Ear, Nose & Throat Journal
1–9

DOI: 10.1177/01455613211036236
journals.sagepub.com/home/ear
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# Clinical Trial to Reconfirm the Efficacy and Safety of Cefetamet Pivoxil Treatment in Sinusitis Patients: A Double-Blind, Randomized, Parallel Designed, Multicenter, Active Comparator Study (CASIS Study)

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Received: June 06, 2021; revised: July 07, 2021; accepted: July 12, 2021

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**Abstract**

**Objective:** To evaluate the clinical efficacy and safety of cefetamet pivoxil for the treatment of acute bacterial rhinosinusitis in Korean patients compared to treatment with cefdinir. **Methods:** A prospective, multicenter, randomized double-blind, comparative study was conducted by the Departments of Otorhinolaryngology–Head and Neck Surgery at 17 hospitals or universities in the Republic of Korea from March 2017 to April 2019. A total of 309 patients were screened and 249 patients participated in the study. **Results:** Treatment with cefetamet pivoxil for 2 weeks showed 82.4% clinical cure and improvement rates in patients with acute bacterial rhinosinusitis compared to 84.68% in those taking cefdinir for 2 weeks, showing that cefetamet pivoxil administered twice a day for 2 weeks was as effective as cefdinir 3 times a day for 2 weeks for the treatment of acute bacterial rhinosinusitis. The overall adverse reaction rates of both drugs were 10.56% in the cefetamet pivoxil group and 15.49% in the cefdinir group, without serious adverse events or drug reactions. **Conclusions:** Cefetamet pivoxil twice a day was as efficacious and safe as cefdinir 3 times a day for the treatment of acute bacterial rhinosinusitis, which suggested that cefetamet pivoxil may be a suitable alternative to cefdinir.

**Keywords**

acute bacterial rhinosinusitis, cefdinir, cefetamet, comparative study, double-blinded method

## Introduction

Acute rhinosinusitis (ARS) is a common upper respiratory disease worldwide, including Republic of Korea (ROK). Acute rhinosinusitis, usually caused by a virus and self-limiting, is defined as purulent nasal drainage (anterior, posterior, or both) accompanied by nasal obstruction, and facial pain-pressure-fullness, or both, which are the 3 cardinal symptoms of ARS, for up to 4 weeks.[1,2]

However, if ARS symptoms fail to improve within 10 days or worsen within 10 days after an initial improvement, acute bacterial rhinosinusitis (ABRS) is considered. Additional symptoms and signs of ABRS are cough, fever, hyposmia, anosmia, maxillary dental pain, and ear fullness or pressure.[3]

The American Academy of Otolaryngology–Head and Neck Surgery Foundation (AAO) recommended that the initial management of ABRS should be watchful waiting or antibiotic therapy for adults with uncomplicated ABRS. However, if the patient's condition does not improve by 7 days after the ABRS diagnosis or if it worsens at any time, antibiotics are used.[1]

*Streptococcus pneumoniae*, *Hemophilus influenzae*, and *Moraxella catarrhalis* are usually isolated from pediatric patients with ABRS and *S pneumoniae* and nontypeable *H influenzae* accounted for more than 75% of the bacterial isolates from adults with ABRS.[1,2]

In the clinical field, empirical antibiotics must be chosen in consideration of the abovementioned bacteria for ARS, regional antibiotic-resistant bacteria, and recent history of antibiotic use.

In ROK, the widespread use of antibiotics to treat upper respiratory infections (URIs) is a big public health problem because high antibiotic usage had increased the rate of antibiotic resistance.[4] *Streptococcus pneumonia, one of the most common pathogen of ABRS, has been reported to show higher penicillin resistance or nonsusceptibility rate(89%) in ROK than in other countries.*[5]

Kang et al reported that the isolates from pediatric acute otitis media patients showed the highest penicillin resistance (92.7%), modest amoxicillin resistance (16.7%), amoxicillin–clavulanate resistance (9.6%), and high cefaclor resistance (above 95%).[6]

Therefore, in ROK, amoxicillin/clavulanate or 2nd or 3rd generation cephalosporins have been usually chosen as first-line antibiotics for adult ABRS therapy but amoxicillin without clavulanate has not been commonly prescribed due to the high rate of antimicrobial resistance in ROK.

Cefdinir is a semisynthetic, broad-spectrum third-generation antibiotic in the cephalosporin class, which was approved by the US Food and Drug Administration (FDA) in 1997 and the Korean FDA (KFDA) in 1998.[7]

Cefetamet pivoxil is also a semisynthetic, beta-lactamase-stable, third-generation cephalosporin, approved by the FDA in 2001 and the KFDA in 2003. After oral ingestion, its ester bond is cleaved to the active form, cefetamet pivoxil.[8]

Both drugs are active against most respiratory pathogens, including *S pneumoniae*, *H influenzae*, *M catarrhalis*, and group A beta-hemolytic streptococci. Cefetamet pivoxil is also active against beta-lactamase-producing *H influenzae* and *M catarrhalis* but showed poor activity against penicillin-resistant *S pneumoniae*.[9]

This study was designed to evaluate the clinical efficacy and safety of cefetamet pivoxil for the treatment of ARS in Korean patients and cefdinir was chosen as the comparator drug because it is commonly used for ARS in adult and pediatric patients in ROK.

## Patients and Methods

### Study Design

This prospective, multicenter, randomized, double-blind, comparative study was conducted by the Department of Otorhinolaryngology–Head and Neck Surgery at 17 hospitals or

universities in ROK from March 2017 to April 2019. All patients with ARS were scheduled to visit clinics 3 to 4 times.

A physical examination, medical and surgical history review, laboratory tests (complete blood counts, blood chemistry, and liver function tests [LFTs]), bacterial cultures of nasal discharge, paranasal sinus X-rays were performed at the baseline visit, and laboratory and paranasal sinus X-rays were repeated at the end-of-therapy visit.

All patients were instructed for this study on screening day (visit 1) or, after agreement of participation in this study, to visit the clinic within 7 days after screening for the initial treatment day (visit 2) and on days 14 $\pm$ 2 (visit 3, end-of-therapy visit) and 21 $\pm$ 3 (visit 4, end-of-study visit) after the initial treatment. In some cases, visit 1 and visit 2 might be same day. At these visits, the physicians evaluated symptom improvement, compliance, and adverse effects.

The study was approved by the institutional review board of each participating hospital or university where the authors worked (2016GR0341, SC17MDMV0007, 3-2017-0004, KUH1110061, H-1609-036-789, SCHCA 2016-09-024, AJIRB-MED-CT4-16-336, YUMC 2016-10-055, CR116055, GBIRB2017-074, HYUH 2016-11-026, CNUH 2016-12-050, 2017AS0682, GURI 2016-11-011, KYUH 2018-06-013, PC18MDDV0047, VC18MODV0144). This clinical trial was registered with the primary national clinical trial registry site, ClinicalTrials.gov (NCT04664803). Written informed consent was obtained from the patients or their legal representative prior to enrollment in the study.

## Patient Selection

Patients older than 12 years with a clinical diagnosis of ABRS were recruited from the outpatient clinics, and ARBS was diagnosed based on the clinical practice guidelines of the AAO–Head and Neck Surgery.[1,2]

The inclusion criteria were:

1. Patients aged 12 to 75 years.
2. Patients with the onset of the first ARS symptoms within 3 weeks prior to enrollment in the study.
3. Patients with symptoms and signs of ARS not to improve within 10 days or to be worsened within 10 days after an initial improvement.
4. Patients with:
   a. Two more clinical symptoms of purulent nasal discharge, facial pain, nasal obstruction maxillary tooth pain, frontal headache, new onset of fetor oris, or cough.
   b. More than one clinical sign of purulent secretion from the sinus ostia, pain over the sinuses, or facial swelling.
5. No penicillin or cephalosporin allergies.
6. A willingness to attend the follow-up visits.
7. A normal electrocardiogram (ECG).

The exclusion criteria were:

1. Patients who had allergic or another rhinitis, 3 or more episodes of ARS within a year or a month prior to enrollment in the study.
2. Patients who were recently enrolled in another clinical study.
3. Patients who showed abnormal ECG results, creatinine clearance (<40 mL/min), and LFT results (AST/ALT/total bilirubin levels more than 3 times the normal values).
4. Patients who had a history of drug or alcohol abuse.
5. Pregnant or lactating women, or patients who were diagnosed with any malignancy or recurrent malignancy within 5 years.

## Dosage and Schedule of Antibiotics and Other Treatments

The patients and doctors were double-blinded and patients randomly assigned to the cefetamet pivoxil or cefdinir group took cefetamet pivoxil (500 mg, twice daily, orally) or cefdinir (100 mg, 3 times daily, orally) for the treatment of ARS for 2 weeks ($\pm$2 days). Cefetamet pivoxil was administrated as 500 mg capsules with a cefdinir-placebo capsule in the morning and the evening, and a placebo capsule in the afternoon.

Cefdinir was administered as 100 mg capsules with a cefetamet pivoxil-placebo capsule in the morning and the evening, and a cefdinir capsule in the afternoon.

Other antimicrobial, antifungal, mucolytics, or antitussive drugs were prohibited and newly prescribed steroids were also prohibited.

## Assessments of Efficacy

The primary outcome measure was the clinical cure and improvement rates, expressed as the ratio of cured and improved ABRS patients to the total patients per group on days 14 and 21 after the initial treatment.

The patient responses were classified as cured (no symptoms and signs after treatment), improved (more than 50% improvement in the clinical symptoms, no newly onset symptoms, and more than 1 point improvement in the clinical signs after treatment), failure (none or less than 50% improvement in the clinical symptoms, new symptom onset, or the cessation of antibiotic treatments due to adverse events during the study), and relapse (clinical improvement at the day-14 visit but the reappearance of clinical signs and symptoms at the day-21 visit).

The clinical signs and symptom checklists for ABRS were graded using a Likert 3-point grading scale for symptoms, nasal endoscopy, and physical examination (0 = absent, 1 = mild, 2 = moderate, and 3 = severe, for a total of 21 points). The secondary outcome measures were based on the clinical cure rate, clinical improvement rate, and antimicrobial activity.

### Assessments of Safety

The proportions of patients with adverse events, severe adverse events, and severe adverse drug reactions related to the trial medication in each group were calculated.

### Statistical Analysis

We assumed a response (cure and improvement in ABRS) rate of 88%, a power of 80%, a significance level of 5%, 2-sidedness, and a noninferiority margin of 12%, which yielded a sample size of 232 (116 in each group) patients. Assuming that the primary outcome could not be evaluated in 20% of the patients, 288 (144 in each group) patients needed to be included in the study.

To calculate the number of statistically meaningful samples for testing noninferiority of the drug, a 2-tailed 95% CI, a 5% significance level, and 80% power were set. The minimum 95% CI value by the DerSimonian and Laird method for the active drug was 85.2%, and the maximum 95% CI value by the DerSimonian and Laird method for the placebo was 60.8%. The noninferiority margin was set as half of the difference between the upper 95% CI limit of cefetamet pivoxil efficacy and the lower 95% CI limit of cefdinir efficacy. If the upper 95% CI limit applied was less than the noninferiority margin of 12%, the test group was judged to be noninferior to the control group.

The clinical cure rates were analyzed by Pearson $\chi^2$ test and the clinical signs and symptoms at baseline, follow-up visits, and changes were compared between the groups using Wilcoxon rank sum test and changes within the groups were analyzed using Wilcoxon signed-rank test. 95% CIs were calculated by the Wald asymptotic CI method and Wilson score method. Efficacy analysis was performed by applying last observation carried forward. *P* values of <.05 were considered statistically significant. All analyses were performed using SAS version 9.4 (SAS Institute).

## Results

### Study Population

After the clinical evaluation, a total of 309 patients were initially enrolled. However, 21 patients were excluded because they withdrew their consent (n = 9) or met the exclusion criteria (n = 12). Finally, a total of 288 eligible patients were enrolled at 17 study centers in ROK between March 2017 and April 2019 and randomized to the cefetamet pivoxil (n = 144) or cefdinir (n = 144) groups.

In the safety set, 2 patients were excluded from each group due to the withdrawal of consent and unwillingness to take the medications. A total of 142 patients in each group (full analysis set, FAS) participated until the end of the study. However, in the per-protocol set (PPS), a total of 35 patients were excluded due to taking other banned medications, poor compliance, inappropriate inclusion, or dropping out.

Finally, 125 patients in the cefetamet pivoxil group and 124 patients in the cefdinir group were enrolled and analyzed for the primary and secondary outcome measures (Figure 1).

### Demographics and Clinical Characteristics

Of the 142 enrolled patients in each group (FAS), there were no statistically significant differences in age, age distribution, weight, height, ECG, and X-ray between the 2 groups (Table 1).

### Efficacy

The analysis of the PPS showed that the ARBS patients who received cefetamet pivoxil for 2 weeks showed 82.4% clinical cure and improvement rates (primary outcome measure) compared to 84.68% of ABRS patients receiving cefdinir for 2 weeks. Noninferiority of cefetamet pivoxil was confirmed using Wald's asymptotic CI method on days 14 and 21 because the differences in the 95% CIs between the cefetamet pivoxil and cefdinir groups were 0.71 and 2.28%, respectively (Table 2).

As one of the secondary outcome measures, moderate clinical cure rates at day 14 and 21 were achieved with cefetamet pivoxil (24.0% and 22.4%, respectively) and cefdinir (20.97% and 20.16%, respectively) treatment, and there were no significant differences in the clinical cure rates between the cefetamet pivoxil and cefdinir groups on days 14 ($P = .5666$) and 21 ($P = .6661$; Table 3).

The changes in total scores for the clinical symptoms and signs between the cefetamet pivoxil and cefdinir groups were also similar at baseline and 2 or 3 weeks after taking the medications ($P = .2264$, .4307, and .4403, respectively). However, within each cefetamet pivoxil, cefdinir, or total groups, there were statistically significant differences in scores between baseline and day 14, and between baseline and day 21 of taking the medications ($P \leq .001$, <.001, and <.001, respectively; Table 4).

Bacteria including *S pneumoniae*, *H influenzae*, *M catarrhalis*, and others were identified in only 15 patients in the cefetamet pivoxil group (n = 124) and 17 patients in the cefdinir group (n = 125).

The bacterial eradication rates in patients in each group with bacteriologically proven infections were 86.67% versus 88.24% on day 14 and 73.33% versus 82.35% on day 21, which were not statistically significant ($P = .9999$ and .6783, respectively).

The clinical cure and improvement rates on day 21 and the bacterial eradication rates in the cefetamet pivoxil and cefdinir groups are shown in Figure 2.

### Adverse Reactions and Safety

Adverse reactions were reported in 10.56% of the patients in the cefetamet pivoxil group (n = 15) and 15.49% of the patients

**Table 1.** Demographic Characteristics.

| Parameters | | Cefetamet pivoxil (n = 142) | Cefdinir (n = 142) | Total (n = 284) | *P* value |
|---|---|---|---|---|---|
| Gender | Male | 63 (44.37%) | 62 (43.66%) | 125 (44.01%) | .9048[a] |
| | Female | 79 (55.63%) | 80 (56.34%) | 159 (55.99%) | |
| Age (years) | Mean (±SD) | 43.14 ± 14.93 | 43.25 ± 15.38 | 43.20 ± 15.13 | |
| Age distribution | <19 years | 2 (1.41%) | 5 (3.52%) | 7 (2.46%) | .3309[a] |
| | 19-29 | 26 (18.31%) | 22 (15.49%) | 48 (16.90%) | |
| | 30-39 | 32 (22.54%) | 33 (23.24%) | 65 (22.89%) | |
| | 40-49 | 27 (19.01%) | 30 (21.13%) | 57 (20.07%) | |
| | 50-59 | 33 (23.24%) | 20 (14.08%) | 53 (18.66%) | |
| | 60-69 | 18 (12.68%) | 27 (19.01%) | 45 (15.85%) | |
| | ≥70 | 4 (2.82%) | 5 (3.52%) | 9 (3.17%) | |
| Weight (kg) | Mean (±SD) | 65.37 ± 13.08 | 65.18 ± 12.17 | 65.27 ± 12.61 | >.9999[b] |
| Height (cm) | Mean (±SD) | 164.74 ± 8.38 | 164.61 ± 8.39 | 164.68 ± 8.37 | |
| Childbearing age 1) | Total | 79 | 80 | 159 | |
| | Females of nonchildbearing age | 27 (34.18%) | 25 (31.25%) | 52 (32.70%) | .6940[a] |
| | Females of childbearing age | 52 (65.82%) | 55 (68.75%) | 107 (67.30%) | |
| Pregnancy test in females of childbearing age | Negative | 52 (48.60%) | 55 (51.40%) | 107 (100%) | - |
| Breast-feeding in females of childbearing age | None | 79 (100%) | 80 (100%) | 159 (100%) | - |
| ECG | Normal | 142 (100%) | 142 (100%) | 284 (100%) | — |
| | Abnormal | 0 (0%) | 0 (0%) | 0 (0%) | |
| Sinus X-ray | Normal | 58 (40.85%) | 49 (34.51%) | 107 (37.68%) | .2704[a] |
| | Abnormal | 84 (59.15%) | 93 (65.49%) | 177 (62.32%) | |

Abbreviation: ECG, electrocardiogram.
[a]Pearson $\chi^2$ test.
[b]Wilcoxon rank-sum test.

**Table 2.** Clinical Cure/Improvement Rates on Days 14 and 21.

| | | Number of patients (%) | | |
|---|---|---|---|---|
| Response | Assessment | Cefetamet pivoxil | Cefdinir | Total |
| No. of patients | | 125 | 124 | 249 |
| clinical cure and improvement rate on days 14 | Cure/improvement | 110 (88.00%) | 110 (88.71%) | 220 (88.35%) |
| | Failure/relapse | 15 (12.00%) | 14 (11.29%) | 29 (11.65%) |
| | Difference in 95% CI between cefetamet pivoxil and cefdinir[a]: 0.71% (−7.26 to 8.68) | | | |
| number of patients(rate) on day 21 | Cure/improvement | 103 (82.40%) | 105 (84.68%) | 208 (83.53%) |
| | Failure/relapse | 22 (17.60%) | 19 (15.32%) | 41 (16.47%) |
| | Difference in 95% CI between cefetamet pivoxil and cefdinir[a]: 2.28 (−6.93 to 11.48) | | | |

[a]Wald asymptotic CI method.

**Table 3.** Clinical Cure Rate on Days 14 and 21.

| | Number of patients (%) | | | |
|---|---|---|---|---|
| Assessment | Cefetamet pivoxil | Cefdinir | Total | *P* value |
| Cure | 30 (24.00%) | 26 (20.97%) | 56 (22.49%) | |
| Noncure | 95 (76.00%) | 98 (79.03%) | 193 (77.51%) | |
| Clinical cure rate 95% CI on day 14[a] | (17.36-32.19) | (14.73-28.95) | | .5666[b] |
| Cure | 28 (22.40%) | 25 (20.16%) | 53 (21.29%) | |
| Noncure | 97 (77.60%) | 99 (79.84%) | 196 (78.71%) | |
| Clinical cure rate 95% CI on day 21[a] | (15.98-30.47) | (14.05-28.07) | | .6661[b] |

[a]Wilson Score method.
[b]Pearson $\chi^2$ test.

**Table 4.** Changes in Total Scores of Clinical Signs and Symptoms on Days 14 and 21 Compared to Baseline.[a]

| Time/Period | Cefetamet pivoxil | Cefdinir | Total | *P* value |
|---|---|---|---|---|
| Baseline | 12.35 ± 5.54 | 12.95 ± 5.07 | 12.65 ± 5.31 | .2264[b] |
| Day 14 (end of taking medicine) | 2.14 ± 2.38 | 2.58 ± 2.81 | 2.36 ± 2.61 | .4307[b] |
| Day 21 (end of study) | 1.37 ± 1.97 | 1.30 ± 2.20 | 1.33 ± 2.08 | .4403[b] |
| Baseline to day14 | −10.22 ± 6.19 <0.0001[c] | −10.37 ± 5.30 <0.0001[c] | −10.29 ± 5.76 <0.0001[c] | .4587[b] |
| Baseline to day 21 | −10.98 ± 5.99 <0.0001[c] | −11.65 ± 5.12 <0.0001[c] | −11.32 ± 5.57 <0.0001[c] | .1254[b] |
| | *P* value in cefetamet pivoxil | *P* value in cefdinir | *P* value in total | |

[a]Mean (±SD).
[b]Wilcoxon rank-sum test.
[c]Wilcoxon signed-rank test.

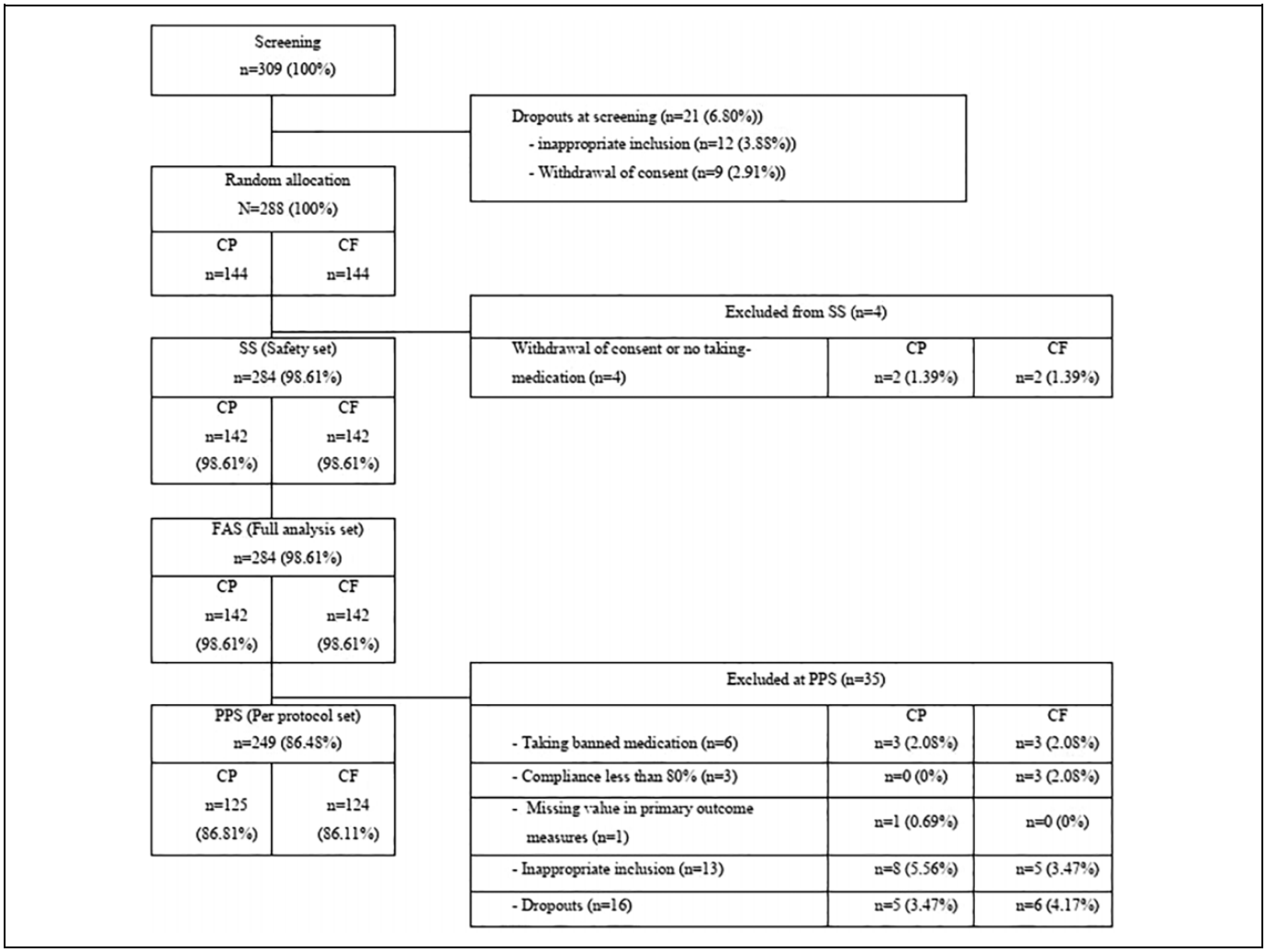


**Figure 1.** Flowchart of the study population.

in the cefdinir group (n = 22) during the study, out of a total of 284 patients.

Diarrhea was the most common adverse event reported in both groups (cefetamet pivoxil, 2.11%, n = 3; and cefdinir, 2.82%, n = 4). All other adverse events reported during the study are listed in Table 5.

During the study, no serious adverse events or drug reactions were identified in either group (Table 5).

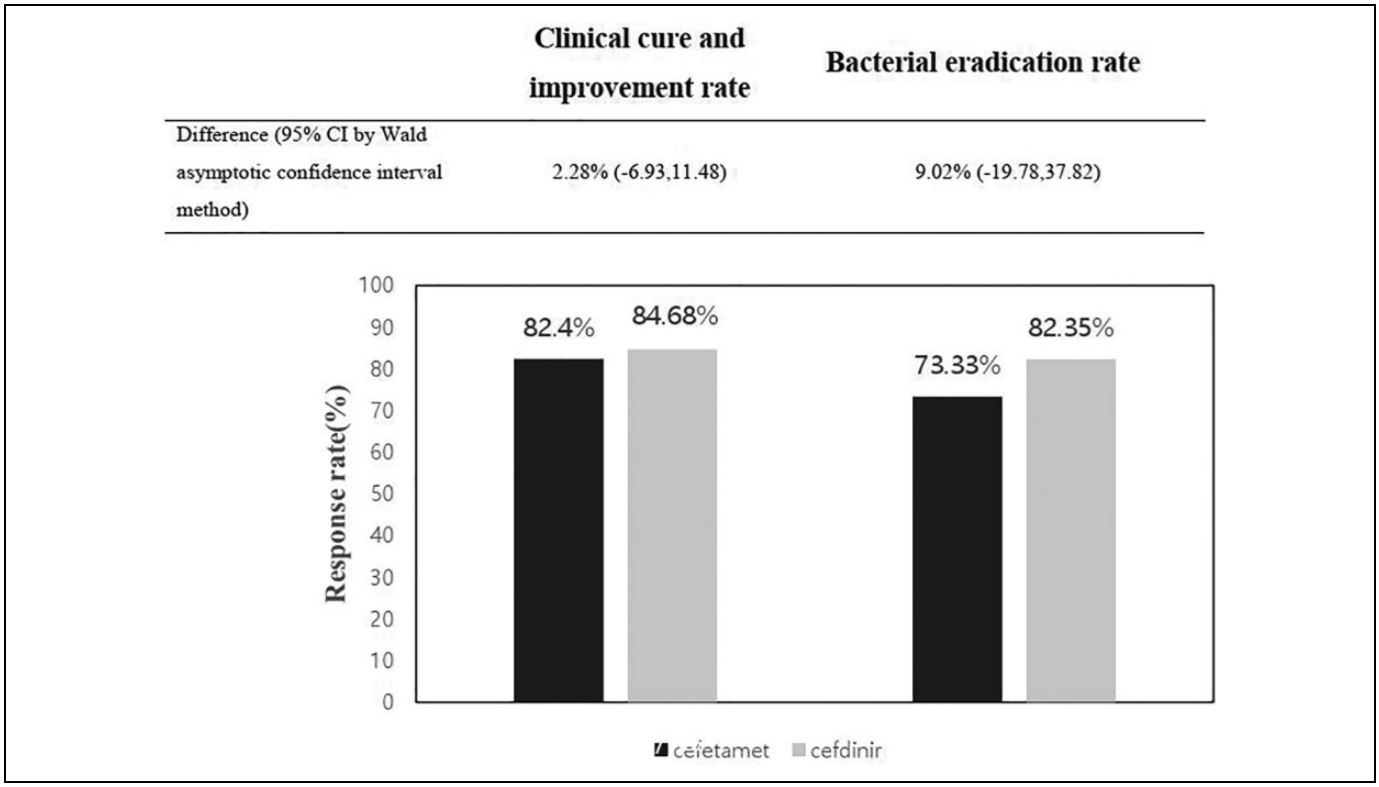


**Figure 2.** Clinical cure and improvement rates and bacterial eradication rate on day 21.

## Discussion

Acute and chronic rhinosinusitis are very common diseases, usually caused by an upper respiratory viral infection. In the United States, over 30 million cases are diagnosed annually, affecting one in 8 adults, approximately 12% of the US population.[10,11] However, only about 0.5% to 2.0% of the acute viral rhinosinusitis (AVRS) cases or flu-like URIs in adults are complicated by bacterial infections.[12]

Therefore, in the early stages of ARS, it is important to discriminate AVRS from ABRS, which is usually very difficult because the general presentation of both types of ARS is very similar, for the proper management of ARS. Many guidelines have suggested that AVRS and ABRS might be discriminated based on the duration, severity, or pattern of symptoms.

The management of ARS is decided according to the clinical diagnosis. Acute viral rhinosinusitis is usually treated with supportive and symptomatic treatments without antibiotics. In the case of ABRS, about 65% of placebo-treated patients spontaneously resolved their symptoms, which can also be interpreted as a result of being potentially misdiagnosed with ABRS. Patients with mild symptoms and uncertain to be diagnosed with ABRS could be watched carefully without treatment, but it is not recommended to watch if appropriate for diagnosis with ABRS.

In general, ABRS may be spontaneously recovered within 1 month. However, IDSA clinical practice guideline13 for ABRS showed that about 65% of placebo-treated patients spontaneously resolved their ABRS symptoms, compared to 72.9% of antibiotics-treated adult patients.

Therefore, patients with mild symptoms and uncertain diagnosis of ABRS could also be watched carefully without treatment, unless the diagnosis of ABRS is appropriate as follows; more than 10 days of persistent symptoms or signs compatible with ARS without clinical improvements, at least 3 to 4 days of severe high fever and purulent nasal discharge of facial pain at the beginning of illness, 5 to 6 days of worsening fever, headache, or nasal discharge increment.[13-15] If ABRS is suspected based on the duration of symptoms (more than 10-14 days), disease progression (not improved or worsened within 10 days of an initial improvement), or the severity of symptoms, empirical treatment with antibiotics or antibiotics based on culture and sensitivity tests can be considered.[1,2,16,17]

*Hemophilus influenzae, Morracella catarrhalis*, and *S pneumoniae* are 3 etiologic pathogens commonly found in the sinus aspirate or endoscopic sampling of middle meatus discharge of ABRS patients and so empirical treatment for ABRS should be effective for these common bacteria.[18]

Although amoxicillin or amoxicillin–clavulanate are recommended as first-line treatments to treat ABRS, many antibiotics including cefdinir have been tried and showed effectiveness in treating ABRS.

The prevalence of antimicrobial resistance, especially that of *S pneumoniae* to penicillin and erythromycin, increased until the 1990s or early 2000s, but after the introduction of pneumococcal conjugate vaccine and efforts to decrease the use of

**Table 5.** Adverse Reactions.

| Symptom/Disease | Cefetamet pivoxil (n = 142) | Cefdinir (n = 142) |
|---|---|---|
| Diarrhea | 3 (2.11) | 4 (2.82) |
| Abdominal pain | 0 (0) | 2 (1.41) |
| Abdominal discomfort | 0 (0) | 1 (0.70) |
| Abdominal distension | 1 (0.70) | 0 (0) |
| Mouth ulceration | 0 (0) | 1 (0.70) |
| Esophagitis | 0 (0) | 1 (0.70) |
| Salivary gland pain | 1 (0.70) | 0 (0) |
| Vomiting | 0 (0) | 1 (0.70) |
| Pruritus | 0 (0) | 3 (2.11) |
| Dermatitis | 0 (0) | 1 (0.70) |
| Dermatitis contact | 1 (0.70) | 0 (0) |
| Prurigo | 1 (0.70) | 0 (0) |
| Urticaria | 0 (0) | 1 (0.70) |
| Nasopharyngitis | 1 (0.70) | 2 (1.41) |
| Bronchitis | 0 (0) | 1 (0.70) |
| Pharyngitis | 1 (0.70) | 0 (0) |
| Rhinitis | 0 (0) | 1 (0.70) |
| Headache | 0 (0) | 3 (2.11) |
| Paraesthesia | 0 (0) | 1 (0.70) |
| Musculoskeletal pain | 1 (0.70) | 1 (0.70) |
| Myalgia | 1 (0.70) | 0 (0) |
| Cough | 1 (0.70) | 0 (0) |
| Rhinitis (allergic) | 1 (0.70) | 0 (0) |
| Eye discharge | 1 (0.70) | 0 (0) |
| Chest pain | 0 (0) | 1 (0.70) |
| Alanine aminotransferase increase | 1 (0.70) | 0 (0) |
| Insomnia | 0 (0) | 1 (0.70) |
| Amenorrhea | 0 (0) | 1 (0.70) |
| Total number of adverse events related to trial medication | 15 (10.56%) | 22 (15.49%) |
| Serious adverse events (SAEs) | 0 | 0 |
| Serious adverse drug reactions (SADRs) | 0 | 0 |

antibiotics, a significant decline has been seen, especially in the United States.[19,20]

In ROK, although high rates of antimicrobial resistance, especially beta-lactam and macrolide resistance among *S pneumoniae* and *H influenzae* have been reported, amoxicillin–clavulanate or cephalosporin except for cefaclor and cefprozil are usually prescribed as initial antibiotics for ABRS.[21,22] The market shares of amoxicillin–clavulanate or cephalosporins in the total per oral antibiotic prescription are approximately 25% and 41%, respectively.

Among the many cephalosporins, cefdinir was reported to be effective in treating ABRS and has been one of the frequently prescribed orally cephalosporins since it was introduced in ROK in 1998.[23] Compared to cefdinir, cefetamet pivoxil has not been frequently prescribed since it was introduced in ROK in 2003 and has been off the market for the last 6 years.

As a part of the reevaluation of drug efficacy by the KFDA, in this multicenter, randomized, double-blind trial, the drug efficacy of cefetamet pivoxil was comparable to cefdinir in patients with ABRS. Treatment with cefetamet pivoxil for 2 weeks showed 82.4% clinical cure and improvement rates in patients with ABRS compared to 84.68% in patients treated with cefdinir for 2 weeks, which confirmed noninferiority using the 95% CI method introduced by Wald. These results showed that cefetamet pivoxil administered twice a day for 2 weeks was as effective as cefdinir 3 times a day for 2 weeks for the treatment of ABRS.

The overall adverse reaction rates of both drugs were 10.56% in the cefetamet pivoxil group and 15.49% in the cefdinir group ($P = .2172$), and no serious adverse events or drug reactions were reported in either group. The most common adverse reactions observed with both drugs was mild gastrointestinal problems (eg, diarrhea and abdominal pain), and the safety profile of cefetamet pivoxil was similar to that reported for other cephalosporins.[23-25]

However, it should be noted that the positive bacterial culture rate was low (7.2% in the cefetamet pivoxil group and 8.1% in the cefdinir group) and so the information on the overall antibacterial efficacy and efficacy of both drugs on resistant strains was limited.

## Conclusion

This study demonstrated that cefetamet pivoxil twice a day was as efficacious and safe as cefdinir 3 times a day for the treatment of ABRS, which suggested that cefetamet pivoxil may be a suitable alternative to cefdinir.

### Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

### Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was financially supported by the Korea United Pharm. Inc but the funder had no role in the study progress, data collection, decision to publish, or preparation of the manuscript.

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### References

1. Rosenfeld RM, Andes D, Bhattacharyya N, et al. Clinical practice guideline: adult sinusitis. *Otolaryngol Head Neck Surg*. 2007; 137(3 suppl):S1-S31. doi:10.1016/j.otohns.2007.06.726
2. Rosenfeld RM, Piccirillo JF, Chandrasekhar SS, et al. Clinical practice guideline (update): adult sinusitis. *Otolaryngol Head Neck Surg*. 2015;152(2 suppl):S1-S39. doi:10.1177/0194599815572097
3. Lanza DC, Kennedy DW. Adult rhinosinusitis defined. *Otolaryngol Head Neck Surg*. 1997;117(3 pt 2):S1-S7. doi:10.1016/s0194-5998(97)70001-9

4. Park S, Moon OR. Patterns of antibiotics utilization in some respiratory diseases in clinics. *J Kor Soc Qual Assur Health Care*. 1998;5(1):58-90.
5. World Health Organization. *Antimicrobial Resistance: Global Report on Surveillance*. World Health Organization; 2014.
6. Kang JH, Kim SM, Kim JH, et al. Penicillin resistant distribution and in-vitro susceptibility of oral antibiotics against Streptococcus pneumoniae, isolated from pediatric patients with community- acquired respiratory infections in Korea. *Clin Exp Pediatr*. 2005;48(1):40-47.
7. Information NCfB. PubChem Database. Cefdinir. July 4, 2020.
8. Information NCfB. PubChem Database. Cefetamet pivoxil. June 17, 2020.
9. Bryson HM, Brogden RN. Cefetamet pivoxil. A review of its antibacterial activity, pharmacokinetic properties and therapeutic use. *Drugs*. 1993;45(4):589-621. doi:10.2165/00003495-199345040-00009
10. Lethbridge-Çejku M, Rose D, Vickerie J. Summary health statistics for u.s. adults: national health interview survey, 2004. *Vital Health Stat* 10. 2006;(228):1-164.
11. Blackwell DL, Lucas JW, Clarke TC. Summary health statistics for U.S. adults: national health interview survey, 2012. *Vital Health Stat* 10. 2014;(260):1-161.
12. Gwaltney JMJr. Acute community-acquired sinusitis. *Clin Infect Dis*. 1996;23(6):1209-1223; quiz 1224-5. doi:10.1093/clinids/23.6.1209
13. Mori F, Fiocchi A, Barni S, et al. Management of acute rhinosinusitis. *Pediatr Allergy Immunol*. 2012;23(suppl 22):27-31. doi:10.1111/j.1399-3038.2012.01321.x
14. Gwaltney JM Jr, Hendley JO, Simon G, Jordan WSJr. Rhinovirus infections in an industrial population. II. Characteristics of illness and antibody response. *JAMA*. 1967;202(6):494-500.
15. Chow AW, Benninger MS, Brook I, et al. IDSA clinical practice guideline for acute bacterial rhinosinusitis in children and adults. *Clin Infect Dis*. 2012;54(8):e72-e112. doi:10.1093/cid/cir1043
16. Meltzer EO, Hamilos DL. Rhinosinusitis diagnosis and management for the clinician: a synopsis of recent consensus guidelines. *Mayo Clin Proc*. 2011;86(5):427-443. doi:10.4065/mcp.2010.0392
17. Gwaltney JM Jr, Wiesinger BA, Patrie JT. Acute community-acquired bacterial sinusitis: the value of antimicrobial treatment and the natural history. *Clin Infect Dis*. 2004;38(2):227-233. doi:10.1086/380641
18. Talbot GH, Kennedy DW, Scheld WM, Granito K. Rigid nasal endoscopy versus sinus puncture and aspiration for microbiologic documentation of acute bacterial maxillary sinusitis. *Clin Infect Dis*. 2001;33(10):1668-1675. doi:10.1086/323813
19. Song JH, Jung SI, Ko KS, et al. High prevalence of antimicrobial resistance among clinical Streptococcus pneumoniae isolates in Asia (an ANSORP study). *Antimicrob Agents Chemother*. 2004;48(6):2101-2107. doi:10.1128/aac.48.6.2101-2107.2004
20. Liñares J, Ardanuy C, Pallares R, Fenoll A. Changes in antimicrobial resistance, serotypes and genotypes in Streptococcus pneumoniae over a 30-year period. *Clin Microbiol Infect*. 2010;16(5):402-410. doi:10.1111/j.1469-0691.2010.03182.x
21. Kim SH, Bae IK, Park D, et al. Serotype distribution and antimicrobial resistance of Streptococcus pneumoniae isolates causing invasive and noninvasive pneumococcal diseases in Korea from 2008 to 2014. *Biomed Res Int*. 2016;2016. doi:10.1155/2016/6950482
22. Han SB, Kim JH, Kang JH, et al. Recent epidemiology of Streptococcus pneumoniae in nasopharynxes of Korean children with acute otitis media. *J Infect Chemother*. 2017;23(3):136-141. doi:10.1016/j.jiac.2016.10.006
23. Gwaltney JM Jr, Savolainen S, Rivas P, et al. Comparative effectiveness and safety of cefdinir and amoxicillin-clavulanate in treatment of acute community-acquired bacterial sinusitis. cefdinir sinusitis study group. *Antimicrob Agents Chemother*. 1997;41(7):1517-1520. doi:10.1128/aac.41.7.1517
24. File TM Jr, Segreti J, Dunbar L, et al. A multicenter, randomized study comparing the efficacy and safety of intravenous and/or oral levofloxacin versus ceftriaxone and/or cefuroxime axetil in treatment of adults with community-acquired pneumonia. *Antimicrob Agents Chemother*. 1997;41(9):1965-1972. doi:10.1128/aac.41.9.1965
25. Neu HC, Chick TW. Efficacy and safety of clarithromycin compared to cefixime as outpatient treatment of lower respiratory tract infections. *Chest*. 1993;104(5):1393-1399. doi:10.1378/chest.104.5.1393