〈NOTE〉

# *In vitro* antimicrobial activity of cefditoren and other oral antibiotics against *Streptococcus pneumoniae*, isolated from children with community acquired respiratory tract infections

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The antibacterial susceptibility to frequently prescribed antibiotics of *Streptococcus pneumoniae* isolated from the pediatric patients with acute respiratory infectious diseases was investigated in a study of three medical institutions in Korea. Total 143 clinical isolates of *S. pneumoniae* were available for susceptibility tests between May 2003 and July 2007. Antimicrobial susceptibility data for *S. pneumoniae* were analyzed by using agents of amoxicillin, cefaclor, cefuroxime, cefdinir, and cefditoren as the test antibiotics.

The prevalence of each resistance class, penicillin-resistant *S. pneumoniae* (PRSP) were high with the proportion of MIC range (susceptible=8.4%, intermediate resistance=18.2%, resistance=73.4%). $MIC_{90}$ and susceptible (S) rate of antimicrobial agents to the strains tested were amoxicillin ($MIC_{90}$=4 $\mu$g/ml, S=76.2%), cefaclor ($MIC_{90}$=128 $\mu$g/ml, S=8.4%), cefuroxime ($MIC_{90}$=16 $\mu$g/ml, S=24.5%), cefdinir ($MIC_{90}$=16 $\mu$g/ml, S=21.8%), and cefditoren ($MIC_{90}$=0.5 $\mu$g/ml, S=90.2%) respectively.

Against clinical isolates including PRSP, cefditoren demonstrated the strongest antibacterial activity intrinsically among the antibiotics tested. Conclusively, the antimicrobial activity of cefditoren to *S. pneumoniae* strains isolated from pediatric patients with acute respiratory infection is very high. In South Korea, where the antibiotic resistance of *S. pneumoniae* is issued, cefditoren is expected to be used as a primary or secondary antibiotic. Moreover, cefditoren may serve as a useful option for secondary antibiotics after failure of amoxicillin treatment, which is most primarily used for acute respiratory *S. pneumoniae* infection in children.

*S. pneumoniae* is widely accepted as one of the most important and common pathogen for bacterial respiratory infection and central nervous system infection. Since PRSP was reported in 1960s, epidemic multidrug-resistant *S. pneumoniae* was reported in 1977[1)], and recently multidrug-resistance of PRSP is gradually increasing. Especially, the prevalence of PRSP is very high, more than 55%, in Far Eastern Asia including Hong Kong, Taiwan, South Korea and Japan with high multidrug-resistance[2)]. Furthermore, severe infection caused by highly resistant bacteria has been clinically issued, which requires very special care in choosing antibiotics.

The prevalence of PRSP in South Korea has abruptly increased since the year of 2000, and has become the highest in the world, unfortunately[3)]. Thus, epidemiological and antibiotic susceptibility-related researches of this bacterium have been widely and aggressively conducted. This bacterium is clinically characterized by more frequent infection in upper and lower respiratory tract and central nervous system in children with 5 years or less of age[4)]. As the antibiotic resistance rate is generally higher in children than adults in the countries with higher prevalence of antibiotic resistant *S. pneumoniae*[5)], basic epidemiological research should be accomplished to investigate the prevalence of this bacteria in nasal cavity and the penicillin resistance rate in young children. Experience-based treatment is generally provided for outpatients or patients with acute respiratory infection without complications. In this case, evidence-oriented antibiotic treatment is required based on the repetitive researches of exact resistance patterns about region-specific causative pathogens for respiratory infection[6)]. Therefore, it is essential to perform region-specific overall antibacterial assessment of *S. pneumoniae*, which is the most common and important pathogen for acute bacterial respiratory infections in young children. It is also important to investigate the antibacterial activities of oral antibiotics frequently used for pneumococcal respiratory infections. These investigations may lead to the appropriate use of right antibiotics for *S. pneumoniae*, and thus ultimately reduced antibiotic resistance.

The objective of this study was to evaluate the PRSP isolated from the patients with acute otitis media, acute sinusitis and pneumonia in Korean children, and to evaluate the antibacterial activities of frequently prescribed oral antibiotics which are available in Korea for the community acquired pneumococcal infections. Five oral antibiotics for pediatric use in Korea were selected for the test; amoxicillin, the most frequently prescribed aminopenicillin for children, cefaclor and cefuroxime, the frequently prescribed agents of the first- and second-generation oral cephalosporins, and cefdinir and cefditoren, the representative agents of the third-generation oral cephalosporins to evaluate the antibacterial potentiality of the third-generation agents against the clinical isolates among antibiotics tested.

Total 143 specimens of *S. pneumoniae* were isolated and analyzed from the patients with community acquired respiratory infections including acute otitis media, acute sinusitis or pneumonia, who visited Seoul St. Mary's Hospital, Incheon St. Mary's Hospital, and St. Vincent's Hospital from May 2003 to July 2007.

For acute otitis media patients, specimens were readily collected in the case of natural perforation, or collected after paracentesis of ear drum, if indicated and applicable. For acute sinusitis patients, specimens were collected and incubated by calcium alginate swabs (Fisher Scientific Co., Georgia, USA) from the orifice of middle meatus, or paracentesis of sinuses. For pneumonia patients, *S. pneumoniae* specimens were isolated from inpatients only, following blood or sputum culture. The isolates were aliquoted into microplates in Mueller-Hinton broth (MHB, BBL, Cat. No. 431138, USA) with 5% lysed horse blood, and stored at −70°C before use.

The minimal inhibitory concentration (MIC) was determined by broth dilution method in accordance with the criteria of Clinical and Laboratory Standards Institute (CLSI). After determination of $MIC_{50}$ and $MIC_{90}$, the susceptibility range was established according to the standards for antimicrobial susceptibility testing of CLSI 2007[7]. There is no CLSI standard of antimicrobial susceptibility or resistance for cefditoren, however, this agent was evaluated based on the standard of the Spanish Drug Agency[8].

As the results, the antimicrobial concentration of penicillin against *S. pneumoniae* ranged from 0.015 $\mu$g/ml to 16 $\mu$g/ml with 8.4% of susceptibility, 91.6% of resistance rate (intermediate resistance: 18.2%, resistance: 73.4%), 4 $\mu$g/ml of $MIC_{50}$ and 8 $\mu$g/ml of $MIC_{90}$ (Table 1). Amoxicillin showed 76.2% of the susceptibility of the study bacteria and 23.8% of resistance rate (intermediate resistance: 18.2%, resistance: 5.6%) with 1 $\mu$g/ml of $MIC_{50}$ and 4 $\mu$g/ml of $MIC_{90}$, suggesting substantially higher antibacterial potency than penicillin. However, the susceptibility of *S. pneumoniae* to cefaclor was 8.4% with 91.6% of resistance rate (intermediate resistance: 5.6%, high resistance: 86.0%), which suggests very low antibacterial potency similar to that of penicillin. Furthermore, cefaclor showed significantly low intrinsic activities with 64 $\mu$g/ml of $MIC_{50}$ and 128 $\mu$g/ml of $MIC_{90}$. Cefuroxime showed 24.5% of the susceptibility of the study bacteria and 75.5% of resistance rate (intermediate resistance: 13.3%, resistance: 62.2%) with 4 $\mu$g/ml of $MIC_{50}$ and 16 $\mu$g/ml of $MIC_{90}$. Similarly, cefdinir displayed 21.8% of susceptibility and 78.2% of resistance rate (intermediate resistance: 1.3%, resistance 76.9%) with 4 $\mu$g/ml of $MIC_{50}$ and 16 $\mu$g/ml of $MIC_{90}$. However, cefditoren showed 90.2% of susceptibility and 9.8% of resistance rate (intermediate resistance: 8.4%, resistance: 1.4%) suggesting the highest susceptibility. Moreover, it also displayed the greatest intrinsic activity with 0.5 $\mu$g/ml of $MIC_{50}$ and 0.5 $\mu$g/ml of $MIC_{90}$ (Table 1).

In this study, we found that pneumococcal susceptibility to cefaclor, cefuroxime and cefdinir was very high level of resistant proportion with 62～86%, while amoxicillin and cefditoren, in particular, showed substantially low rate (5.6% and 1.4%, respectively) of resistant proportion.

In South Korea, Lee *et al.* reported the results of antibacterial activity assessment about cephalosporins in 2005, where MIC range of cefditoren was 0.125～1 $\mu$g/ml with 0.5 $\mu$g/ml and 1 $\mu$g/ml of $MIC_{50}$ and $MIC_{90}$, while $MIC_{50}$ and $MIC_{90}$ of cefdinir, cefprozil, and cefpodoxime were 4 $\mu$g/ml and 8 $\mu$g/ml, 8 $\mu$g/ml and 16 $\mu$g/ml, and 64 $\mu$g/ml and 128 $\mu$g/ml, respectively, which suggests cefditoren is superior to any other cephalosporins[9]. In this study, we conducted cefditoren sus-

Table 1. Susceptibility of 143 clinical isolated *S. pneumoniae* from children.

| | MIC μg/ml | | | | | | | | | | | | | | | | | (%) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Antimicrobials** | **0.015** | **0.03** | **0.06** | **0.12** | **0.25** | **0.5** | **1** | **2** | **4** | **8** | **16** | **32** | **64** | **128** | **256** | **MIC50** | **MIC90** | **S** | **I** | **R** |
| Penicillin | 5 | 4 | 3 | 2 | 5 | 10 | 9 | 31 | 35 | 34 | 5 | | | | | 4 | 8 | 8.4 | 18.2 | 73.4 |
| Amoxicillin | 12 | | 3 | 7 | 10 | 12 | 36 | 29 | 26 | 7 | 1 | | | | | 1 | 4 | 76.2 | 18.2 | 5.6 |
| Cefaclor | | | | | 6 | 3 | 3 | 8 | 5 | 8 | 4 | 16 | 31 | 47 | 12 | 64 | 128 | 8.4 | 5.6 | 86.0 |
| Cefuroxime | 2 | 10 | 1 | 7 | 10 | 2 | 3 | 19 | 33 | 25 | 31 | | | | | 4 | 16 | 24.5 | 13.3 | 62.2 |
| Cefdinir | 6 | 2 | 5 | 5 | 4 | 9 | 2 | 16 | 35 | 41 | 18 | | | | | 4 | 16 | 21.8 | 1.3 | 76.9 |
| Cefditoren | 16 | 2 | 5 | 8 | 25 | 73 | 12 | 1 | | 1 | | | | | | 0.5 | 0.5 | 90.2 | 8.4 | 1.4 |

MIC interpretive standards (μg/ml)

| | Penicillin* | Amoxicillin* | Cefaclor* | Cefuroxime* | Cefdinir* | Cefditoren** |
|---|---|---|---|---|---|---|
| Susceptible (S) | ≤0.06 | ≤2 | ≤1 | ≤1 | ≤0.5 | ≤0.5 |
| Intermediate ( I ) | 0.12-1 | 4 | 2 | 2 | 1 | 1 |
| Resistance (R) | ≥2 | ≥8 | ≥4 | ≥4 | ≥2 | ≥2 |

* CLSI MIC interpretive standard

** The Spanish Drug Agency MIC interpretive standard

ceptibility assay against *S. pneumoniae* isolated from 143 pediatric patients with acute respiratory infection. The result showed that $MIC_{50}$ and $MIC_{90}$ were almost similar with that of Lee *et al.* in 2005. Subculture study also showed that cefditoren is associated with lower occurrence of mutant strains with intrinsic resistance[10]. Persistence of the present antimicrobial activities of cefditoren is expected from this study forward.

Recently, it was also reported that cefditoren shows antibacterial activities even to penicillin-or ampicillin-resistant strains, and it exerts the highest antimicrobial activity to *S. pneumoniae*[11,12]. However, there is no established consensus about the standard for susceptibility of cefditoren. Fuchs *et al.* suggested less than 0.25 μg/ml of MIC for susceptibility standard of cefditoren to *S. pneumoniae*, 0.5～1 μg/ml of MIC for intermediate resistance, and more than 2 μg/ml of MIC for high resistance[13], while Jones *et al.* suggested 0.5～1 μg/ml of MIC for susceptibility standard[14]. In addition, Japanese Chemotherapy Committee applied 1 μg/ml of MIC for susceptibility standard of cefditoren to *S. pneumoniae*[15], and the Spanish Drug Agency determined less than 0.5 μg/ml of MIC as susceptibility standard, 1 μg/ml of MIC as intermediate resistance, and more than 2 μg/ml as high resistance[8]. This study was conducted based on the standard provided by the Spanish Drug Agency[8]. As this issue limits the potential significance of this study about the comparison of susceptibility and antimicrobial activity, re-evaluation might be required based on the established standard in future. And, treatment effects need to be continuously further investigated in clinical practice.

In conclusion, we investigated *in vitro* susceptibility of *S. pneumoniae* strains isolated from pediatric acute respiratory infection patients and found that the antimicrobacterial activity of cefditoren to *S. pneumoniae* is so high. In South Korea, where the antibiotic resistance of *S. pneumoniae* is issued, cefditoren is expected to be used as a primary or secondary antibiotic. Furthermore, cefditoren may serve as a useful option for secondary antibiotics after failure of amoxicillin treatment, which is most primarily used for acute respiratory *S. pneumoniae* infection in Korean children.

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# 韓国における小児市中急性呼吸器感染症から分離した肺炎球菌に対するセフジトレンおよびその他の経口抗生物質の抗菌力

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韓国小児の急性呼吸器感染症から分離された*Streptococcus pneumoniae*に対して，韓国で繁用されている経口抗生物質の抗菌力を測定した。2003年5月から2007年7月の間に韓国内3医療施設から143株の*S. pneumoniae*を臨床分離して被験菌株とし，抗生物質amoxicillin, cefaclor, cefuroxime, cefdinir, cefditorenの抗菌活性を調査検討した。分離した*S. pneumoniae*のペニシリン

耐性率は高く MIC レンジは (susceptible＝8.4%, intermediate resistance＝18.2%, resistance＝73.4%) であった。そしてその菌株に対する試験薬の $MIC_{90}$ 値と susceptible (S) 比率は，amoxicillin ($MIC_{90}$＝4 μg/ml, S＝76.2%), cefaclor ($MIC_{90}$＝128 μg/ml, S＝8.4%), cefuroxime ($MIC_{90}$＝16 μg/ml, S＝24.5%), cefdinir ($MIC_{90}$＝16 μg/ml, S＝21.8%), cefditoren ($MIC_{90}$＝0.5 μg/ml, S＝90.2%) であった。

ペニシリン耐性株を含む臨床分離 *S. pneumoniae* に対して cefditoren は試験薬剤の中，単独で最も強い抗菌力を示した。結果として小児の急性呼吸器感染症における *S. pneumoniae* に対して cefditoren の抗菌薬有用性はもっとも高いものであると示唆される。*S. pneumoniae* の抗菌薬耐性化が問題となっている韓国において，cefditoren は第一選択もしくは第二選択の抗菌薬として有用性が期待できる。また小児の急性呼吸器感染症で最も多く使われている抗菌薬 amoxicillin が無効の場合には，cefditoren が最も有用な抗菌薬になると考えられた。