

Potential for Cefazolin as De-escalation Therapy for *Klebsiella Pneumoniae* Bacteraemia

Dear Editor,

Klebsiella pneumoniae causes the syndrome of liver abscess, meningitis and endophthalmitis associated with capsular serotype K1/K2, mucoid phenotype and aerobactin production as virulence factors.¹ Overall mortality from *Klebsiella pneumoniae* bacteraemia ranged from 19% to 55%.²

Chromosomally mediated SHV-1 beta-lactamase in *K. pneumoniae* could inactivate cefazolin in an inoculum-dependent manner.³ Cefotaxime and ceftriaxone were superior to cefazolin in murine pneumonia.⁴ A Taiwanese study comparing cefazolin with extended-spectrum cephalosporins in *K. pneumoniae* found more metastatic complications in the cefazolin group.⁵ However, cefazolin was superior to ceftazidime in bactericidal activity in vitro against *Escherichia coli* and *K. pneumoniae*.⁶ In *K. pneumoniae* bacteraemia, mortality with monotherapy with first-generation cephalosporin was 6%, second-generation 11% and third-generation 19%.² Narrow-spectrum cephalosporin was used effectively for *K. pneumoniae* liver abscess in Taiwan.⁷

In this retrospective study, we evaluated the clinical efficacy of culture-guided de-escalation to cefazolin 2 g 8-hourly, compared the clinical and microbiological outcome of culture-guided use of cefazolin versus ceftriaxone, and determined independent risk factors for 30-day mortality in patients with *K. pneumoniae* bacteraemia.

From 1 January 2008 to 31 December 2008, *K. pneumoniae* bacteraemia at Tan Tock Seng Hospital (TTSH), a 1400-bed university teaching hospital in Singapore, which was extended-spectrum beta-lactamase (ESBL)-negative on modified double disc synergy test (Becton-Dickinson, Sparks, Maryland, USA) and sensitive to ceftriaxone and ceftazidime was studied. Antimicrobial susceptibility was performed by disc diffusion per Clinical and Laboratory Standards Institute (CLSI) criteria. Ethics approval was granted.

Age, gender, comorbidities and Charlson's comorbidity score, source of bacteraemia, polymicrobial bacteraemia, Pitt bacteraemia score, therapeutic drainage, antimicrobial therapy, and antibiotic susceptibility of *K. pneumoniae* were extracted from medical records. Outcomes measured from the day of bacteraemia included 30-day mortality, duration

of hospitalisation, 7-day clinical response (resolution of symptoms and signs), 14-day microbiological response (where microbiology was repeated), and 30-day relapsed bacteraemia.

Empiric antibiotics were administered before blood culture and antibiotic susceptibility test results, and definitive antibiotic was given after these results. Antibiotics were determined by prescribers. Disseminated *K. pneumoniae* infection occurred with infective foci other than the suspected source within 48 hours of bacteraemia. Severe complications were metastatic infections, pulmonary complications, intensive care unit (ICU) admission or death more than 72 hours after active antibiotics and within 30 days of bacteraemia.⁵ Metastatic infections occurred with infective foci other than the initial source after more than 72 hours of active antibiotic.

Categorical variables were compared for statistical significance using the Pearson's chi-square or Fisher's exact test, and continuous variables were compared using the Mann-Whitney U test. Univariate and multivariate analyses incorporating all dependent variables with $P < 0.05$ on univariate analysis for 30-day mortality were performed using binomial logistic regression. Statistical analysis was carried out using PASW statistics 18 (SPSS Inc., Chicago, Ill.). A P value < 0.05 indicated statistical significance.

Of 147 patients reviewed, 13 patients were excluded (incomplete data in 4, blood clot specimen rather than bacteraemia in 1, no antibiotics given in 2, irretrievable medical records in 6). Of 134 patients, median age was 72 years (range, 19 to 98 years) and 78 (58.2%) were male. Median Charlson's comorbidity score was 4 (range, 0 to 11) and median Pitt bacteraemia score was 4 (range, 4 to 10).

Common sources of bacteraemia were hepatobiliary (46 [36.3%], of which 19 had liver abscess), urinary (40 [29.9%]) and respiratory (27 [20.1%]). Nine patients had polymicrobial bacteraemia (*E. coli* in 5, *Enterococcus faecium* in 2, and 1 each had *E. tarda*, *Enterobacter cloacae* and *Aeromonas* species respectively). Four patients had disseminated infection namely eye ($n = 1$), abdominal ($n = 1$), respiratory ($n = 1$) and urinary ($n = 1$) specimens. Nineteen (12.8%) patients needed drainage of their foci of infection, 18 patients underwent drainage and 7 had drainage within 3 days of bacteraemia. Other details are

shown in Table 1. In terms of active empiric antibiotic, 96.3% of patients received third-generation cephalosporins (75 [58.9%]) and beta-lactam/beta-lactamase inhibitors (24 [18.6%]); none received cefazolin. Notably, 5 (3.7%) patients did not receive any empiric therapy. Definitive therapy comprised cefazolin (47 [35.1%]), beta-lactam/beta-lactamase inhibitors (24 [17.9%]) and third-generation cephalosporins (20 [14.9%]). Seventeen (11.4%) patients did not receive definitive antibiotic as they died before bacteraemia was known. All patients who survived till blood culture results received active definitive therapy.

Complications included pulmonary complications (1 [0.7%]), ICU admissions (1 [0.7%]) and death (13 [9.7%]). Overall 30-day mortality was 23.1%. Eighteen of the 31 deaths occurred within 72 hours of active antibiotics. No metastatic infections occurred. Clinical response occurred in 79.1% and microbiological response in 92.9%. The median duration of hospitalisation was 10 days (range, 0 to 130 days). Two patients experienced relapsed *K. pneumoniae* bacteraemia; both received cefazolin as definitive antibiotic therapy for acute cholecystitis and pyelonephritis respectively.

Overall, independent risk factors of 30-day mortality were age, Pitt bacteraemia score and cancer.

Patients who received empiric third-generation cephalosporin had lower 30-day mortality (66.0% vs 32.3%, $P = 0.001$) versus other antibiotics; this was not significant upon multivariate analysis. In patients with early mortality, cancer, Charlson's score and empiric fluoroquinolone increased risk while empiric third-generation cephalosporin reduced risk; there was no independent risk factor of early mortality upon multivariate analysis (Table 2). Among patients with definitive therapy, cancer was the only independent risk factor associated with 30-day mortality. Empiric therapy with third-generation cephalosporin was independently associated with lower early mortality (Table 2).

Pitt bacteraemia scores were comparable between patients with and without empiric third-generation cephalosporin, but there was a significant distribution of more severely ill patients in the third-generation cephalosporin group ($P = 0.041$). Patients with empiric third-generation cephalosporin had significantly less pneumonia, fewer severe complications >72 hours after active antibiotic and lower 30-day mortality and length of stay, and similar clinical and microbiological response, and relapse rates.

Between patients with definitive cefazolin ($n = 47$) and third-generation cephalosporin ($n = 20$), baseline characteristics were similar without statistically significant different patient outcomes (Table 3). Severe complications were 10.6% vs 15.0% ($P = 0.687$) and 30-day mortality

Table 1. Baseline Characteristics and Antibiotic Therapy of 134 Patients with *Klebsiella Pneumoniae* Bacteraemia with and without 30-Day Mortality

30-Day Mortality	No (n = 103)	Yes (n = 31)	P Value
Median age, years (range)	70 (19 – 98)	76 (47 – 96)	0.060
Male	62 (60.2)	16 (51.6)	0.396
Pitt bacteraemia score, median (range)	4 (4 – 9)	4 (4 – 10)	0.088
Charlson's comorbidity index, median (range)	4 (0 – 10)	5 (0 – 11)	0.014
Comorbidities			
Cerebrovascular disease	22 (21.4)	7 (22.6)	0.885
Dementia	11 (10.7)	3 (9.7)	1.00
Diabetes mellitus	51 (49.5)	14 (45.2)	0.671
Moderate to severe renal disease	15 (14.6)	6 (19.4)	0.520
Cancer	12 (11.7)	15 (48.5)	<0.0001
Source of bacteraemia			
Hepatobiliary	41 (39.8)	5 (16.1)	0.015
Intra-abdominal	5 (4.9)	3 (9.7)	0.320
Respiratory	14 (13.6)	13 (41.9)	0.001
Unknown	5 (4.9)	3 (9.7)	0.386
Urinary system	35 (34.0)	5 (16.1)	0.057
Others*	4 (3.9)	2 (6.5)	0.622
Disseminated infections	4 (3.9)	0 (0.0)	0.573
Antibiotic therapy			
Delayed active therapy >24 hours†	4 (3.9)	1 (3.2)	1.00
Active empiric therapy	99 (96.1)	30 (96.8)	0.865
No empiric therapy received	4 (3.9)	1 (3.2)	1.000
No definitive therapy received	0 (0.0)	17 (54.8)	<0.001
Empiric therapy			
Beta-lactam/beta-lactamase inhibitors	15 (14.6)	8 (25.8)	0.146
Third-generation cephalosporins	68 (66.0)	10 (32.3)	0.001
Fluoroquinolones	7 (6.8)	4 (12.9)	0.278
Carbapenems	4 (3.9)	4 (12.9)	0.083
Monobactam	1 (1.0)	0 (0.0)	1.000
Combination	4 (3.9)	3 (9.7)	0.352
Definitive therapy			
Beta-lactam/beta-lactamase inhibitors	22 (21.4)	2 (6.5)	0.065
Cefazolin	42 (40.8)	5 (16.1)	0.012
Third-generation cephalosporins	16 (15.5)	4 (12.9)	1.00
Fluoroquinolones	12 (11.7)	3 (9.7)	1.00
Others	11 (10.7)	0 (0.0)	0.067

All variables are expressed as number (percentage) unless otherwise stated.

*Others: 1 central nervous system, 1 otorhinolaryngological, 1 soft and skin tissue, and 1 line-related bloodstream infection.

†Delayed active therapy included both empiric and definitive antibiotic therapy.

Table 2. Independent Risk Factors of Mortality for Patients with *Klebsiella Pneumoniae* Bacteraemia

	30-Day Mortality aOR (95% ,CI)	P Value	Early Mortality (≤3 Days) aOR (95% ,CI)	P Value
All Patients (n = 134)				
Age (years)	1.061 (1.014 – 1.019)	0.01		
Pitt bacteremia score	1.969 (1.281 – 3.025)	0.002		
Charlson's score	0.934 (0.736 – 1.184)	0.571	1.330 (0.952 – 1.859)	0.095
Cancer	14.897 (3.097 – 71.665)	0.001		
Hepatobiliary source	0.336 (0.074 – 1.536)	0.16	3.554 (0.620 – 20.358)	0.155
Respiratory source	2.033 (0.483 – 8.550)	0.333		
Urinary source	0.354 (0.074 – 1.692)	0.193		
Empiric 3 rd generation cephalosporin	0.466 (0.155 – 1.402)	0.174	0.225 (0.040 – 1.249)	0.088
Carbapenems	0.750 (0.111 – 5.061)	0.768		
Empiric quinolones			7.392 (0.929 – 58.798)	0.059
Definitive Therapy (n = 117)				
Age (years)	1.037 (0.964 – 1.115)	0.330		
Male	0.425 (0.087 – 2.078)	0.290		
Charlson's score	1.191 (0.829 – 1.709)	0.344	1.311 (0.946 – 1.818)	0.104
Cancer	8.552 (1.243 – 58.837)	0.029	5.214 (0.929 – 29.283)	0.061
Intra-abdominal source	1.780 (0.223 – 14.214)	0.586		
Empiric 3 rd generation cephalosporin	0.220 (0.039 – 1.226)	0.084	0.152 (0.026 – 0.893)	0.037
Empiric quinolones	4.896 (0.501 – 47.852)	0.172	4.463 (0.540 – 36.912)	0.165

Table 3. Comparisons of Patients who Received Definitive Therapy with Cefazolin and Third-Generation Cephalosporins in the Treatment of *Klebsiella Pneumoniae* Bacteraemia

Definitive Therapy	Cefazolin	Third-Generation Cephalosporins	P Value
Number	47	20	
Pitt bacteraemia score, median (range)	4 (4 – 7)	6 (4 – 7)	0.481
Source of bacteraemia			
Hepatobiliary	17 (36.2)	12 (60.0)	0.072
Intra-abdominal	2 (4.3)	2 (10.0)	0.364
Respiratory	5 (10.6)	0 (0.0)	0.312
Unknown	4 (8.5)	0 (0.0)	0.309
Urinary	16 (34.0)	6 (30.0)	0.747
Outcomes			
Severe complications >72 hours after active antibiotics	5 (10.6)	3 (15.0)	0.628
Clinical response at day 7	45 (95.7)	18 (90.0)	0.687
Microbiological response at day 14	8/10 (80.0)	1/1 (100.0)	1.00
30-day mortality	5 (10.6)	4 (20.0)	0.434
Median hospital length of stay, days (range)	13 (4 – 130)	15 (3 – 55)	0.426
Relapse of bacteraemia	2 (4.3)	0 (0.0)	1.00

All variables expressed as number (percentage) unless otherwise stated.

was 10.6% vs 20.0% ($P = 0.434$) for cefazolin versus third-generation cephalosporin groups.

A retrospective study of 107 cases of *K. pneumoniae* liver abscess suggested cefazolin was not as effective as third-generation cephalosporin in preventing severe complications but mortality was similar (8.5% vs 4.2%, $P = 0.42$); cefazolin was dosed at 1 g 8-hourly.⁵ One gram of cefazolin in humans achieved a mean serum level of 64 mcg/mL 1 hour after intramuscular administration.⁸ A similar mean serum level of 59.2 mcg/mL in murine pneumonia was associated with microbiological failure.⁴ In murine pneumonia, microbiological response to cefazolin occurred at a higher dose of 60 mg/kg with a mean serum level of 115.4 mcg/mL after 1 hour. We used 2 g 8-hourly of cefazolin for *K. pneumoniae* bacteraemia in our institution.

In 110 episodes of *K. pneumoniae* liver abscess (61% had bacteraemia), 86.3% received cefazolin for more than 3 days;⁹ 4.3% developed metastatic infections and mortality was 5.3%, similar to patients treated with extended-spectrum cephalosporin.⁵

Limitations of our study included its retrospective design and arbitrary treatment decisions by physicians. Our finding of effective cefazolin therapy was supported by an in vitro study⁶ and 3 human studies.^{2,7,9} With worsening antimicrobial resistance and diminishing antimicrobial pipeline, our data provides evidence for the culture-guided step-down use of an effective narrow-spectrum “old” antibiotic (cefazolin) for *K pneumoniae* bacteraemia.

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