

# Treatment of Nosocomial Pneumonia with Cefoperazone/Sulbactam

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## Abstract

Twenty-four patients with gram-negative nosocomial pneumonia were enrolled in the study of efficacy and safety of cefoperazone/sulbactam. Cefoperazone/sulbactam was given intravenously at the dose of 2 g (1 g of cefoperazone plus 1 g of sulbactam) every 12 hours for approximately 13 days. The most common pathogen found in the sputum was *Pseudomonas aeruginosa*. Clinical cure and improvement were observed in 15 patients (63%) and 2 patients (8%) respectively. Causative pathogens were eradicated from sputum in 16 patients (67%) at the end of therapy. Side effects of cefoperazone/sulbactam were observed in 3 patients (13%); all were mild, transient and self-limited. It is suggested that cefoperazone/sulbactam is efficacious and safe in therapy of gram-negative nosocomial pneumonia. (*J Infect Dis Antimicrob Agents* 1999;16:65-8.)

## INTRODUCTION

In Thailand, 12 per cent of hospitalized patients develop nosocomial infections.<sup>1</sup> Pneumonia is found to be second most common nosocomial infection and accounted for 15 percent of the nosocomial infections cases or more than 10,000 cases each year. Nosocomial pneumonia is associated with high mortality for ICU patients<sup>2</sup> and is the leading cause of infection-related death in hospitalized patients.<sup>3-5</sup> Common causative agents of nosocomial pneumonia are multidrug resistant gram-negative bacilli (MDR-GNB) notably *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Klebsiella pneumoniae*, *Escherichia coli*, *Enterobacter* spp. Antimicrobial effective for gram-negative bacteria with coverage for MDR-GNB are recommended for empiric therapy of nosocomial

pneumonia. Cefoperazone is a third-generation cephalosporin with good activity against gram-negative bacilli, including *Pseudomonas aeruginosa*. The addition of sulbactam to cefoperazone expands the spectrum of activity of cefoperazone in beta-lactamase producing organisms<sup>6</sup> and this combination should be useful for treating hospital acquired infections, including nosocomial pneumonia.

The objective of the study is to evaluate the efficacy and safety of cefoperazone/sulbactam in the treatment of nosocomial pneumonia in Thai patients.

## PATIENTS AND METHODS

Study patients were selected from patients aged 16 years and older who developed pneumonia after having been hospitalized in Chulalongkorn Hospital,

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Pramongkutklao Hospital or Central Chest Hospital for at least 48 hours. The diagnostic criteria of gram-negative bacterial pneumonia were fever, dyspnea, purulent sputum, new pulmonary infiltrates on chest X-rays and the presence of gram-negative bacilli in the sputum. All the study patients gave their informed consent prior to study enrollment. Excluded from the study were patients allergic to beta-lactams, pregnant or lactating, terminally ill (might succumb within few days), or had causative pathogens resistant to cefoperazone/sulbactam.

Cefoperazone/sulbactam was given intravenously at the dose of 1-2 g of cefoperazone plus 1-2 g of sulbactam every 12 hours. The maximum recommended daily dose of cefoperazone/sulbactam was 8 g (4 g of cefoperazone plus 4 g of sulbactam). The dosage regimen of cefoperazone/sulbactam was adjusted according to body weight and/or renal function results. The duration of antibiotic therapy was approximately 13 days (range 10-21). All study patients received vitamin K 10 mg parenterally thrice a week until cefoperazone/sulbactam was discontinued.

Each patient was assessed for clinical response, microbiological response and safety. Clinical response was classified as cure (disappearance of all pre-treatment symptoms and signs of infection), improvement (partial disappearance of symptoms and signs of infection), failure (no change or worsening of symptoms and signs of infection) and relapse (improvement or disappearance of symptoms and signs of infection followed by worsening or reappearance of infection within 2 weeks after cessation of cefoperazone/sulbactam therapy). Microbiological response was classified as eradication (loss of pre-treatment pathogen and no emergence of new pathogen), persistence (of pre-treatment pathogen), super-infection (appearance of a new pathogen even though the pre-treatment pathogen is eradicated) and re-infection or relapse (eradication and then reappearance of pre-treatment pathogen).

## RESULTS

Twenty-four patients were eligible for the study during December 1994 to August 1995. Fifteen were from Chulalongkorn Hospital, seven cases from Pramongkutklao Hospital, and 2 cases from Central Chest Hospital. Fourteen patients were male. The mean age was 56 years. The causative agents

of pneumonia discovered in sputum cultures were shown in Table 1. Most of them were *Pseudomonas aeruginosa*. The same pathogen was found in both the blood and sputum of 3 patients (*Acinetobacter anitratus* in 2 cases and *Klebsiella pneumoniae* in the other). The average duration of cefoperazone/sulbactam therapy for the patients who responded to treatment was 13 days (range 10-21 days). Clinical response and microbiological response were shown in Table 2 and 3. Most of the patients were cured (63%) or improved (8%) and the eradication of the causative pathogens from the sputum was observed in 67 percent of the patients. Two of the three patients who had a positive blood culture failed the therapy. Adverse drug reactions were observed in 3 patients (13%): 2 had mild and transient increase in liver enzymes and 1 had thrombophlebitis.

**Table 1. Causative agents of nosocomial pneumonia in 24 study patients.**

Organism	n (%)
<i>Pseudomonas aeruginosa</i>	9 (37.5%)
<i>Klebsiella pneumoniae</i>	4 (16.7%)
<i>Acinetobacter anitratus</i>	4 (16.7%)
<i>Enterobacter cloacae</i>	2 (8.3%)
<i>Pseudomonas aeruginosa</i> + <i>Klebsiella pneumoniae</i>	1 (4.2%)
<i>Pseudomonas aeruginosa</i> + <i>Serratia marcescens</i>	1 (4.2%)
<i>Escherichia coli</i>	1 (4.2%)
<i>Pseudomonas cepacia</i>	1 (4.2%)
<i>Serratia marcescens</i>	1 (4.2%)

**Table 2. Clinical response of 24 study patients.**

Type of clinical response	n (%)
Cure	15 (63%)
Improvement	2 (8%)
Failure	7 (29%)

**Table 3. Microbiological response of 24 study patients.**

Type of microbiological response	n (%)
Eradication	16 (67%)
Persistence	7 (29%)
Super-infection	1 (4%)

## DISCUSSION

The principal causative agents of nosocomial pneumonia are gram-negative bacteria especially *Pseudomonas aeruginosa*. Most of them are resistant to first and third-generation cephalosporins as well as some aminoglycosides.<sup>7</sup> The American Thoracic Society recommends a beta-lactam/beta-lactamase inhibitor combination or a second- or third-generation cephalosporin for empiric therapy of early-onset nosocomial pneumonia and combination antibiotics, including either an aminoglycoside or ciprofloxacin and any of a group of extended-spectrum beta-lactam antibiotics for late-onset nosocomial pneumonia (more than 5 days after admission).<sup>8</sup> The recommendations are based on the type of causative organisms. The early-onset nosocomial pneumonias are most likely caused by enterobacteriaceae, streptococci, hemophilus whereas the late-onset nosocomial pneumonias are commonly due to *Pseudomonas aeruginosa*, *Acinetobacter* spp. Cefoperazone/sulbactam is a combination of anti-pseudomonas third-generation cephalosporin and beta-lactamase inhibitor and should be suitable for empiric therapy of nosocomial pneumonia.

This study also found that *Pseudomonas aeruginosa* was the most common causative pathogen of nosocomial pneumonia so an antibiotic with anti-pseudomonas activity should be the drug of choice. Third-generation cephalosporins with anti-pseudomonas activity, ceftazidime and cefoperazone, are commonly prescribed for nosocomial pneumonia. Ceftazidime has been shown to be effective in treating nosocomial pneumonia like cefoperazone, ticarcillin plus tobramycin and cefazolin plus tobramycin.<sup>9</sup> Cefoperazone has been shown to be efficacious for monotherapy of nosocomial pneumonia with a response rate of 80 percent.<sup>10</sup>

Mangi et al compared cefoperazone monotherapy of nosocomial pneumonia with either a combination of clindamycin plus gentamicin or a combination cefazolin plus gentamicin in a randomized controlled trial.<sup>11</sup> Cefoperazone was as effective as the combination therapy, cure rates were 87 percent and 72 percent for cefoperazone and combination therapy respectively.

The addition of sulbactam to cefoperazone not only expand the activity of cefoperazone on beta-lactamase producing bacteria, but also expands it to cover *Acinetobacter* spp.<sup>12</sup> which is one of the most

common pathogens of nosocomial infections and nosocomial pneumonia.<sup>13</sup> Thus the empiric therapy recommended by the American Thoracic Society was most often not appropriate against *Acinetobacter* spp.

*Acinetobacter anitratus* was isolated from the sputum of 4 patients (16.7%) in this study. The response rate of gram-negative nosocomial pneumonia treated with cefoperazone/sulbactam was 71 percent whereas the response rate for ceftazidime, imipenem, aztreonam, fluoroquinolone, meropenem monotherapy for nosocomial pneumonia was 70-90 percent.<sup>11,14-16</sup> As a result, cefoperazone/sulbactam should be appropriate for empiric therapy of gram-negative nosocomial pneumonia.

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