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Efficacy of Appropriate Antimicrobial Therapy on the Survival of Patients With Carbapenem Nonsusceptible *Klebsiella Pneumoniae* Infection

A Multicenter Study in Taiwan

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Abstract: The impact of antimicrobial treatment on the outcome of carbapenem nonsusceptible *Klebsiella pneumoniae* (CnsKP) infections needs to be elucidated. This nationwide, multicenter study was conducted to evaluate the impact of appropriate antimicrobial therapy on 14-day mortality among patients with CnsKP infection in Taiwan.

Patients with CnsKP infections from 11 medical centers and 4 regional hospitals in Taiwan were enrolled in 2013. Carbapenem nonsusceptibility was defined as a minimum inhibitory concentration of ≥2 mg/L for imipenem or meropenem. Predictors of 14-day mortality were determined using the Cox proportional regression model. The influence of infection severity on the impact of appropriate use of antimicrobials on 14-day mortality was determined using the Acute Physiology and Chronic Health Evaluation (APACHE) II score.

Overall 14-day mortality was 31.8% (49/154). Unadjusted mortality for appropriate antimicrobial therapy was 23.1% (18/78 patients). Appropriate therapy was independently associated with reduced mortality (hazard ratio [HR], 0.44; 95% confidence interval [CI], 0.24–0.80; $P = 0.007$). A subgroup analysis revealed that the benefit of appropriate therapy was limited to patients with higher APACHE II scores (HR for patients with scores >15 and ≤35, 0.46; 95% CI 0.23–0.92; and for those with scores >35, 0.14; 95% CI, 0.02–0.99).

In conclusion, appropriate antimicrobial therapy significantly reduces 14-day mortality for CnsKP infections. Survival benefit is more notable among more severely ill patients.

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Abbreviations: APACHE = Acute Physiology and Chronic Health Evaluation, CI = confidence interval, CLSI = Clinical and Laboratory Standards Institute, CnsKP = carbapenem nonsusceptible *Klebsiella pneumoniae*, COPD = chronic obstructive pulmonary disease, ESBL = extended-spectrum β-lactamase, HR = hazard ratio, KPC = *Klebsiella pneumoniae* carbapenemase, MIC = minimum inhibitory concentration.

INTRODUCTION

Klebsiella pneumoniae is an important pathogen of community- and nosocomial-acquired infection worldwide.[1,2] Carbapenems have been used widely against severe bacterial infections because of the increasing prevalence of extended-spectrum β-lactamase (ESBL)-producing *Enterobacteriaceae*, and thereby contribute to carbapenem nonsusceptibility among these organisms, especially for *K pneumoniae*.[3] The emergence of carbapenem-resistant *K pneumoniae* infection has alerted the medical community of the urgent need for effective treatment owing to its high mortality (reported to be 18%–60%).[4]

One of the 2 main mechanisms of carbapenem-resistant *K pneumoniae* is overproduction of AmpC β-lactamases or ESBL with decreased porin penetration. The other resistance mechanism is through carbapenemases.[3,5] *K pneumoniae* carbapenemase (KPC)-producing *K pneumoniae* has become a significant problem in terms of public health and clinical outcome owing to its rapid spread around the world.[6] The emergence and rapid spread of KPC-2-producing *K pneumoniae* has also become an important problem in Taiwan since 2012.[7]

Because of its extensive resistance to most β-lactams, the treatment options for carbapenem-resistant *K pneumoniae* infection are usually limited to colistin, tigecycline, or aminoglycosides, according to susceptibility in vitro.[8] Some studies have reported no significant survival benefit in patients treated with active antimicrobial agents,[9–11] whereas others have shown positive results.[12,13] Because of the heterogeneity of disease severity, infection focus, and difficulty in conducting a randomized controlled study to eliminate all possible unmeasured confounding factors, the impact of antimicrobial

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treatment on the outcome of carbapenem-resistant *K pneumoniae* infection needs to be elucidated.

We conducted a nationwide, multicenter study to evaluate the impact of appropriate antimicrobial therapy on 14-day mortality among patients with carbapenem nonsusceptible *K pneumoniae* (CnsKP) infection in Taiwan. Particular attention was focused on the outcome related to different levels of disease severity.

METHODS

Study Site

This retrospective cohort study was conducted from January 2013 to December 2013 at 15 hospitals, including 11 medical centers (National Taiwan University Hospital, Taipei Veterans General Hospital, Tri-Service General Hospital, and Linkou Chang Gung Memorial Hospital in the north; Chung Shan Medical University Hospital, and China Medical University Hospital in the center of the country; Chi Mei Medical Center, National Cheng Kung University Hospital, Kaohsiung Chang Gung Memorial Hospital and Kaohsiung Medical University Hospital in the south; Buddhist Tzu Chi General Hospital in the east). The other 4 hospitals were Keelung Chang Gung Memorial Hospital, Taoyuan Armed Forces General Hospital, Chiayi Chang Gung Memorial Hospital, and Kaohsiung Municipal Hsiaokang Hospital. The study protocol was approved by the review board of each participating hospital.

Microbiologic Methods

During the study period, CnsKP isolates were collected from clinical specimens and sent for culture to the microbiological laboratories of participating hospitals. Only the first episode of CnsKP infection was collected for each patient. Nonsusceptibility to carbapenem was defined as a minimum inhibitory concentration (MIC) of $\geq 2\,\mu g/mL$ for imipenem or meropenem based on the interpretative criteria from the Clinical and Laboratory Standards Institute (CLSI) published in 2012.[14] Isolates collected from each hospital were sent to the National Health Research Institutes (Miaoli, Taiwan) and stored at $-70\,^{\circ}C$ in 10% glycerol Luria–Bertani medium before analyses. The Vitek 2 automated system (bioMérieux, Marcy l'Etoile, France) was used for bacterial identification.

MICs were determined by broth microdilution (Sensititre, Trek Diagnostic Systems, Cleveland, OH) for all antibiotics except tigecycline and colistin, as described previously.[7] CLSI M100-S22 interpretive breakpoints were used to evaluate the MIC results for all antimicrobial agents studied, except tigecycline and colistin.[14] Susceptibility to colistin was based on the European Committee on Antimicrobial Susceptibility Testing (susceptible, MIC $\leq 2\,mg/L$; resistant, MIC $>2\,mg/L$), as described previously.[15] MICs for tigecycline were determined using the E-test (AB Biodisk, Solna, Sweden) on Mueller–Hinton media. Susceptibility to tigecycline was defined based on criteria set by the US Food and Drug Administration (susceptible, MIC $\leq 2\,mg/L$; resistant, MIC $\geq 8\,mg/L$), as described previously.[16]

Isolates were subjected to polymerase chain reaction detection of carbapenemase genes, plasmid-borne AmpC-like genes, and ESBL genes, as described previously.[7] Identification of outer-membrane porins (OMPK35 and OMPK36) was carried out as described previously.[7]

Collection of Clinical Data and Definitions

The clinical data of all consecutive patients infected with CnsKP from different specimens were collected retrospectively. Definitions of CnsKP infection were as described previously.[17] Patients younger than 20 years and those with incomplete medical records were excluded. Surveillance cultures were not taken during the study period.

Infections were defined to be ''nosocomial-acquired'' if the index culture had been collected $>48\,h$ after hospital admission. The isolates were defined to be ''healthcare-associated'' if patients met any of the following criteria: received intravenous therapy at home or in an outpatient clinic during the previous 30 days; received renal dialysis in a hospital or clinic during the previous 30 days; underwent hospitalization for ≥ 2 days during the previous 90 days; or resided in a nursing home or long-term care facility.[18] Severity of illness at the time of onset of infection was assessed by the acute physiology and chronic health evaluation (APACHE) II score, as described previously.[19] ''Appropriate antimicrobial therapy'' was defined as treatment with at least 1 agent for $\geq 48\,h$ after isolation of a clinical culture specimen to which the isolate was susceptible in vitro.[13] ''Combination therapy'' was defined as administration of ≥ 2 in vitro active antimicrobial agents for $>48\,h$ after isolation of a clinical culture specimen, and the duration of each antimicrobial agent has overlapped for $\geq 48\,h$. Tigecycline for an infection of the bloodstream or urinary-tract infection was defined as ''appropriate therapy'' if the tigecycline MIC was $\leq 0.5\,mg/L$ at standard dosing.[20] The primary outcome measure was 14-day mortality after the onset of infection. Polymicrobial isolation was defined as at least 1 pathogen other than CnsKP isolated from the same specimen. The co-pathogens in polymicrobial infections that were not treated with appropriate antibiotic therapy were excluded in this analysis.

Statistical Analyses

Analyses were processed with Statistical Package for the Social Sciences (SPSS) v19.0 (SPSS, Chicago, IL). Bivariate associations between the binary outcome of 14-day mortality and patient characteristics were analyzed using the χ^2 test or Fisher exact test for discrete variables, and the Student *t* test or Mann–Whitney rank test for continuous variables. The Cox proportional regression model was used to explore factors associated with 14-day mortality. Univariate analyses were done separately for each of the variables to ascertain the hazard ratio (HR) and 95% confidence interval (CI). All biologically plausible variables with $P \leq 0.10$ in the univariate analysis were considered for inclusion in the Cox regression model for the multivariate analysis.

RESULTS

Microbiologic Characteristics of CnsKP Isolates

A total of 154 patients infected with CnsKP were identified during the study period. The samples were as follows: sputum (n = 73), bronchoalveolar lavage (n = 2), pleural effusion (n = 2), urine (n = 38), ascites (n = 5), synovial fluid (n = 1), tip of a central venous catheter (n = 2), tip of abdominal drain (n = 2), blood (n = 20), wound (n = 7), and bile (n = 2). Fifty-two isolates (33.8%) had genes that encoded carbapenemases: KPC-2 (n = 43), KPC-3 (n = 1), VIM-1 (n = 5), IMP-8 (n = 2), KPC-2, and IMP-8 (n = 1). The most common mechanism of carbapenem non-susceptibility was

TABLE 1. In Vitro Activities of Tested Antimicrobial Agents Against 154 CnsKP Isolates

Antimicrobial Agent	MIC Range, μg/mL	MIC_{50}*, μg/mL	MIC_{90}†, μg/mL	No. (%) of Isolates Susceptible
Ciprofloxacin	≤0.06–≥4	≥4	≥4	6 (3.9)
Levofloxacin	≤0.50–≥8	≥8	≥8	11 (7.1)
Ampicillin-sulbactam	>32	≥32	≥32	0 (0)
Piperacillin-tazobactam	8–≥128	≥128	≥128	2 (1.3)
Cefazolin	≥32	≥32	≥32	0 (0)
Ceftriaxone	≥32	≥32	≥32	0 (0)
Ceftazidime	16–≥32	≥32	≥32	0 (0)
Cefepime	≤1–≥32	≥32	≥32	18 (11.7)
Amikacin	≤4–≥64	≤4	≥64	122 (79.2)
Gentamicin	≤1–≥16	2	≥16	81 (52.6)
Ertapenem	1–≥8	≥8	≥8	0 (0)
Imipenem	2–≥8	≥8	≥8	0 (0)
Meropenem	≤0.25–≥8	≥8	≥8	23 (14.9)
Doripenem	≤0.25–≥8	4	≥8	22 (14.3)
Colistin	≤0.5–≥4	≤0.5	≥4	132 (85.7)
Tigecycline	≤0.25–≥4	0.5	1	150 (97.4)

MIC = minimal inhibitory concentration.
* MIC_{50}: MIC for 50% of isolates.
† MIC_{90}: MIC for 90% of isolates.

production of AmpC-mediated β-lactamases or ESBL plus porin defects, which was identified in 102 cases.

The MIC ranges, MIC_{50} values, and MIC_{90} values of various antimicrobial agents against CnSKP isolates are listed in Table 1. The MIC of imipenem was ≥8 μg/mL for 120 (78.0%) isolates, 4 μg/mL for 11 (7.1%) isolates, and 2 μg/mL for 23 (14.9%) isolates. Most isolates were susceptible to tigecycline (n = 150, 97.4%), colistin (n = 132, 85.7%) and amikacin (n = 123, 79.9%), but showed moderate susceptibility to gentamicin (n = 81, 52.6%).

Factors Associated with 14-day Mortality in Patients with CnsKP

The 14-day mortality associated with CnsKP infection was 31.8% (49/154). The overall in-hospital mortality associated with CnsKP infection was 53.2% (82/154). The median duration of hospital stay after isolation of these pathogens was 19.5 days (interquartile range: 7–43).

A comparison of the clinical features between survivors and non-survivors 14 days after CnsKP infection is shown on Table 2. In the univariate analysis, advanced age, pneumonia, chronic obstructive pulmonary disease, higher Charlson score, and higher APACHE II score were significantly associated with 14-day mortality. Polymicrobial isolation and appropriate antimicrobial therapy were associated with survival. Multivariate analyses showed the APACHE II score (HR 1.11; 95% CI 1.07–1.14; $P < 0.001$) to be an independent factor associated with 14-day mortality. Polymicrobial isolation (HR 0.40; 95% CI 0.25–0.97; $P = 0.040$) and appropriate antimicrobial therapy (HR, 0.44; 95% CI 0.24–0.80; $P = 0.007$) were independent protective factors for 14-day mortality (Table 3).

The 14-day mortality of patients receiving appropriate antimicrobial therapy was significantly lower than that for those receiving inappropriate antimicrobial therapy (23.1% vs 40.8%, $P = 0.018$). We further compared the demographic and clinical characteristics between patients who received appropriate (n = 78) and inappropriate antimicrobial therapy (n = 76). There was no significant difference in age, sex, comorbid conditions, APACHE II score, source of infection, acquisition of infection in the intensive care unit, or days of hospitalization before infection (data not shown). Among patients receiving appropriate antimicrobial therapy, most patients received monotherapy (n = 68, 87.2%). The most common in vitro active antimicrobial used was tigecycline (n = 33, 42.3%), followed by colistin (n = 27, 34.6%). The 14-day mortality of patients receiving appropriate antimicrobial therapy with tigecycline was 15.2% (5/33). The 14-day mortality of patients receiving appropriate antimicrobial therapy with colistin was 33.3% (9/27). The most common combination was colistin plus tigecycline, which was used in 6 cases. The standard dose of tigecycline was administered in patients throughout this study.

Impact of Appropriate Antimicrobial Therapy on 14-day Mortality in Patients With Different Severities of Infection

The adjusted HRs by multivariate analysis for 14-day mortality of patients receiving appropriate antimicrobial therapy with APACHE II score >15, >20, >25, >30, and >35 were 0.39 (95% CI 0.21–0.73; $P = 0.003$), 0.42 (95% CI 0.23–0.80; $P = 0.008$), 0.32 (95% CI 0.15–0.72; $P = 0.006$), 0.29 (95% CI 0.09–0.92; $P = 0.035$), and 0.14 (95% CI, 0.02–0.99, $P = 0.049$), respectively. Appropriate antimicrobial therapy showed the most notable effect among patients with the most severe illness (APACHE II score >35). Patients were then categorized into 3 groups according to APACHE II score (Table 4). In group 1 (score ≤15), appropriate antimicrobial therapy was not associated with a significantly better outcome. However, among patients in group 2 (score, 16–35) and group 3 (score >35), appropriate antimicrobial therapy significantly reduced 14-day mortality (HR, 0.46 [95% CI, 0.23–0.92] and 0.14 [95% CI 0.02–0.99], respectively).

TABLE 2. Characteristics of Patients With CnsKP Infection Stratified by 14-day Mortality

Variable	14-Day Survivors (n = 105)	14-Day Nonsurvivors (n = 49)	*P*
Demographics			
Age, y, mean ± SD	75.03 ± 13.76	79.94 ± 10.90	0.019
Male sex	69 (65.7)	35 (71.4)	0.603
Nosocomial-acquired isolate	90 (85.7)	41 (83.7)	0.930
Healthcare-associated isolate	8 (7.6)	3 (6.1)	1.000
ICU-acquired isolate	34 (32.4)	18 (36.7)	0.727
LOS before CnsKP isolation, days, median (IQR)	24 (6–27)	31 (10.5–50)	0.468
Carbapenemase-producing CnsKP	31 (29.5)	21 (42.9)	0.148
Previous hospitalization*	51 (48.6)	23 (46.9)	0.987
Clinical syndrome			
Pneumonia	52 (49.5)	33 (67.3)	0.058
Urinary tract infection	31 (29.5)	11 (22.4)	0.469
Intra-abdominal infection	11 (10.5)	3 (6.1)	0.550
Skin and soft tissue infection	6 (5.7)	2 (4.1)	1.000
Catheter-associated infection	3 (2.9)	0 (0.0)	0.552
Primary bacteremia	1 (1.0)	0 (0.0)	1.000
Others	1 (1.0)	0 (0.0)	1.000
Bacteremia	13 (12.4)	7 (14.3)	0.944
Imipenem MIC ≥4	88 (83.8)	43 (87.8)	0.691
Imipenem MIC ≥8	79 (75.2)	41 (83.7)	0.334
Polymicrobial isolation	46 (43.8)	12 (24.5)	0.033
Comorbidities			
Diabetes mellitus	42 (40.0)	26 (53.1)	0.178
COPD	11 (10.5)	14 (28.6)	0.009
Heart failure	13 (12.4)	12 (24.5)	0.096
Cerebrovascular disease	28 (26.7)	14 (28.6)	0.958
Chronic renal failure	53 (50.5)	31 (63.3)	0.190
Liver cirrhosis	6 (5.7)	3 (6.1)	1.000
Malignancy	32 (30.5)	10 (20.4)	0.266
Immunocompromised state	16 (15.2)	9 (18.4)	0.798
Charlson Comorbidity Index, mean ± SD	3.66 ± 2.70	4.65 ± 2.77	0.036
Indwelling central venous catheter	50 (47.6)	26 (53.1)	0.648
Indwelling urinary catheter	77 (73.3)	38 (77.6)	0.718
Surgical drainage	13 (12.4)	8 (16.3)	0.680
Mechanically ventilated at isolation	35 (33.3)	22 (44.9)	0.228
Renal dialysis at isolation	19 (18.1)	11 (22.4)	0.677
Previous surgery†	10 (9.5)	2 (4.1)	0.340
APACHE II score, mean ± SD	20.84 ± 7.76	30.33 ± 9.69	<0.001
Appropriate antimicrobial therapy, no. (%)	60 (57.1)	18 (36.7)	0.029

Data are the number (%) unless specified otherwise. APACHE = Acute Physiology and Chronic Health Evaluation, BSI = bloodstream infection, CI = confidence interval, CnsKP = carbapenem nonsusceptible *Klebsiella pneumonia*, COPD = chronic obstructive pulmonary disease, IQR = interquartile range, LOS = length of hospital stay, SD = standard deviation.

* During the 3 months preceding infection onset.

† During the 30 days preceding infection onset.

DISCUSSION

The present study represented one of the largest series focusing on CnsKP infection, and reported 14-day mortality of 31.8%, highlighting the high mortality caused by this pathogen. This retrospective study showed that appropriate antimicrobial therapy reduced 14-day mortality independently after adjustment for various factors. We further demonstrated that appropriate antimicrobial therapy significantly benefited more severely ill patients.

In general, inadequate antibiotic therapy can influence outcome. The detrimental effects of inadequate antibiotic therapy seem to become weaker in patients who are not severely ill as well as the most severely infected patients with short life expectancies.[21] It is reasonable to assume that less severely ill patients should have a better prognosis and might recover without specific therapeutic interventions. Nevertheless, one recent study showed that appropriate antimicrobial therapy was the potential life-saving measure for patients with *Acinetobacter baumannii* bacteremia in the most severe cases.[22] The present study was the first to analyze the efficacy of antimicrobial therapy in CnsKP infections with different disease severity stratified by APACHE II score. Our observation that appropriate antimicrobial therapy did not significantly benefit patients with APACHE II scores ≤15 is in accordance with the previous studies. Furthermore, we showed that appropriate

TABLE 3. Cox Proportional Regression Analysis of Predictors for 14-day Mortality Among 154 Patients With CnsKP Infection

Variable	Univariate Analysis		Multivariable Analysis	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Age	1.03 (1.00–1.05)	0.036		
Pneumonia	1.90 (1.05–3.45)	0.035		
COPD	2.51 (1.35–4.67)	0.004		
Heart failure	1.79 (0.93–3.42)	0.081		
Charlson Comorbidity Index, mean ± SD	1.10 (1.00–1.21)	0.041		
Polymicrobial infection or colonization	0.49 (0.26–0.95)	0.034	0.40 (0.25–0.97)	0.040
APACHE II score	1.12 (1.08–1.16)	<0.001	1.11 (1.07–1.14)	<0.001
Appropriate antimicrobial therapy, no. (%)	0.45 (0.25–0.81)	0.008	0.44 (0.24–0.80)	0.007

All biologically relevant variables with $P < 0.1$ in the univariate cox proportional regression analyses were included in the multivariate analysis. APACHE = Acute Physiology and Chronic Health Evaluation, CI = confidence interval, CnsKP = carbapenem nonsusceptible *Klebsiella pneumonia*, COPD = chronic obstructive pulmonary disease, HR = hazard ratio, SD = standard deviation.

antimicrobial therapy benefited patients with more severe illness. Studies on bloodstream infections caused by KPC-producing *K pneumoniae* CnsKP did not take account of disease severity on the effect of antimicrobial therapy.[10,12,13] Recently, Daikos et al[23] stratified patients with KPC-producing *K pneumoniae* bacteremia by the severity of sepsis and underlying diseases, and found the superiority of combination therapy in patients with rapidly fatal underlying disease and septic shock. Tumbarello et al[24] also demonstrated treatment with ≥2 drugs displaying activity against KPC-producing *K pneumoniae* isolates improves survival, mainly in patients with APACHE III scores ≥15. Bass et al[25] suggested that appropriate therapy benefited critically ill patients with carbapenem-resistant bacteremia, but the analysis from patients with different severity was not performed. It is evident that objective measurement of disease severity should be included in future clinical studies if evaluating the impact of appropriate antimicrobial therapy on the mortality caused by CnsKP infections.

Treatment of carbapenem-resistant *Enterobacteriaceae* is derived primarily from experiences in carbapenemase-producing *K pneumoniae* infection.[3,26] Data from the literature suggest that treatment with a single in vitro active agent results in mortality not significantly different from that observed in patients treated with no active therapy, whereas combination therapy with ≥2 in vitro active agents is superior to monotherapy providing a clear survival benefit. The lowest mortality has been observed in patients treated with carbapenem-containing combinations.[3,26] Combination therapy has been recommended for CnsKP infection by some experts,[4,27] but the inherent limitations of those studies related to their observational design and sample size weaken the evidence to support the use of combination therapies against CnsKP.[28] One recent study showed that combination therapy was not superior to monotherapy to treat KPC-producing Enterobacteriaceae infections.[29] Because of the regulations for National Health Insurance Reimbursement in Taiwan, only a few cases in the present study received combination therapy. The uncommon practice of combination therapy provided the opportunity to analyze the significance of monotherapy in CnsKP. Our analyses supported the evidence that appropriate monotherapy had an important role in the outcome of CnsKP infection. Our study implied that appropriate therapy is the cornerstone determining the outcome in CnsKP infection.

In the present study, the major resistance mechanism of CnsKP was production of AmpC-mediated β-lactamases or ESBL plus porin defects, which is different from the mechanism of carbapenemase production described in the literature.[3] The different genetic background behind the MIC may also play a part in prediction of the outcome. Whether the different resistance mechanisms accounted for the efficacy of antimicrobial therapy needs further investigation. Not all laboratories were able to determine the mechanism of resistance in clinical practice. Therefore, the findings of the present study provide evidence that administration of appropriate therapy according to MIC testing is essential to manage these infections.

Our study was limited by its retrospective design. However, our data have important clinical implications because of the limited number of therapeutic options for CnsKP and the weak evidence for the clinical use of these regimens. Our study

TABLE 4. Adjusted Hazard Ratios of Appropriate Antimicrobial Therapy for 14-day Mortality Among Patients With CnsKP Infection, Stratified by Severity of Illness

Group	APACHE II	Patient Number	14-Day Mortality	Adjusted HR (95% CI)	*P*
1	≤15	31	9.7%	0.47 (0.04–5.23)	0.540
2	>15 and ≤35	106	32.1%	0.46 (0.23–0.92)	0.029
3	>35	17	70.6%	0.14 (0.02–0.99)	0.049

The variables with $P < 0.1$ in previous univariate Cox proportional regression analysis were included in the multivariate analysis after stratification by severity of illness, including: age, pneumonia, chronic obstructive pulmonary disease , heart failure, Charlson Comorbidity Index, mixed infection, appropriate therapy). APACHE = Acute Physiology and Chronic Health Evaluation, CI = confidence interval, CnsKP = carbapenem nonsusceptible *Klebsiella pneumonia*, HR = hazard ratio.

was also strengthened by the inclusion of a large number of patients with various sites and severities of infection, and a well-defined endpoint of 14-day mortality. Another limitation is that we cannot analyze the role of combination antibiotic therapy due to the rare utilization. Finally, co-isolation with other pathogens was quite common (37.7%, 58/154 patients). The relationship between polymicrobial isolation and the outcome needs more studies to clarify. Some reports have excluded cases of polymicrobial infection or limited the cases in bacteremia, but this method would limit generalizability. Therefore, the present study represents real-life clinical experiences and provides important clinical information.

In conclusion, appropriate antimicrobial therapy (even with a single active agent) was found to reduce 14-day mortality in subjects with CnsKP infection. The survival benefit was more notable among more severely ill patients.

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