ORIGINAL RESEARCH

Clinical Efficacy of Cefoperazone-Sulbactam versus Piperacillin-Tazobactam in the Treatment of Hospital-Acquired Pneumonia and Ventilator-Associated Pneumonia

Chia-Hung Chen [1]
Chih-Yen Tu [1]
Wei-Chih Chen [2]
Li-Kuo Kuo [3]
Yao-Tung Wang [4]
Pin-Kuei Fu [5]
Shih-Chi Ku [6]
Wen-Feng Fang [7]
Chin-Ming Chen [8]
Chih-Cheng Lai [9]

[1]Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, China Medical University Hospital, Taichung, Taiwan; [2]Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan; [3]Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Mackay Memorial Hospital, Taipei, Taiwan; [4]Division of Pulmonary Medicine, Department of Internal Medicine, Chung Shan Medical University Hospital, Taichung, Taiwan; [5]Department of Critical Care Medicine, Taichung Veterans General Hospital, Taichung, Taiwan; [6]Division of Chest Medicine, Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan; [7]Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan; [8]Department of Intensive Care Medicine, Chi Mei Medical Center, Tainan, Taiwan; [9]Department of Internal Medicine, Kaohsiung Veterans General Hospital, Tainan Branch, Tainan, Taiwan

Correspondence: Chih-Cheng Lai
Email dtmed141@gmail.com

Objective: The aim of this study was to compare the usefulness of cefoperazone-sulbactam and that of piperacillin-tazobactam in the treatment of hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP).

Methods: This retrospective study included the adult patients receiving cefoperazone-sulbactam or piperacillin-tazobactam against HAP/VAP in nine hospitals in Taiwan from March 1, 2018 to May 30, 2019. Primary outcome was clinical cure rate.

Results: A total of 410 patients were enrolled. Among them, 209 patients received cefoperazone-sulbactam and 201 patients received piperacillin-tazobactam. Overall, cefoperazone-sulbactam group had similar distribution of age, sex, or SOFA scores as piperacillin-tazobactam group. However, cefoperazone-sulbactam had higher comorbidity score and disease severity than piperacillin-tazobactam group (Charlson score: 6.5 ± 2.9 vs 5.7 ± 2.7, p < 0.001; APACHE II score: 21.4 ± 6.2 vs 19.3 ± 6.0, p = 0.002). Regarding clinical outcomes, no significant difference in clinical cure and failure rates was observed between cefoperazone-sulbactam and piperacillin-tazobactam group (clinical cure rate: 80.9% vs 80.1% and clinical failure rate: 17.2% vs 18.4%, p = 0.943). Moreover, no significant difference in clinical effectiveness and ineffectiveness rates was observed between cefoperazone-sulbactam and piperacillin-tazobactam group (clinical effective rate: 80.9% vs 80.6% and clinical ineffective rate: 17.7% vs 18.9%, p = 0.711). The all-cause mortality rates of the cefoperazone-sulbactam and piperacillin-tazobactam groups were similar (23.9% vs 20.9%, p = 0.48). After adjustment of Charlson score and APACHE II score, the similarities in these clinical outcomes did not change in overall patients and patients with HAP or VAP.

Conclusion: For treating adult patients with nosocomial pneumonia, cefoperazone-sulbactam was as effective as piperacillin-tazobactam.

Keywords: cefoperazone-sulbactam, hospital-acquired pneumonia, piperacillin-tazobactam, ventilator-associated pneumonia

Introduction

Hospital-acquired pneumonia (HAP) is the most common type of hospital-acquired infections,[1,2] and ventilator-associated pneumonia (VAP) is also a common type of infection in intensive care units (ICUs).[3] Importantly, both HAP and VAP are associated with high morbidity, mortality, and health-care expenditure.[2–4] Although administration of appropriate antibiotics remains the most important treatment for patients with HAP/VAP,[2,3] the emergence of antibiotic resistance among causative pathogens—

multidrug resistant organisms (MDROs)—has largely limited therapeutic options. Gram-negative bacilli (GNB), such as *Pseudomonas aeruginosa* and *Enterobacteriaceae*, play an important role in HAP/VAP,[5–7] and many kinds of antibiotic-resistance mechanism have been detected among these pathogens.[8,9] Therefore, a combination of ß-lactam and ß-lactamase inhibitor as a broad-spectrum antibiotic was recommended as one of therapeutic options in the treatment of HAP/VAP.

Cefoperazone-sulbactam is one of combinations of ß-lactam and ß-lactamase inhibitors.[10] Many studies have demonstrated its potent in vitro activity against commonly encountered respiratory pathogens and also MDROs, including ESBL-producing *Escherichia coli* and *Klebsiella pneumoniae*.[10–15] However, very few clinical studies have assessed the effectiveness of cefoperazone-sulbactam for the treatment of HAP/VAP.[16,17] We conducted this study to compare the clinical efficacy of cefoperazone-sulbactam with that of piperacillin-tazobactam, which is another commonly used ß-lactam and ß-lactamase inhibitor antibiotic in the treatment of HAP/VAP.

Methods
Study Design and Data Collection
This study was based on retrospective analyses, using clinical information extracted from BATTLE study, which investigated the efficacy and safety of Brosym® (TTY Biopharm Company, Taiwan) in the treatment of adult patients with severe community-acquired pneumonia (SCAP) and nosocomial pneumonia. The patients enrolled in BATTLE study were those receiving empirical cefoperazone-sulbactam or piperacillin-tazobactam for treating SCAP, HAP and VAP, in which study subjects were identified from the electronic database in each study sites. BATTLE study was conducted in eight medical centers and one regional hospital in Taiwan between March 2018 and May 2019. All three hospitals were located in north, central, and south Taiwan. The present study evaluated the clinical efficacy of cefoperazone-sulbactam or piperacillin-tazobactam for the treatment of HAP or VAP. The diagnosis of pneumonia was made based on the newly developed or progressive radiographic lung infiltration/consolidation in patients with 2 or more of the following: cough, fever, hypothermia, purulent sputum or respiratory secretion, and characteristic physical signs.[3] In each study site, respiratory specimens and blood were routinely sampling for culture before prescribing antibiotics. In patients with HAP, pneumonia developed ≥ 48 hours after hospitalization; whereas in

patients with VAP, pneumonia developed after receiving mechanical ventilation for more than 48 hours.[3] In this study, primary dose of cefoperazone-sulbactam (1 gram/1 gram) was 4 g every 12 hours and piperacillin-tazobactam (2 gm/250 mg) was 4.5 g every 8 hours before dose adjustment according to renal function. Data pertaining to the demographic characteristics of the patients, their underlying disease/conditions, disease severity, microbiological information, antibiotic treatment, and clinical outcomes were retrospectively collected after obtaining approval from local ethics committees or institutional review boards. Informed consent was not required by the approving ethics committees because all data were collected on a routine basis, and the analysis was conducted retrospectively. All methods, including patient data confidentiality, were performed in accordance with the Declaration of Helsinki.

Outcome
The primary outcome measured was clinical cure rate, which was defined as the proportion of patients in which the clinical symptoms or signs resolved or improved 7 days after the end of treatment, and in which no additional antibiotics were required. In contrast, clinical failure was defined as one of the following scenarios: clinical symptoms or signs deteriorated or persisted during treatment and required additional antibiotics for management; death due to pneumonia after 3 days of antibiotic treatment; or the development of complications, such as empyema or a lung abscess. An indeterminate outcome was defined as one of the following: the patient was transferred to another hospital or refused further treatment; death due to pneumonia within 2 days of antibiotic treatment; death due to a cause other than pneumonia during treatment; or incomplete treatment due to allergy, severe adverse events, or other personal reasons. The secondary outcomes measured were the clinical effective rate, the risk of adverse events, and in-hospital mortality. Clinical effectiveness was defined as the improvement of clinical symptoms and signs; radiographic findings; or inflammation markers, such as white blood cell counts, procalcitonin, or c-reactive protein levels. Ineffectiveness was defined as when any one of the three criteria listed above was not achieved. Indeterminate effectiveness was defined as when the above three criteria could not be assessed.

Statistical Analysis
Continuous variables are reported as the mean and standard deviation (SD). Categorical variables are presented as frequency counts with percentages. The differences in baseline

characteristics and clinical variables between the cefopera-zone-sulbactam and piperacillin-tazobactam groups were eval-uated using the Fisher's exact test (for continuous variables) and the Wilcoxon rank sum test (for categorical variables). Significance was set at p <0.05 (two-tailed). Differences in the crude relative risk (RR) and adjusted RR (adjusted for propen-sity score) of the outcomes between the cefoperazone-sulbactam and piperacillin-tazobactam groups were calculated using Statistical Analysis System® (SAS) for Windows (Version 9.4 or higher, SAS Institute, Cary, North Carolina, USA).

Results
Demographic Data
During the study period, 410 patients (n = 345 in HAP, n = 65 in VAP) were enrolled. Of these, 209 patients received cefoperazone-sulbactam and 201 patients received pipera-cillin-tazobactam. The mean age of patients receiving cefoperazone-sulbactam was 75.1 ± 14.8 years and 141 (67.5%) were male. The median treatment duration was 9.0 days. Their Charlson, APACHE II, and SOFA scores were 6.5 (± 2.9), 21.4 (± 6.2), and 5.3 (± 2.9), respectively. Patients who received cefoperazone-sulbactam had higher occurrences of myocardial infarction, stroke and dementia than patients receiving piperacillin-tazobactam (all p < 0.05). In addition, the Charlson and APACHE II score were significantly higher in cefoperazone-sulbactam group than piperacillin-tazobactam group. In contrast, there were no significant differences in age, sex, or SOFA scores between patients receiving cefoperazone-sulbactam and piperacillin-tazobactam (Table 1).

Microbiologic Distribution
For all patients, blood and respiratory specimens were sampled for culture to identify pathogens; however, only 64.1% (n = 134) of cefoperazone-sulbactam group and 39.3% (n = 79) of piperacillin-tazobactam group had iden-tified pathogens. In the cefoperazone-sulbactam group, *P. aeruginosa* (18.2%, n = 38) and *Acinetobacter* spp. (17.6%, n = 36) were the most common bacteria, followed by *K. pneumoniae* (17.2%, n = 32). Similar findings were observed in patients receiving piperacillin-tazobactam; the most common bacteria were *P. aeruginosa* (9.5%), fol-lowed by *Acinetobacter* spp. (9.0%) and *K. pneumoniae* (6.5%) (Table 2). In addition, concomitant bacteremia was found in 5.2% (n = 11) and 10.9% (n = 22) of patients receiving cefoperazone-sulbactam and piperacillin-

tazobactam, respectively. No significant difference was observed in terms of microbiologic distribution and the incidence of concomitant bacteremia (all p > 0.05).

Outcomes
Cefoperazone-sulbactam group had their clinical cure rate of 80.9% and the clinical failure rate was 17.2%. Overall, these clinical outcomes of cefoperazone-sulbactam group were similar to those of piperacillin-tazobactam group (p = 0.943). Regarding secondary outcomes, the cefoperazone-sulbactam group had a clinical effective rate of 80.9% and an ineffective rate of 17.7%, which were similar to piperacillin-tazobactam group (p = 0.711). The all-cause mortality of the cefoperazone-sulbactam group and piperacillin-tazobactam was similar, too (23.9% vs 20.9%, p = 0.480). A similar trend was observed for pneumonia-related mortality (cefoperazone-sulbactam vs piperacillin-tazobactam, 12.9% vs 9.0%, p = 0.304; Table 3). Subgroup analysis based on the different study sites revealed no significant differences in the primary outcome (the clinical cure rate) or secondary outcomes (the clinical effective rate, in-hospital mortality, and pneumonia-related mortality) between patients who received cefoperazone-sulbactam and piperacillin-tazobactam in each hospital (data not shown, all p > 0.05). However, one site only enrolled patients in the cefoperazone-sulbactam group. In addition, the clinical out-come and mortality between patients receiving cefoperazone-sulbactam and piperacillin for HAP and VAP was similar (Figures 1 and 2). Among HAP patients, patients receiving cefoperazone-sulbactam had less requirement of mechanical ventilation (MV) and further ICU admission than those receiv-ing piperacillin-tazobactam (MV use: 18.0% versus 34.7%, p = 0.0007; ICU admission: 15.1% versus 36.4%, p < 0.0001). Moreover, the clinical cure rate between cefoperazone-sulbactam and piperacillin-tazobactam group did not differ for causative pathogens, including *E. coli* (90.0% [9/10] vs 71.4% [5/7]), *K. pneumoniae* (81.3% [26/32] vs 76.9% [10/13]), *P. aeruginosa* (76.3% [29/38] vs 78.9% [15/19]) and *Acinetobacter* spp. (77.8% [28/36] vs 61.1% [11/18]) (all p > 0.05). Regarding the adverse events, only one patient in cefo-perazone-sulbactam group had skin rash and two patients in piperacillin-tazobactam had diarrhea group. Among cefoper-azone-sulbactam group, only 30 patients had received interna-tional normalized ratio (INR) test during both pre- and post-treatment after one week. No significant difference between the pre- and post-treatment INR was found in this population (1.10 ± 0.15 versus 1.19 ± 0.21, p = 0.06) and no significant bleeding was reported in both groups.

Table 1 Demographic Characteristics of the Patients Receiving Cefoperazone-Sulbactam and Piperacillin-Tazobactam

Variable	Cefoperazone-Sulbactam, n = 209	Piperacillin-Tazobactam, n = 201	p
Age	75.1±14.8	74.6±16.6	0.794
Sex			0.671
Male	141 (67.5)	140 (69.7)	
Female	68 (32.5)	61 (30.3)	
Type of infection			0.344
Hospital-acquired pneumonia	172 (82.3)	173 (86.1)	
Ventilator-associated pneumonia	37 (17.7)	28 (13.9)	
Underlying disease			
Dementia	91 (43.5)	38 (18.9)	<0.001
Diabetes mellitus	65 (31.1)	80 (39.8))	0.079
Chronic pulmonary disease	56 (26.8)	48 (23.9)	0.570
Congestive heart failure	45 (21.5)	32 (15.9)	0.165
Stroke	40 (19.1)	14 (7.0)	<0.001
Peptic ulcer disease	33 (15.8)	23 (11.4)	0.250
Myocardial infarction	31 (14.8)	13 (6.5)	0.007
Chronic kidney disease	27 (12.9)	31 (15.4)	<0.001
Solid cancer	18 (8.6)	17 (8.5)	>0.999
Chronic liver disease	18 (8.6)	11 (5.5)	0.250
Peripheral vascular disease	11 (5.3)	4 (2.0)	0.113
Charlson score	6.5±2.9	5.7±2.7	<0.001
APACHE II score	21.4±6.2 (n = 171)	19.3±6.0 (n = 109)	0.002
SOFA score	5.3±2.9 (n = 171)	5.8±3.5 (n = 112)	0.257

Table 2 Microbiological Distribution of Major Pathogens

Pathogens	No (%) of Pathogen					
	All		Hospital-Acquired Pneumonia		Ventilator-Associated Pneumonia	
	Cefoperazone-Sulbactam, n = 209	Piperacillin-Tazobactam, n = 201	Cefoperazone-Sulbactam, n = 172	Piperacillin-Tazobactam, n = 173	Cefoperazone-Sulbactam, n = 37	Piperacillin-Tazobactam, n = 28
Pseudomonas aeruginosa	38 (18.2)	19 (9.5)	34 (19.8)	14 (8.1)	4 (10.8)	5 (17.9)
Acinetobacter spp.	36 (17.2)	18 (9.0)	22 (12.8)	17 (9.8)	14 (37.8)	1 (3.6)
Klebsiella pneumoniae	32 (15.3)	13 (6.5)	29 (16.9)	10 (5.8)	3 (3.0)	3 (10.7)
Escherichia coli	10 (4.8)	7 (3.5)	10 (5.8)	7 (4.0)	0 (0)	0 (0)
Streptococcus spp.	7 (3.3)	12 (6.0)	5 (2.9)	12 (6.9)	2 (5.4)	0 (0)

Outcome Analysis

Because different comorbidities and disease severity were found between the cefoperazone-sulbactam and piperacillin-tazobactam groups, we used propensity score method to adjust for these two confounding factors. After adjusting the APACHE II and Charlson scores, the clinical cure rate of cefoperazone-sulbactam remained comparable to that of piperacillin-tazobactam (adjusted RR [aRR], 0.93; 95% confidence interval [95% CI], 0.82–1.05) in the overall population (Table 3). No significant difference was observed in terms of the clinical cure rate of cefoperazone-sulbactam and piperacillin-tazobactam in the treatment

Table 3 Clinical Outcomes Between Cefoperazone-Sulbactam and Piperacillin-Tazobactam Groups

Variable	Cefoperazone-Sulbactam, n = 209	Piperacillin-Tazobactam, n = 201	p
Primary outcome			0.943
Clinical cure	169 (80.9)	161 (80.1)	
Failure	36 (17.2)	37 (18.4)	
Indeterminate	4 (1.9)	3 (1.5)	
Secondary outcome			0.711
Effective	169 (80.9)	162 (80.6)	
Ineffective	37 (17.7)	38 (18.9)	
Indeterminate	3 (1.4)	1 (0.5)	
In-hospital mortality			
All-cause mortality	50 (23.9)	42 (20.9)	0.480
Pneumonia related	27 (12.9)	18 (9.0)	0.304

patients with HAP (aRR, 0.89; 95% CI, 0.77–1.03), and VAP (aRR, 1.33; 95% CI, 0.33–1.92) (Table 4). Regarding secondary outcomes, cefoperazone-sulbactam was comparable to piperacillin in terms of clinical efficacy rate, in-hospital mortality, and pneumonia-related mortality, which remained unchanged in the overall population, HAP, and VAP groups (Table 3).

Discussion

This retrospective study determined the clinical efficacy of cefoperazone-sulbactam for treating patients with HAP/VAP; it was comparable to piperacillin-tazobactam in terms of both primary and secondary outcomes. First, the clinical cure and failure rate of cefoperazone-sulbactam were similar to those of piperacillin-tazobactam. Moreover, there was no statistically
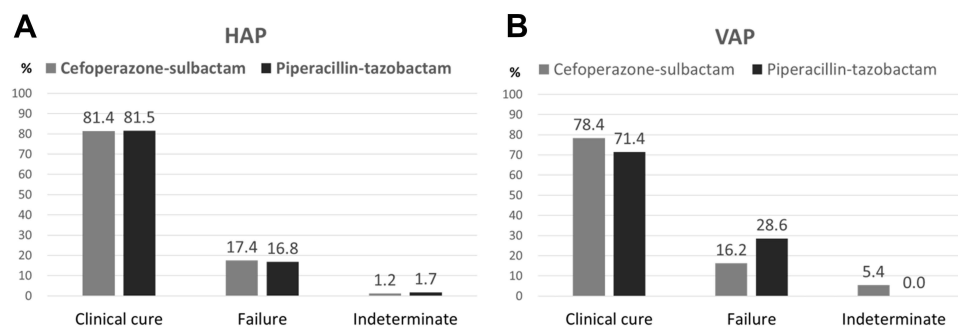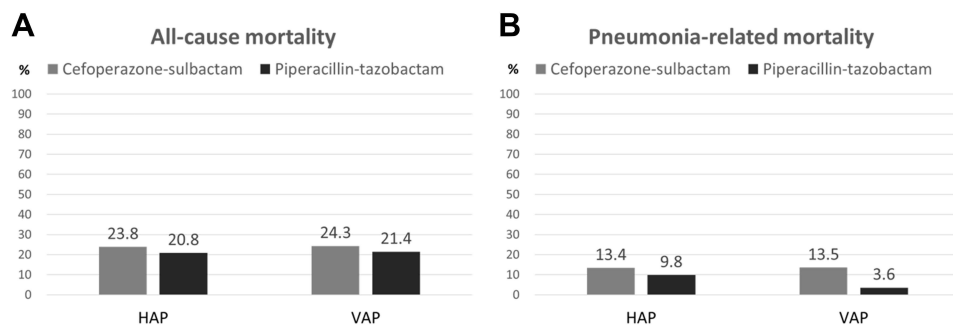

Figure 1 Clinical outcome of patients receiving cefoperazone-sulbactam and piperacillin-tazobactam for hospital-acquired pneumonia (HAP) (**A**) and ventilator-associated pneumonia (VAP) (**B**).

Figure 2 All-cause mortality (**A**) and pneumonia-related mortality (**B**) of patients receiving cefoperazone-sulbactam and piperacillin-tazobactam for hospital-acquired pneumonia (HAP) and ventilator associated pneumonia (VAP).

Table 4 Outcome Analysis

Variable	All		Hospital-Acquired Pneumonia		Ventilator-Associated Pneumonia	
	Crude RR (95% CI)	Adjust RR* (95% CI)	Crude RR (95% CI)	Adjust RR* (95% CI)	Crude RR (95% CI)	Adjust RR* (95% CI)
Clinical cure	1.01 (0.92, 1.11)	0.93 (0.82, 1.05)	1.00 (0.90, 1.10)	0.89 (0.77, 1.03)	1.10 (0.82, 1.46)	1.33 (0.93, 1.92)
Clinical effectiveness	1.00 (0.91, 1.10)	0.90 (0.80, 1.03)	0.98 (0.89, 1.09)	0.84 (0.73, 0.98)	1.14 0.86, 1.50)	1.33 (0.93, 1.92)
In-hospital mortality						
All-cause mortality	1.14 (0.80, 1.64)	1.10 (0.65, 1.84)	1.15 (0.77, 1.70)	1.31 (0.75, 2.30)	1.14 (0.46, 2.82)	0.60 (0.17, 2.14)
Pneumonia related	1.26 (0.82, 1.94)	1.01 (0.51, 2.00)	1.19 (0.77, 1.84)	0.76 (0.40, 1.47)	2.67 (0.39, 18.42)	1.67 (0.16, 17.89)

Note: *Adjusted APACHE II and Charlson score using propensity score matching.

significant difference between the clinical effective and ineffective rates of cefoperazone-sulbactam and piperacillin-tazobactam. Second, the all-cause and pneumonia-related mortality of patients receiving cefoperazone-sulbactam was similar to that of patients receiving piperacillin-tazobactam. Third, cefoperazone-sulbactam was found to be comparable to piperacillin-tazobactam in all analyses, including the subgroup analysis based on the study sites, causative pathogens and the HAP and VAP groups. Finally, after adjustment for Charlson and APACHE II scores, cefoperazone-sulbactam exhibited similar clinical outcomes compared with piperacillin-tazobactam in the HAP/VAP, HAP, and VAP groups. Furthermore, the mortality rate of HAP/VAP, when treated with cefoperazone-sulbactam, was 23.9%, which was consistent with the findings of previous studies.[7,18,19] Similar to the findings of the ASPECT-NP trial,[7] the rates of 28-day all-cause mortality in patients with nosocomial pneumonia were 24.0% (87/362) and 25.3% (92/364) among the ceftolozane-tazobactam and meropenem groups, respectively. A similar finding was shown in another retrospective analysis of patients with HAP/VAP, in which the 30-day mortality was 18.1%–22.8%.[18] Therefore, our results suggest that cefoperazone-sulbactam, like piperacillin-tazobactam, could be an effective therapeutic option for the management of patients with HAP/VAP.

In this study, *P. aeruginosa, Acinetobacter* spp., and *K. pneumoniae* were found to be the most common pathogens causing HAP/VAP, which was in line with previous studies.[7,19–21] In the REPROVE trial,[6] *P. aeruginosa* and *K. pneumoniae* were the most common GNBs causing nosocomial pneumonia, followed by *Enterobacter cloacae* and *E. coli*, whereas, in the ASPECT-NP trial,[7] *Enterobacteriaceae* and *P. aeruginosa* were the predominant gram-negative pathogens. Together, these findings suggest that broad-spectrum antibiotics should be used in

the treatment of HAP/VAP, to ensure they act against these prevalent pathogens. An in vitro study[22] showed that the susceptibility rates of *E. coli, K. pneumoniae, Citrobacter freundii, Serratia marcescens*, and *Proteus mirabilis* to cefoperazone-sulbactam were all ≥90%, and only ≤15% of *P. aeruginosa, Acinetobacte*r spp., and *Enterobacter cloacae* strains were resistant to cefoperazone-sulbactam. Even for MDROs, the susceptibility rates of ESBL-*E. coli*, ESBL- *K. pneumoniae*, carbapenem-resistant *E. coli*, and carbapenem-resistant *A. baumannii* to cefoperazone-sulbactam were 97.0%, 75.8%, 67.6% and 68%, respectively.[23] Only carbapenem-resistant *P. aeruginosa* displayed high resistance against cefoperazone-sulbactam.[11,23] Therefore, cefoperazone-sulbactam could be an appropriate antibiotic for patients the treatment of patients with HAP/VAP caused by most GNBs.

Safety, especially in the context of coagulopathy, is a serious concern for clinicians prescribing cefoperazone-sulbactam.[24–26] No significant difference in pre- and post-treatment INR was observed in 30 patients receiving cefoperazone, but most of the patients did not have the assessment of coagulation disorder in this study. According to retrospective review of medical chart, no patients receiving cefoperazone-sulbactam had significant bleeding. In addition, only one patient reported skin rash during the use of cefoperazone-sulbactam, but no serious adverse events related to cefoperazone-sulbactam were reported in this retrospective study. Therefore, based on the present findings, cefoperazone-sulbactam was well tolerated.

This study had several limitations. First, unlike a randomized controlled study, this retrospective study could not ensure that baseline characteristics and disease severity were equal between the cefoperazone-sulbactam and piperacillin-tazobactam groups. Therefore, we used propensity score method to adjust the baseline characteristics

and disease severity and showed that the clinical efficacy of cefoperazone-sulbactam remained comparable to piperacillin-tazobactam. Second, because the in vitro activity of cefoperazone-sulbactam was not assessed in most study sites, only 18 clinical isolates had results of cefoperazone-sulbactam susceptibility tests, and two of them, including one *P. aeruginosa* and one *K. pneumoniae* isolates were not susceptible to cefoperazone-sulbactam. Therefore, we were unable to evaluate the cefoperazone-sulbactam resistance rate of causative pathogens and their impact on the clinical outcome. In addition, susceptibility of GNB could vary according to different sites, so the results of this comparison should be different and empirical treatment of late HAP/VAP should be made based on the local epidemiology. Third, although the risk of adverse events was evaluated in this study, some mild adverse events which may not have been recorded in the chart could have been missed. Thus, the risk of adverse events might have been underestimated. Forth, this study did not further classify the type of VAP – early or late VAP and did not measure the microbiological eradication rate. Further large-scale study is warranted to investigate these issues. Finally, most of subgroup analyses were based on small number, which might contribute to non-difference on the treatment outcome.

Conclusions

In the management of adult patients with HAP/VAP, cefoperazone-sulbactam is as effective as piperacillin-tazobactam.

Ethical Approval

This study was approved by the ethics committee of Taipei Veterans General Hospital (2019-08-006AC), Mackay Memorial Hospital (19MMHIS282e), Chung Shan Medical University Hospital (CS18126), Taichung Veterans General Hospital (CE18223A#2), National Taiwan University Hospital (201805123RINB), Kaohsiung Chang Gung Memorial Hospital (201900932B0C501), Chi Mei Medical Center (10806-008) and Chi Mei Medical Center, Liouying (10808-L01).

Disclosure

The authors declare that they have no competing interests.

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