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ORIGINAL ARTICLE

Impact of revised susceptibility breakpoints on bacteremia of *Klebsiella pneumoniae*: Minimum inhibitory concentration of cefazolin and clinical outcomes

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Background: The Clinical and Laboratory Standards Institute (CLSI) revised the susceptibility breakpoints of cephalosporins for Enterobacteriaceae in 2010 and 2011. However, there is a lack of clinical data about the correlation of minimum inhibitory concentrations (MICs) and clinical outcome. Data for the distribution of MICs and clinical outcomes were analyzed in this study to evaluate the impact of changes in the CLSI breakpoints on the treatment of *Klebsiella pneumoniae* bacteremia.
Methods: Ninety-seven bacteremic *K. pneumoniae* isolates from Taichung Veterans General Hospital, Taichung, Taiwan were collected for study during the period 2009–2011. The cefazolin MIC was determined by the broth microdilution method according to the recommendations of the CLSI. The MIC distribution of cefazolin and the clinical responses to definitive cefazolin treatment were analyzed.
Results: The modal cefazolin MIC among the 97 isolates was 1 μg/mL and accounted for 73 (75.3%) isolates. There were 18 (18.6%) isolates with a cefazolin MIC of 2 μg/mL. The conventional dosage regimens of cefazolin (1 g every 6 hours or 8 hours) achieved a clinical cure in 70 (97.2%) of 72 patients in the group with a cefazolin MIC ≤1 μg/mL and in 14 (87.5%) of 16 patients in the group with a cefazolin MIC of 2 μg/mL. With the conventional dose, the cumulative clinical cure rate for *K. pneumoniae* bacteremia with cefazolin MIC ≤2 μg/mL was 95.5% (84/88 patients).

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Conclusion: The conventional cefazolin dose still can result in satisfactory clinical cure rates for bacteremic episodes due to *K. pneumoniae* with cefazolin MIC ≤2 μg/mL, the revised susceptible breakpoint of CLSI 2011.

Introduction

Klebsiella pneumoniae is a common pathogen that causes urinary tract infections,[1] biliary tract infections,[2] liver abscesses,[3,4] pneumonia,[5,6] and bacteremia.[7] The reported case fatality rates of *K. pneumoniae* bacteremia are 20–40%.[4,8–10]

Before 2010, the breakpoints of cephalosporins for Enterobacteriaceae had been set for several decades.[11] As a result of the growing prevalence of extended spectrum beta-lactamase (ESBL)-producing isolates around the world,[12,13] screening and confirmatory tests for ESBLs in *K. pneumoniae* and *Escherichia coli* were developed by the National Committee for Clinical Laboratory Standards in 1999.[14] Based on an evaluation of the microbiological data, clinical outcomes, and pharmacodynamic-pharmacokinetic (PK-PD) properties for susceptibility breakpoints, the Clinical and Laboratory Standards Institute (CLSI) performance standards in 2010 revised the interpretive criteria for cephalosporins and aztreonam.[15] The minimum inhibitory concentration (MIC) breakpoints for cefazolin were revised in 2010: the susceptible breakpoint changed from ≤8 μg/mL to ≤1 μg/mL, the intermediate breakpoint from 16 μg/mL to 2 μg/mL, and the resistant breakpoint from ≥32 μg/mL to ≥4 μg/mL.[15] However, using the CLSI breakpoints published in 2010, the strains with cefazolin MICs of 2–8 μg/mL are regarded as intermediate or resistant to cefazolin. Consequently, this revision would preclude the use of cefazolin, a conventionally effective drug, for the prevention and treatment of infection caused by Enterobacteriaceae that do not have a resistance mechanism.[11] To prevent this impact, the breakpoints of cefazolin for Enterobacteriaceae was further revised by the CLSI in 2011 (susceptible, ≤2 μg/mL; intermediate, 4 μg/mL; and resistant, ≥8 μg/mL), according to Monte Carlo simulations of PK-PD data and recent laboratory data.[11]

To define the microbiological breakpoints which differentiate wild-type strains from those with resistance mechanisms, moderate to large numbers of *in vitro* MIC tests are needed to provide the patterns of MIC distribution.[11] However, there is a lack of data on the natural antibiotic MIC distribution of *K. pneumoniae*.[16,17] A few published clinical studies on the treatment of urinary tract infections caused by Enterobacteriaceae with cefazolin have been conducted.[18,19] The dose and frequency of the regimen varied widely among the studies.[18–21] Data about the correlation of MIC and cephalosporin dose from clinical trials are also lacking.[18–21]

We therefore conducted this study to evaluate the MIC distribution of cefazolin among *K. pneumoniae* isolates, to analyze the correlation of MICs and the clinical outcomes of patients with *K. pneumoniae* bacteremia, and to analyze the impact of cefazolin breakpoint changes of CLSI in 2011 on treatment.

Materials and methods

Bacterial strains

During the period from January 2009 to December 2011, 721 *K. pneumoniae* non-duplicate isolates from blood specimens were identified at the Microbiology Laboratory of Taichung Veterans General Hospital, Taichung, Taiwan. The susceptibility tests of these isolates were performed by the disk diffusion method and read according to the CLSI 2009 recommendations.[22] There were 630 isolates susceptible to cefazolin and 91 isolates resistant to cefazolin (using the disk diffusion test, including the double-disk diffusion method of the CLSI 2009 ESBL confirmatory test[22]). The medical records were reviewed for all 721 patients with *K. pneumoniae* bacteremia. Only 97 patients with bacteremia due to cefazolin-susceptible isolates (disk diffusion test, CLSI 2009[22]) were included with the condition that cefazolin had been initiated within 2 days of the report of *K. pneumoniae* bacteremia and used for at least 7 days. These 97 isolates were selected for the MIC study. Among 91 cefazolin-resistant isolates, only 82 isolates were available for MIC tests.

Susceptibility test

The cefazolin MICs were measured by the broth microdilution method according to the CLSI recommendations.[23] *E. coli* ATCC 25922 and *Pseudomonas aeruginosa* ATCC 27853 were used as the quality control strains. The susceptibility breakpoints of cefazolin were ≤8 μg/mL, ≤1 μg/mL, ≤2 μg/mL, according to the CLSI recommendations issued in 2009,[22] 2010,[15] and 2011,[28] respectively.

Clinical and bacteriological assessments

The clinical outcomes of the 179 patients with bacteremia of *K. pneumoniae* (97 cefazolin-susceptible and 82 cefazolin-resistant, selected by the disk diffusion tests according to CLSI 2009[22]) were analyzed by a review of the medical records. The clinical conditions (such as age, sex, source of infection, length of stay, days to defervescence after antimicrobial treatment, clinical response, and death) associated with the acquisition of *K. pneumoniae*

bacteremia were reviewed. The efficacy was assessed by the clinical and bacteriological response.[24] The clinical response was evaluated at the end of antimicrobial treatment and defined as cure (disappearance of acute signs and symptoms related to the infection or sufficient improvement such that additional or alternative antimicrobial treatment was not required), failure (insufficient improvement of the signs and symptoms of infection and additional or alternative antimicrobial treatment was required), or indeterminate (a clinical assessment was not possible for any reason). The bacteriological response was evaluated at the 7th day after the discontinuation of antimicrobial treatment and defined as eradication (no more positive blood cultures yielded), presumed eradication (absence of evaluable culture in a patient with clinical cure), persistence (presence of baseline pathogen in a patient with clinical failure of treatment), presumed persistence (absence of evaluable culture in a patient with clinical failure of treatment), or indeterminate (if bacteriological response was not evaluable for any reason). Bacteriological success was defined if eradication or presumed eradication were present. Bacteriological failure was rated as persistence or presumed persistence. The 14-day mortality rates after bacteremia were analyzed.

The clinical characteristics and outcomes of these 97 patients with *K. pneumoniae* bacteremia were classified into three groups according to cefazolin MICs: $\leq$1 μg/mL, 2 μg/mL, and 4–8 μg/mL.

Statistical analysis

Categorical variables were analyzed by two-tailed χ^2 test; continuous variables were analyzed by the Student *t* test and analysis of variance test. $p < 0.05$ was considered statistically significant. All statistical analyses were performed with SPSS version 22.0.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results

During the study period, 97 clinically evaluable patients with cefazolin-susceptible *K. pneumoniae* bacteremia were treated with cefazolin. The MICs for the 97 isolates were $\leq$8 μg/mL, including $\leq$1 μg/mL for 75 (77.3%) isolates, 2 μg/mL for 18 (18.6%) isolates, and 4–8 μg/mL for four (4.1%) isolates (Fig. 1). The clinical characteristics and outcomes of 97 patients with *K. pneumoniae* bacteremia (classified into three groups, cefazolin MIC $\leq$1 μg/mL, 2 μg/mL, and 4–8 μg/mL) are given in Table 1. There was no statistically significant difference in the demographic characteristics and outcomes among the three groups, except for skin and soft tissue infection and length of stay in hospital. The length of stay in hospital in the three groups of cefazolin MIC $\leq$1 μg/mL, 2 μg/mL, and 4–8 μg/mL were 17 ± 1.1 days, 25 ± 3.5 days, and 34 ± 9.6 days, respectively. There were statistically significant differences in the length of stay among these three groups ($p < 0.05$). The patients in the group with a higher MIC had longer lengths of stay ($p < 0.05$). The periods to defervescence in the three groups of cefazolin MIC $\leq$1 μg/mL, 2 μg/mL, and 4–8 μg/mL were 2.2 ± 0.1 days, 1.3 ± 0.1 days, and 1.6 ± 0.3 days, respectively ($p = 0.056$). The duration of

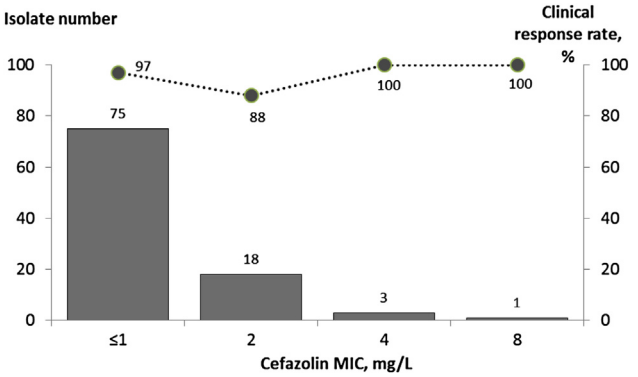

Figure 1. Minimum inhibitory concentration (MIC) distribution of cefazolin and correlated rates of clinical cure among the 97 *Klebsiella pneumoniae* isolates included in the study.

treatment in the three groups of cefazolin MIC $\leq$1 μg/mL, 2 μg/mL, and 4–8 μg/mL were 12.8 ± 0.7 days, 14.3 ± 2.3 days, and 15 ± 3.2 days, respectively ($p = 0.634$).

There were 25 patients with *K. pneumoniae* bacteremia and liver abscess. Among 25 isolates from patients with liver abscess, there were 20 isolates with cefazolin MIC $\leq$1 μg/mL, four isolates with a cefazolin MIC of 2 μg/mL, and one isolate with a cefazolin MIC of 4 μg/mL. All patients with *K. pneumoniae* bacteremia and liver abscess were clinically cured.

All 97 isolates were negative for the double-disk diffusion method of the ESBL confirmatory test. The modal cefazolin MIC was 1 μg/mL and accounted for 73 (75.3%) isolates. The cumulative percentage for MIC $\leq$2 μg/mL was 95.9%.

Cefazolin MICs of 82 cefazolin-resistant isolates (by disk diffusion test, CLSI 2009[22]) ranged from 16 μg/mL to >256 μg/mL, including 16 μg/mL for two isolates; 32 μg/mL for five isolates; 64 μg/mL for one isolate; 128 μg/mL for seven isolates; 256 μg/mL for two isolates; and >256 μg/mL for 65 (79.3%) isolates. The 82 patients with cefazolin-resistant *K. pneumoniae* bacteremia were treated with carbapenem, fluoroquinolones, or third-generation cephalosporins.

The rates of clinical cure were 97% (73/75), 88.9% (16/18), 100% (3/3), and 100% (1/1) for the patients in the groups with cefazolin MICs of $\leq$1 μg/mL, 2 μg/mL, 4 μg/mL, and 8 μg/mL, respectively (Fig. 1). Table 2 gives the rates of clinical cure correlated with the MIC and dosage regimen. Among 72 patients in the group with cefazolin MIC $\leq$1 μg/mL and treated with the conventional dose (cefazolin given as 1 g every 6 hours or 8 hours), the rate of clinical cure was 97.2%. During antimicrobial treatment, one patient died as a result of arrhythmia with sudden death and the other died from terminal lung cancer with multiple organ failure. Although clinical improvement was observed in these two patients, clinical cure was not achieved due to death before the end of the scheduled antimicrobial treatment. Among 16 patients in the group with a cefazolin MIC of 2 μg/mL and treated with the conventional dose (cefazolin given as 1 g every 6 hours or 8 hours), the rate of clinical cure was 87.5% (14/16 patients). Two patients died from liver cirrhosis and lung cancer with multiple organ failure, respectively, before the end of the scheduled antimicrobial treatment.

Table 1 Comparison of clinical characteristics and outcomes of 97 patients with *Klebsiella pneumoniae* bacteremia, classified by cefazolin minimum inhibitory concentration of the bacteremic isolate: ≤1 μg/mL, 2 μg/mL, and 4–8 μg/mL

Clinical characteristic	Cefazolin MIC (μg/mL)			*p*
	≤1 (*n* = 75)	2 (*n* = 18)	4–8 (*n* = 4)	
Age (y)	62 ± 12.8	65 ± 13.7	80 ± 13.2	0.089
Male sex	50 (66.7)	13 (72.2)	3 (75.0)	0.926
Source of infection				
Intra-abdominal infection	50 (66.7)	11 (61.1)	2 (50.0)	0.492
Liver abscess	20 (26.7)	4 (22.2)	1 (25.0)	0.625
Skin and soft tissue infection	1 (1.3)	0 (0.0)	1 (25.0)	<0.05
Urinary tract infection	10 (13.3)	7 (38.8)	0 (0.0)	0.051
Central line related	0 (0.0)	1 (5.5)	0 (0.0)	0.142
Unknown	14 (18.6)	1 (5.5)	1 (25.0)	0.299
Length of stay in hospital (d)	17 ± 1.1	25 ± 3.5	34 ± 9.6	<0.05
Time to defervescence (d)	2.2 ± 0.1	1.3 ± 0.1	1.6 ± 0.3	0.056
Treatment duration (d)	12.8 ± 0.7	14.3 ± 2.3	15.1 ± 3.2	0.634
Co-morbidity				
Liver function impairment	34 (45.3)	8 (44.4)	0 (0.0)	0.191
Renal insufficiency	9 (12.0)	1 (5.5)	3 (75.0)	<0.05
Heart failure	8 (10.6)	1 (5.5)	1 (25.0)	0.463
Diabetes mellitus	29 (38.6)	5 (27.7)	3 (75.0)	0.152
Malignancy	28 (37.3)	7 (38.8)	0 (0.0)	0.312
Absolute neutrophil count <500/mm^3	3 (4.0)	0 (0.0)	0 (0.0)	0.613
Immunosuppression treatment	13 (17.3)	4 (22.2)	0 (0.0)	0.633
14-day mortality	2 (2.6)	2 (11.1)	0 (0.0)	0.321

Data are presented as *n* (%) or mean ± standard deviation.
MIC = minimum inhibitory concentration.

Five patients were treated with cefazolin 1 g every 12 hours as a result of renal insufficiency and one patient with cefazolin 0.5 g every day as a result of uremia. The bacteriological success rate was 100% for all 93 patients with a complete course of treatment with cefazolin. The patients in the group with cefazolin MIC ≤8 μg/mL had a lower 14-day mortality rate than those in the group with cefazolin MIC >8 μg/mL (4.1% vs. 47.5%; $p < 0.001$).

Discussion

The breakpoints of cefazolin for Enterobacteriaceae revised by the CLSI in 2010[15] were ≤1 μg/mL as susceptible, 2 μg/mL intermediate, and ≥4 μg/mL resistant. Accordingly 22 (22.7%) of 97 isolates with cefazolin MICs of 2–8 μg/mL in the current study would fall into the intermediate or resistant categories. However, the clinical outcome of these 22 patients was evaluated as achieving clinical cure and bacteriological eradication, arguing for the latest susceptible breakpoint of cefazolin, i.e., ≤2 μg/mL.

From the viewpoint of the microbiological data, the modal cefazolin MIC among 97 cefazolin-susceptible isolates in this study was 1 μg/mL and accounted for 73 (75.3%) isolates. The cumulative percentage for MIC ≤2 μg/mL was 95.9%. If the susceptibility breakpoint was 1 μg/mL (CLSI 2010[15]), 18.6% of isolates with MIC of 2 μg/mL would be interpreted as intermediate. This would result in a great

Table 2 Clinical cure rates categorized by cefazolin minimum inhibitory concentration of bacteremic isolates and cefazolin dosage among 97 patients with *Klebsiella pneumoniae* bacteremia (MIC ≤ 8 μg/mL)

Cefazolin MIC (μg/mL)	Cefazolin dose [a]			
	Normal renal function		Renal insufficiency	Hemodialysis
	1g Q6H	1g Q8H	1g Q12H	0.5g QD
0.25		0/1 (0)		
0.5	1/1 (100)			
1	40/40 (100)	29/30 (97.6)	2/2 (100)	1/1 (100)
2	8/10 (80)	6/6 (100)	2/2 (100)	
4		2/2 (100)	1/1 (100)	
8		1/1 (100)		

[a] Q6H = every 6 hours; Q8H = every 8 hours; Q12H = every 12 hours; QD = every day.
Data are presented as *n* (%).
MIC = minimum inhibitory concentration.

impact on the choice of cefazolin for the treatment of Enterobacteriaceae infections. Hence, we examined data from other studies before interpretating our data. The MIC distribution of wild-type microorganisms are available on the EUCAST website.[25] Of 208 wild-type *K. pneumoniae* isolates, there were 71 (34.1%) isolates had a cefazolin MIC of 1 μg/mL and 82 (39.4%) isolates had an MIC of 2 μg/mL. The cumulative percentage for MIC ≤2 μg/mL was 73.6%. In another study conducted in the Mayo Clinic (Rochester, MN, USA), 199 consecutive clinical isolates of *E. coli* ($n = 180$), *K. pneumoniae* ($n = 8$), and *Klebsiella oxytoca* ($n = 11$) were studied for their cephalosporin MIC.[16] Among the 191 isolates without acquired secondary β-lactamases (ESBL or AmpC), there were 34 (17.8%) isolates with a cefazolin MIC of 1 μg/mL and 98 (51.3%) isolates with a cefazolin MIC of 2 μg/mL.[16] The cumulative percentage for MIC ≤2 μg/mL was 69.1%. The cumulative percentages of the isolates with MIC ≤2 μg/mL ranged from 69.1% to 95.9%, accounting for the majority of isolates without a resistance mechanism in these three studies. Hence it is reasonable to revise the interpretive criteria of cefazolin from 1 μg/mL (CLSI 2010[15]) to 2 μg/mL (CLSI 2011[28]) based on these microbiological data.

According to PK-PD data, the cefazolin susceptibility breakpoint of 2 μg/mL based on a higher dosage regimen (2 g every 8 hours) was suggested by CLSI 2011.[28] The decision for the revised breakpoints by CLSI 2011[28] was based on the Monte Carlo simulation analysis.[26,27] The target attainment rates for 50% $T >$ MIC can achieve 94% for the isolates with a cefazolin MIC of 1 μg/mL and 64% for those of 2 μg/mL at the conventional dose regimen of 1 g every 8 hours.[26] Therefore the susceptibility breakpoint of cefazolin was determined as ≤1 μg/mL for the conventional dose regimen (1 g every 8 hours) by CLSI 2010.[15] However, the target attainment rates would achieve 100% for the isolates with a cefazolin MIC of 1 μg/mL and 94% for those of 2 μg/mL at a higher cefazolin dose (2 g every 8 hours).[26] Therefore the interpretive criteria for cefazolin in the CLSI 2011[28] were revised (susceptible, ≤2 μg/mL; intermediate, 4 μg/mL; and resistant, ≥8 μg/mL) based on a higher dose regimen.

The clinical outcome data, as well as the microbiological data, should be evaluated to determine the optimum susceptibility breakpoint of cefazolin. The conventional dose regimens of cefazolin (1 g every 6 hours or 8 hours) achieved clinical cure in 97.2% of 72 patients in the group with a cefazolin MIC ≤1 μg/mL and in 87.5% of 16 patients in the group with a cefazolin MIC of 2 μg/mL. With conventional doses, the rate of clinical cure for bacteremia of *K. pneumoniae* with cefazolin MIC ≤2 μg/mL was 95.5%. Such study findings can support the revised cefazolin susceptibility breakpoint of 2 μg/mL (CLSI 2011[28]).

There were some limitations in this study. First, a relatively small number of patients, especially those in the group with a cefazolin MIC of 4—8 μg/mL, was not sufficient to demonstrate significant associations between cefazolin MIC and clinical outcome, although they were successfully treated with cefazolin. Second, the 30-day mortality was not analyzed, because the patients were treated with a mean duration of 13.1 days and a mean hospital stay of 20.3 days. Third, although clinical cure was achieved in all 25 patients with liver abscess and cefazolin treatment, the number of patients was limited and this study focused on the clinical response of definitive cefazolin treatment without the inclusion of critically ill patients. Cefazolin in conventional dose regimens has been used for liver abscess for decades.[29] The role of cefazolin treatment for systemic infections due to *K. pneumoniae* with cefazolin MIC ≤2 μg/mL warrants further clinical studies.

In conclusion, conventional cefazolin dosage (1 g every 6 hours or 8 hours) can result in satisfactory clinical cure rates of bacteremic episodes due to *K. pneumoniae* with cefazolin MIC ≤2 μg/mL. Such clinical data argue for the latest cefazolin-susceptible breakpoint of ≤2 μg/mL based on a higher dose regimen.

Conflicts of interest

All contributing authors declare no conflicts of interest.

Acknowledgments

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