achieved the pharmacokinetic/pharmacodynamic [PK/PD] targets at each MIC was calculated and divided by 10,000 to determine the probability of target attainment [PTA] at each MIC dilution. The PK/PD target achievements were defined as a T>MIC more than 40% for amoxicillin-based regimens, a T>MIC more than 50% for cefditoren, and an AUC/MIC ratio greater than 25 for azithromycin[17-21].

The cumulative fraction of responses [CFRs] for each regimen against the population of *S. pneumoniae* were calculated by the PTA at each MIC, and were multiplied by the percentage of organisms in the distribution of the respective MIC. All values were summed to provide a single estimate of the probability of achieving the PK/PD targets for the dose administration regimens against the population of *S. pneumoniae*. A successful bacterial eradication was defined as a PTA and CFR >90%.

Ethical approval

The study was approved by the Institutional Review Board of Naresuan University, based on the Declaration of Helsinki (study protocol number: NU-IRB 293/56).

Results

Microbiology

The *S. pneumoniae* strains were divided into three groups, penicillin-susceptible *S. pneumoniae* [PSSP], penicillin-intermediate *S. pneumoniae* [PISP], and penicillin-resistant *S. pneumoniae* [PRSP], based on the breakpoints of oral penicillin V. The percentages of PSSP, PISP, and PRSP were 35%, 35%, and 30%, respectively. The MIC_{90} values for the amoxicillin-based regimens, cefditoren, and azithromycin were 2 (0.06 to 4), 0.5 (0.03 to 1), and 128 (0.03 to 128) µg/ml, respectively (Table 1). The amoxicillin-based regimens showed the highest in vitro activity against *S. pneumoniae*, with a susceptibility rate of 93%, followed by cefditoren (48%) and azithromycin (40%).

The amoxicillin-based regimens and cefditoren showed good activity against PSSP strains (100% and 94.29%, respectively), while azithromycin showed a susceptibility rate of 62.86%. As for the PISP strains, the amoxicillin-based regimens also showed good activity, with susceptibility rates of 100%, but cefditoren and azithromycin showed poor activity (34.28% and 42.86%, respectively). About 76.67% of the PRSP strains were susceptible to the amoxicillin-based regimens. Cefditoren and azithromycin were low active against PRSP, with susceptibility rates of 10%.

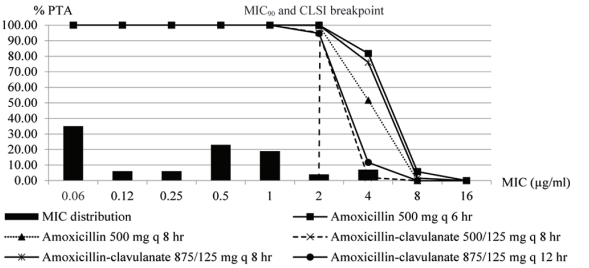

Figure 1. PTA percentages for amoxicillin and amoxicillin/clavulanate regimens for each MIC.

Monte Carlo simulations

PTA: The PTA percentages for amoxicillin and amoxicillin/clavulanate are at Figure 1. The probability of achieving the PK/PD target for the amoxicillin-based regimens was more than 90% for the MIC_{90} values and susceptibility breakpoints (CLSI breakpoint 2011). Amoxicillin 500 mg every six hours showed the highest PTA percentage (100%), followed by amoxicillin/clavulanate 875/125 mg every eight hours (99.96%), amoxicillin 500 mg every eight hours (99.75%), amoxicillin/clavulanate 500/125 mg every eight hours (95.07%), and amoxicillin/clavulanate 875/125 mg every 12 hours (94.71%).

Figure 2 shows the probability of achieving the PK/PD targets for the cefditoren serum concentrations. The probability of attaining the PK/PD targets for all of the cefditoren-based regimens was 100% for the US FDA breakpoint. Cefditoren 200 mg every eight hours showed the highest PTA percentage of 95.17% for the MIC_{90} value, while the PTA percentages for the MIC_{90} value for cefditoren 400 mg every 12 hours and

Table 1. Susceptibility of *S. pneumoniae* isolates (n = 100) to various antimicrobial agents from patients with RTIs

Drugs	MIC (µg/ml)	MIC_{90} (µg/ml)	Number of *S. pneumoniae* isolates, n (%)		
			Susceptible	Intermediate	Resistant
Amoxicillin-based (n = 100)	0.06 to 4	2	93 (93.00)	7 (7.00)	0 (0.00)
PSSP (n = 35)	0.06	0.06	35 (100)	0 (0.00)	0 (0.00)
PISP (n = 35)	0.12 to 0.5	0.5	35 (100)	0 (0.00)	0 (0.00)
PRSP (n = 30)	1 to 4	4	23 (76.67)	7 (23.33)	0 (0.00)
Cefditoren (n = 100)	0.03 to 1	0.5	48 (48.00)	23 (23.00)	29 (29.00)
PSSP (n = 35)	0.03 to 1	0.06	33 (94.29)	0 (0.00)	2 (5.71)
PISP (n = 35)	0.12 to 1	0.5	12 (34.28)	15 (42.86)	8 (22.86)
PRSP (n = 30)	0.12 to 0.5	0.5	3 (10.00)	8 (26.67)	19 (63.33)
Azithromycin (n = 100)	0.03 to 128	128	40 (40.00)	13 (13.00)	47 (47.00)
PSSP (n = 35)	0.03 to 128	128	22 (62.86)	0 (0.00)	13 (37.14)
PISP (n = 35)	0.03 to 128	128	15 (42.86)	6 (17.14)	14 (40.00)
PRSP (n = 30)	0.06 to 128	128	3 (10.00)	7 (23.33)	20 (66.67)

RTIs = respiratory tract infections; MIC = minimum inhibitory concentration; PSSP = penicillin-susceptible *S. pneumoniae*; PISP = penicillin-intermediate *S. pneumoniae*; PRSP = penicillin-resistant *S. pneumoniae*

Susceptibility criteria of *S. pneumoniae* according to CLSI 2011 for amoxicillin-based regimens and azithromycin are ≤2 and 0.5 µg/ml, respectively. Proposed breakpoints in the US FDA indicating susceptibility to cefditoren is ≤0.125 µg/ml for *S. pneumoniae.*

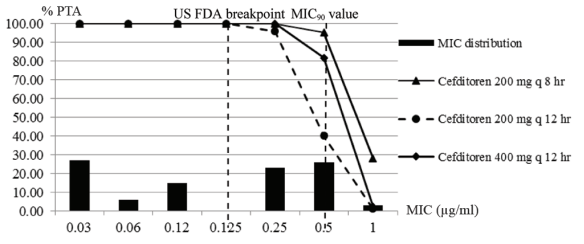

Figure 2. PTA percentages for cefditoren regimens at each MIC.

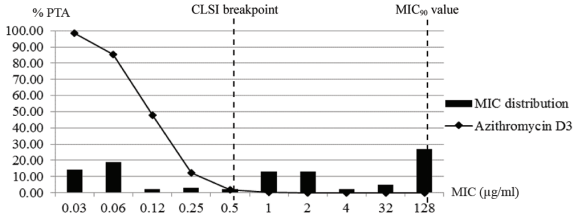

Figure 3. PTA percentage for azithromycin 500 mg every 24 hours for 3 days at each MIC.

of cefditoren 200 mg every 12 hours were 81.73% and 40.11%, respectively.

The probability of achieving the PK/PD target for azithromycin 500 mg every 24 hours for three days was 1.71% and 0% for the susceptibility breakpoints (CLSI breakpoint 2011) and the MIC_{90} value, respectively (Figure 3).

CFRs: The CFRs of the antimicrobial regimens against *S. pneumoniae* are at Table 2. Amoxicillin 500 mg every six hours obtained the highest CFR. All of the amoxicillin-based and the cefditoren regimens (200 mg every eight hours, and 400 mg every 12 hours) achieved a PK/PD exposure of greater than 90% of the patients, while the %CFR of cefditoren 200 mg every 12 hours was 80.50%. Azithromycin had the lowest %CFR (31.40%).

Table 2. Cumulative fraction of response for antimicrobial regimens against *S. pneumoniae*

Drugs	Dosages	PK/PD targets	% CFRs
Amoxicillin	500 mg q 8 hours	T>MIC >40%	96.61
	500 mg q 6 hours		98.72
Amoxicillin/ clavulanate	500/125 mg q 8 hours		92.94
	875/125 mg q 12 hours		93.61
	875/125 mg q 8 hours		98.32
Cefditoren	200 mg q 12 hours	T>MIC >50%	80.50
	200 mg q 8 hours		96.59
	400 mg q 12 hours		92.31
Azithromycin	500 mg q 24 hours	AUC/MIC >25	31.40

PK/PD = pharmacokinetic/pharmacodynamics; CFRs = cumulative fraction of responses; q = every; T>MIC = time over minimum inhibitory concentration; AUC/MIC = area under the curve per minimum inhibitory concentration

Discussion

The recent increase in the resistance of *S. pneumoniae* to oral antimicrobial agents has resulted in the need to re-evaluate treatment options for RTIs. Many of them have decreased activity against *S. pneumoniae* isolates. In this study, the impacts of the PK/PD profiles of oral amoxicillin, amoxicillin/clavulanate, cefditoren, and azithromycin on the treatment of RTIs from *S. pneumoniae* in Thailand were investigated.

In considering the MIC values of *S. pneumoniae* to penicillin, the authors found a high proportion of PNSP (65%). This result is similar to the results of a survey of antibiotic resistance [SOAR] 2012 to 2014 in Thailand, India, South Korea, and Singapore, with a 51% proportion of PNSP, according to the CLSI[22]. However, when considering the MIC values of *S. pneumoniae* to amoxicillin-based regimens, the authors found that most *S. pneumoniae* were susceptible to an amoxicillin-based regimen (93%), while an intermediate resistance were found to the amoxicillin-based regimens (MIC 4 µg/ml) and to the amoxicillin-based regimens (MIC ≥8 µg/ml) at the rate of 7% and 0%, respectively. All of the PSSP and PISP strains were still susceptible to the amoxicillin-based regimens, and the MIC_{90} values were lower than the susceptible breakpoint (≤2 µg/ml), while the PRSP were susceptible to the amoxicillin-based regimens at the rate of 76.67%. These results are consistent with the SOAR study, in which amoxicillin-based regimens had a 97.1% susceptibility (the MIC_{90} values were 1 µg/ml)[22]. These results might be explained by their pharmacokinetic advantages, such as a better absorption (80%, 60% to 73%), a longer half-life (1.2 hours, 0.5 hours), and a lower protein binding (17%, 65%) than penicillin V[23]. All of these pharmacokinetic profiles contribute to a higher sustained level than penicillin V. In addition, the in vivo study showed that the alteration of the penicillin-binding protein [PBP] 2x and PBP2b appeared to be the predominant changes in the PISP strains, and the alteration of the PBP1a, PBP2x, and PBP2b appeared to correlate with the PRSP strains. However, amoxicillin showed more affinity to these PBPs, which might explain the improved activity of amoxicillin relative to penicillin against many PISP strains. The affinity of amoxicillin for PBP2b decreased for the PISP and PRSP strains, but the affinity of this agent for PBP1a and PBP2x did not decrease for most PISP strains, in agreement with the amoxicillin MICs (0.125 µg/ml) for some PISPs being lower than that for the penicillin MICs (0.5 to 1 µg/ml)[24].

Our Monte Carlo simulation found that all amoxicillin-based regimens provided ≥90% PTA for strains with MIC values ≤2 µg/ml, where the CLSI breakpoint and MIC_{90} value of *S. pneumoniae* in this study is 93% susceptible. However, the PTA percentage fell rapidly when the MIC value rose to 4 µg/ml. This is the first Monte Carlo simulation study to report the PTA percentages of amoxicillin-based regimens in adults. However, in the pharmacodynamics studies, in which the concentrations measured in adults following the oral administration of either 500/125 mg every eight hours or 875/125 mg every 12 hours of amoxicillin-clavulanate were simulated, the T>MIC of various amoxicillin-based regimens in strains with MICs values ≤2 µg/ml were 43% and 40%, respectively[19]. In considering the MIC_{90} value of *S. pneumoniae* to the amoxicillin-based regimens in the present study, with an MIC_{90} value of 2 µg/ml, the authors found that the lowest daily dose of amoxicillin-based regimens in this study (500 mg every eight hours) was still appropriate for empirical therapy for *S. pneumoniae*-related RTIs. The coverage included PISP and PRSP isolates, of which 100% and 76.67% had MICs values ≤2 µg/ml. This study provides further support to the CLSI recommendation that the susceptibility breakpoint for amoxicillin-based regimens should be MIC values ≤2 µg/ml[6,25].

Based on the pharmacodynamics simulation that considered treatment according to the overall prevalence of pathogens, the amoxicillin-based regimens achieved an optimal CFR against *S. pneumoniae* of more than 90%. These results were consistent with a previous Monte Carlo simulation study, in which amoxicillin 500 mg every eight hours and amoxicillin/clavulanate 500/125 mg every eight hours achieved over a 90% CFR against *S. pneumoniae*-related RTIs, while amoxicillin/clavulanate 875/125 mg every 12 hours achieved an 88.2% CFR with a more conservative pharmacodynamics profile (50% T>MIC for amoxicillin-based regimens)[26]. In general, a time above the MIC of greater than 40% was required to achieve an 85% to 100% bacteriological cure rate[18]. The findings above demonstrated that amoxicillin is still the drug of choice for the empirical therapy of *S. pneumoniae*-related RTIs.

In this study, only 48% of the *S. pneumoniae* isolates were susceptible to cefditoren. The majority of the PSSP isolates were susceptible to cefditoren (94.29%), while the PISP and PRSP isolates were susceptible to cefditoren at the rate of 34.28% and 10%, respectively with MIC_{90} values of 0.5 µg/ml. The results of this study were different from a report of the in vitro activities of cefditoren against major respiratory tract pathogens from 11 Asian countries. There were 602 isolates of *S. pneumoniae* (53.0% PNSP), of which the majority of *S. pneumoniae* isolates (98.8%) were susceptible to cefditoren (susceptibility breakpoint of ≤2 µg/ml), with MIC_{50} and MIC_{90} values of ≤0.06 µg/ml and 1 µg/ml, respectively. Cefditoren was also active against PRSP isolates, although the resistance rate was 3.5% and the MIC_{90} value was 1 µg/ml[27]. The different results might be explained from there being no breakpoint for cefditoren, as defined by CLSI. However, as the previous study had an MIC_{90} value higher than that in the present study (1 and 0.5 µg/ml, respectively), it is likely to have a higher rate of *S. pneumoniae* resistance to cefditoren than the present study using the same breakpoint.

The probability of attaining the PK/PD target for all cefditoren-based regimens was more than 90% for an MIC value of ≤0.125 µg/ml (US FDA breakpoint). Cefditoren 200 mg every eight hours could cover strains with an MIC value of ≤0.5 µg/ml, while cefditoren 200 mg every 12 hours and cefditoren 400 mg every 12 hours could cover strains with an MIC value of ≤0.25 µg/ml. These results were different from a previous pharmacodynamics study, in which a Monte Carlo simulation was performed using data from healthy volunteers who were given a single dose of cefditoren 400 mg, administered orally after a meal. Considering the target attainment of a time above the MIC of ≥40%, cefditoren covered strains with MIC values ≤0.5 µg/ml in the case of total serum concentration (96.91%)[28]. The different results may be explained by the different PK/PD targets, with a PK/PD target of more than 50% of T>MIC for cefditoren being used for the present study. However, *S. pneumoniae* was treated with oral cephalosporin in a thigh infection model; both reduction and survival in colony-forming units were maximized when T>MIC was maintained at 50%[29]. These findings are consistent with clinical data in patients receiving oral cephalosporin for otitis media, with a time above the MIC of greater than 50% being associated with maximal microbiological eradication[18]. Therefore, all regimens of cefditoren should be considered when cefditoren the MIC is ≤0.25 µg/ml. It may be necessary to maximize the daily dosing frequency to 200 mg every eight hours when the MIC value increases to 0.5 µg/ml. When considering MIC_{90} of *S. pneumoniae* for cefditoren in the present study, with MIC_{90} values of 0.5 µg/ml, cefditoren 200 mg every eight hours is appropriate for

the empirical therapy of *S. pneumoniae*-related RTIs, at least until susceptibilities for the organism are known. Considering the %CFR for cefditoren, cefditoren 200 mg every eight hours and cefditoren 400 mg every 12 hours achieved an optimal CFR against *S. pneumoniae* of more than 90%, while cefditoren 200 mg every 12 hours resulted in 80.5%. The findings demonstrated that the properties of cefditoren are related to time-dependent killing activity, and that the more frequent administration of cefditoren at a slightly lower dose provided a higher microbial eradication rate than a less frequent but higher-dose regimen. Therefore, empirical therapy with cefditoren 200 mg every eight hours for *S. pneumoniae*-related RTI patients should be recommended, due to the highest probabilities of *S. pneumoniae* eradication. These results are consistent with the Thai FDA recommendations.

Regarding the breakpoint for cefditoren, no breakpoint as defined by the CLSI was established. The PK/PD data suggested that the susceptibility breakpoint of cefditoren should be within the range of ≤0.12 to ≤0.5 µg/ml[28]. The US FDA approved the breakpoint in more conservative way (≤0.125 µg/ml). Considering the susceptibility breakpoint using PK/PDs for cefditoren, the MIC breakpoint should be ≤0.25 µg/ml, which is different from the susceptibility breakpoint recommended by the US FDA. The results of this study were consistent with a previous report of in vitro activities of cefditoren against 300 *S. pneumoniae* isolates. If penicillin-resistant pneumococci are to be considered not susceptible to cefditoren, the tentative MIC breakpoints for cefditoren of ≤0.25 µg/ml for susceptible and ≥1 µg/ml for resistant could be selected. With those breakpoints, all PSSPs were susceptible to cefditoren, and the PISPs were mostly susceptible to cefditoren (85%)[30]. Therefore, the susceptibility breakpoint for cefditoren as recommended by the US FDA should be increased to ≤0.25 µg/ml, for all cefditoren regimens can be expected to be effective in the treatment of *S. pneumoniae*-related RTIs.

In this study, *S. pneumoniae* isolates were susceptible to azithromycin at the rate of 40%. In the case of the PSSPs, the authors found that most (approximately 63%) of the *S. pneumoniae* were susceptible to azithromycin, which differed from the susceptibility rates of more than 94% for the other antimicrobials in this study. The ANSORP study showed a high prevalence of erythromycin resistance (72.7%). The resistance to erythromycin showed a relationship with that of azithromycin and clarithromycin. The azithromycin resistance of the pneumococcal isolates in the present study was 47%, a little higher than the erythromycin resistance of 44.3% for pneumococcal isolates that had been reported from Thailand and cited in the ANSORP study[3].

The probability of obtaining the PK/PD target of azithromycin was 1.71% and 0% for the CLSI breakpoint and MIC_{90} value (MIC ≤0.5 µg/ml and ≥128 µg/ml, respectively). Based on the pharmacodynamics simulation that considered treatment according to the overall prevalence of pathogens, azithromycin achieved a 31.40% CFR against *S. pneumoniae*. These results differed from a previous Monte Carlo simulation, in which azithromycin 500 mg achieved a 76.5% CFR against *S. pneumoniae*[26]. The different results may be explained by different MIC distributions. As the previous study had an MIC_{90} value lower than the present study (0.125 and 128 µg/ml, respectively), it likely to have a higher probability of achieving the AUC/MIC target than the present study. Thus, the authors do not recommend an empirical therapy with azithromycin 500 mg for *S. pneumoniae*-related RTIs because of the low probabilities of *S. pneumoniae* eradication. It is probably because azithromycin distributes rapidly from the vascular compartment to body tissues, resulting in lower azithromycin levels in serum[31]. However, the major RTI pathogens are located in the extracellular rather than the intracellular compartment. The high intracellular concentration of macrolides may decrease their therapeutic potential in these infections[32].

Several limitations of this study should be discussed. First, the number of organisms were obtained from a small group of patients from only one teaching hospital. Our findings may not represent the population of *S. pneumoniae*-related RTIs in Thailand as a whole. Second, the antimicrobial regimens selected were based on recommendations from RTI guidelines or Thai FDA labeling; other possible regimens were not incorporated in our analysis, such as amoxicillin 1,000 mg every 12 hours. Third, some antimicrobial regimens could not be analyzed by a Monte Carlo simulation due to insufficient pharmacokinetic data. Finally, all of the pharmacokinetic data were obtained from previously existing studies in healthy volunteers. Some parameters obtained from healthy volunteers may differ from those obtained from actual RTI patients.

Conclusion

Our findings suggest that amoxicillin is still an empirical oral therapy of choice for *S. pneumoniae*-related RTIs. Amoxicillin 500 mg every eight hours

can be expected to be effective in the treatment of *S. pneumoniae*-related RTIs. Amoxicillin/clavulanate regimens should be reserved for patients who require additional beta-lactamase producing organism coverage. Cefditoren 200 mg every eight hours could be an alternative to cover the majority of *S. pneumoniae*. In addition, the authors do not recommend azithromycin as an empirical therapy for *S. pneumoniae*-related RTIs.

What is already known on this topic?

Amoxicillin is considered to be very good choice for *S. pneumoniae*-related RTIs.

What this study adds?

Empirical therapy with cefditoren 200 mg every eight hours in patients with *S. pneumoniae*-related RTIs could be an alternative to an amoxicillin-based regimen. In addition, due to an increasing prevalence of macrolide resistance, empirical therapy with azithromycin for *S. pneumoniae*-related RTIs is not recommended.

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Potential conflicts of interest

The authors declare no conflict of interest.

References

1. Mandell GL, Bennett JE, Dolin R. Mandell, Douglas, and Bennett's principles and practice of infectious diseases. 7th ed. Philadelphia, PA: Churchill Livingstone Elsevier; 2010.
2. Jones RN, Sader HS, Mendes RE, Flamm RK. Update on antimicrobial susceptibility trends among Streptococcus pneumoniae in the United States: report of ceftaroline activity from the SENTRY Antimicrobial Surveillance Program (1998-2011). Diagn Microbiol Infect Dis 2013; 75:107-9.
3. Kim SH, Song JH, Chung DR, Thamlikitkul V, Yang Y, Wang H, et al. Changing trends in antimicrobial resistance and serotypes of Streptococcus pneumoniae isolates in Asian countries: an Asian Network for Surveillance of Resistant Pathogens (ANSORP) study. Antimicrob Agents Chemother 2012;56:1418-26.
4. National Antimicrobial Resistance Surveillance of Thailand (NARST). Antimicrobial resistance rates of Streptococcus pneumoniae by year (NARST-50 hospitals, 2000-2015) [Internet]. 2015 [cited 2016 Jan 15]. Available from: http://narst.dmsc.moph.go.th/data/AMR2000_2015.pdf.
5. Clinical and Laboratory Standards Institute (CLSI). Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; Approved Standard-Eighth Edition. CLSI document M07-A8. Wayne, PA: CLSI; 2009.
6. Clinical and Laboratory Standards Institute (CLSI). Performance standards for antimicrobial susceptibility testing; 21st Informational supplement. CLSI document M100-S21. Wayne, PA: (CLSI); 2011.
7. Food and Drug Administration. Spectracef prescribing information [Internet]. 2014 [cited 2014 Nov 3]. Available from: http://www.crtx.com/docs/spectracef.pdf.
8. American Academy of Pediatrics Subcommittee on Management of Acute Otitis Media. Diagnosis and management of acute otitis media. Pediatrics 2004;113:1451-65.
9. Chow AW, Benninger MS, Brook I, Brozek JL, Goldstein EJ, Hicks LA, et al. IDSA clinical practice guideline for acute bacterial rhinosinusitis in children and adults. Clin Infect Dis 2012;54: e72-112.
10. Mandell LA, Wunderink RG, Anzueto A, Bartlett JG, Campbell GD, Dean NC, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis 2007;44(Suppl 2):S27-72.
11. Glover ML, Reed MD. Lower respiratory tract infections. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, editors. Pharmacotherapy: A pathophysiologic approach. 7th ed. New York: The McGraw-Hill; 2008: 1761-78.
12. MIMs Online. MIMS Thailand: Cefditoren pivoxil [Internet]. 2014 [cited 2014 Nov 3]. Available from: http://www.mims.com/thailand.
13. Pires de Abreu LR, Ortiz RM, de Castro SC, Pedrazzoli J Jr. HPLC determination of amoxicillin comparative bioavailability in healthy volunteers

after a single dose administration. J Pharm Pharm Sci 2003;6:223-30.
14. Vree TB, Dammers E, Exler PS. Identical pattern of highly variable absorption of clavulanic acid from four different oral formulations of co-amoxiclav in healthy subjects. J Antimicrob Chemother 2003;51:373-8.
15. Sádaba B, Azanza JR, Quetglas EG, Campanero MA, Honorato J, Coronel P, et al. Pharmacokinetic/pharmacodynamic serum and urine profile of cefditoren following single-dose and multiple twice- and thrice-daily regimens in healthy volunteers: a phase I study. Rev Esp Quimioter 2007;20:51-60.
16. Liu P, Allaudeen H, Chandra R, Phillips K, Jungnik A, Breen JD, et al. Comparative pharmacokinetics of azithromycin in serum and white blood cells of healthy subjects receiving a single-dose extended-release regimen versus a 3-day immediate-release regimen. Antimicrob Agents Chemother 2007;51:103-9.
17. Cars O. Efficacy of beta-lactam antibiotics: integration of pharmacokinetics and pharmacodynamics. Diagn Microbiol Infect Dis 1997;27: 29-33.
18. Craig WA. Pharmacokinetic/pharmacodynamic parameters: rationale for antibacterial dosing of mice and men. Clin Infect Dis 1998;26:1-10.
19. Woodnutt G, Berry V. Two pharmacodynamic models for assessing the efficacy of amoxicillin-clavulanate against experimental respiratory tract infections caused by strains of Streptococcus pneumoniae. Antimicrob Agents Chemother 1999;43:29-34.
20. Craig WA, Andes DR. In vivo pharmacodynamic activity of cefditoren (CDTR) against Streptococcus pneumoniae [Abstract No. 2248]. 41st Interscience Conference on Antimicrobial Agents and Chemotherapy; 2001 Dec 16-19; Chicago.
21. Owens RC Jr, Shorr AF. Rational dosing of antimicrobial agents: pharmacokinetic and pharmacodynamic strategies. Am J Health Syst Pharm 2009;66(12 Suppl 4):S23-30.
22. Torumkuney D, Chaiwarith R, Reechaipichitkul W, Malatham K, Chareonphaibul V, Rodrigues C, et al. Results from the Survey of Antibiotic Resistance (SOAR) 2012-14 in Thailand, India, South Korea and Singapore. J Antimicrob Chemother 2016;71(Suppl 1):i3-19.
23. Gilbert DN, Chambers HF, Eliopoulos GM, Saag MS, Pavia AT, Black D, et al, editors. The Sanford guide to antimicrobial therapy 2016. 46th ed. Sperryville, VA: Antimicrobial Therapy; 2016.
24. Nagai K, Davies TA, Jacobs MR, Appelbaum PC. Effects of amino acid alterations in penicillin-binding proteins (PBPs) 1a, 2b, and 2x on PBP affinities of penicillin, ampicillin, amoxicillin, cefditoren, cefuroxime, cefprozil, and cefaclor in 18 clinical isolates of penicillin-susceptible, -intermediate, and -resistant pneumococci. Antimicrob Agents Chemother 2002;46:1273-80.
25. Weinstein MP, Klugman KP, Jones RN. Rationale for revised penicillin susceptibility breakpoints versus Streptococcus pneumoniae: coping with antimicrobial susceptibility in an era of resistance. Clin Infect Dis 2009;48:1596-600.
26. Kiffer CR, Pignatari AC. Pharmacodynamic evaluation of commonly prescribed oral antibiotics against respiratory bacterial pathogens. BMC Infect Dis 2011;11:286.
27. Lee MY, Ko KS, Oh WS, Park S, Lee JY, Baek JY, et al. In vitro activity of cefditoren: antimicrobial efficacy against major respiratory pathogens from Asian countries. Int J Antimicrob Agents 2006;28:14-8.
28. Granizo JJ, Sadaba B, Honorato J, Gimenez MJ, Sevillano D, Aguilar L, et al. Monte Carlo simulation describing the pharmacodynamic profile of cefditoren in plasma from healthy volunteers. Int J Antimicrob Agents 2008;31: 396-8.
29. Nicolau DP, Onyeji CO, Zhong M, Tessier PR, Banevicius MA, Nightingale CH. Pharmacodynamic assessment of cefprozil against Streptococcus pneumoniae: implications for breakpoint determinations. Antimicrob Agents Chemother 2000;44:1291-5.
30. Fuchs PC, Barry AL, Brown SD. Susceptibility of Streptococcus pneumoniae and haemophilus influenzae to cefditoren, and provisional interpretive criteria. Diagn Microbiol Infect Dis 2000; 37:265-9.
31. Swainston HT, Keam SJ. Azithromycin extended release: a review of its use in the treatment of acute bacterial sinusitis and community-acquired pneumonia in the US. Drugs 2007;67:773-92.
32. Carbon C, Poole MD. The role of newer macrolides in the treatment of community-acquired respiratory tract infection. A review of experimental and clinical data. J Chemother 1999;11:107-18.