

Impact of appropriate empirical antibiotics on clinical outcomes in *Klebsiella pneumoniae* bacteraemia

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ABSTRACT

Introduction: *Klebsiella pneumoniae* infections can cause septic shock, multiorgan failure, and death.

Methods: This retrospective cohort study included adults with *K pneumoniae* bacteraemia treated from 1 January 2009 to 30 June 2017. Demographics, microbiology, and outcomes were analysed. The primary outcome was 90-day all-cause mortality; secondary outcomes were intensive care unit (ICU) and hospital mortalities, ICU and hospital lengths of stay, and ICU ventilator duration.

Results: In total, 984 patients had *K pneumoniae* bacteraemia; of them, 686 received appropriate empirical antibiotics. Overall, 205 patients required intensive care. Older age (odds ratio [OR]=1.60; 95% confidence interval [CI]=1.120-2.295; P=0.010), chronic kidney disease (OR=1.81; 95% CI=1.181-2.785; P=0.007), mechanical ventilation (OR=1.79; 95% CI=1.188-2.681; P=0.005), pneumonia (OR=1.50; 95% CI=1.030-2.187; P=0.034), and carbapenem-resistant or extended-spectrum beta-lactamase (ESBL)-producing isolates (OR=12.51; 95% CI=7.886-19.487; P<0.001) were associated with greater risk of inappropriate empirical treatment. Ninety-day mortality was significantly higher among patients with inappropriate empirical treatment; independent predictors included pneumonia (hazard ratio [HR]=2.94; 95% CI=2.271-3.808; P<0.001), gastrointestinal infection (HR=2.77; 95% CI=2.055-

3.744; P<0.001), failed empirical antibiotics (HR=2.45; 95% CI=1.928-3.124; P<0.001), older age (HR=1.79; 95% CI=1.356-2.371; P<0.001), solid tumour (HR=1.77; 95% CI=1.401-2.231; P<0.001), carbapenem-resistant or ESBL-producing isolates (HR=1.64; 95% CI=1.170-2.297; P=0.004), patients admitted through the Department of Medicine (HR=1.39; 95% CI=1.076-1.800; P=0.012), and higher total Sequential Organ Failure Assessment score (HR=1.09; 95% CI=1.058-1.112; P=0.023). Among ICU patients, inappropriate empirical antibiotic treatment was significantly associated with increased ventilator duration and 90-day mortality.

Conclusions: *Klebsiella pneumoniae* bacteraemia was associated with high 90-day and ICU mortalities; 90-day mortality increased with inappropriate empirical antibiotic treatment.

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New knowledge added by this study

- This large study of *Klebsiella pneumoniae* bacteraemia among patients in Hong Kong and South East Asia showed that 90-day mortality was significantly higher in patients who received inappropriate empirical treatment.
- Intensive care unit subgroup analysis showed that inappropriate empirical treatment was the strongest predictor of 90-day mortality in critically ill patients.
- Independent predictors for inappropriate empirical treatment were older age, chronic kidney disease, mechanical ventilation, pneumonia, and either carbapenem resistance or extended-spectrum beta-lactamase production.

Implications for clinical practice or policy

- Extensive efforts are needed to facilitate early, appropriate use of empirical antibiotics, including the use of a current antibiogram, implementation of multidisciplinary sepsis management guidelines, and establishment of protocols among pharmacists, microbiologists, clinicians, and nurses.
- Careful assessment of empirical antibiotic treatment may be warranted in patients with pneumonia, gastrointestinal infection, failed empirical antibiotics, older age, solid tumour, patients admitted through the Department of Medicine, and/or higher total Sequential Organ Failure Assessment score.

適當的經驗性抗生素對肺炎克雷伯菌血症臨床結果的影響

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引言：肺炎克雷伯菌感染可導致感染性休克、多重器官衰竭及死亡。

方法：這項回顧性隊列研究納入2009年1月1日至2017年6月30日期間接受治療的肺炎克雷伯菌血症成人患者。分析人口統計學、微生物學和結局。主要結果為90天全因死亡率；次要結果包括重症監護病房（ICU）死亡率和醫院死亡率、ICU逗留時間和住院時間，以及患者使用ICU呼吸機時間。

結果：肺炎克雷伯菌血症共984例；其中686例接受適當的經驗性抗生素治療。共205名患者需要重症監護。年齡較大（比值比=1.60；95%置信區間=1.120-2.295；P=0.010）、慢性腎病（比值比=1.81；95%置信區間=1.181-2.785；P=0.007）、機械通氣（比值比=1.79；95%置信區間=1.188-2.681；P=0.005）、肺炎（比值比=1.50；95%置信區間=1.030-2.187；P=0.034），以及碳青黴烯類耐藥或超廣譜β-內酰胺酶產生的分離株（比值比=12.51；95%置信區間=7.886-19.487；P<0.001）與較大風險有經驗性治療不當相關。經驗性治療不當的患者的90天死亡率顯著更高；獨立預測因素包括肺炎（風險比=2.94；95%置信區間=2.271-3.808；P<0.001）、胃腸道感染（風險比=2.77；95%置信區間=2.055-3.744；P<0.001）、經驗性抗生素無效（風險比=2.45；95%置信區間=1.928-3.124；P<0.001）、年齡較大（風險比=1.79；95%置信區間=1.356-2.371；P<0.001）、實體瘤（風險比=1.77；95%置信區間=1.401-2.231；P<0.001）、碳青黴烯類耐藥或超廣譜β-內酰胺酶產生的分離株（風險比=1.64；95%置信區間=1.170-2.297；P=0.004）、透過內科住院的患者（風險比=1.39；95%置信區間=1.076-1.800；P=0.012），以及連續器官衰竭評估總分較高（風險比=1.09；95%置信區間=1.058-1.112；P=0.023）。在ICU患者中，經驗性抗生素治療不當與患者使用呼吸機時間增加和90天死亡率顯著相關。

結論：肺炎克雷伯菌血症與高90天死亡率和ICU死亡率相關；經驗性抗生素治療不當可增加90天死亡率。

Introduction

Klebsiella pneumoniae causes various clinically important infections. In 2017, *K pneumoniae* was the third most common isolate in intensive care units (ICUs) and second most common isolate in all patients in the Hong Kong East Cluster.¹

The emergence of multidrug-resistant *K pneumoniae* infections is an increasing concern.² There have been outbreaks of extended-spectrum beta-lactamase (ESBL)-producing strains, carbapenem-resistant (CR) and carbapenemase-producing (CP) strains, and hypervirulent *K pneumoniae* infections both in Hong Kong and worldwide.²⁻⁴ In Greece and Italy, CP *K pneumoniae* comprises 68.3% of all *K pneumoniae* strains.⁵

The importance of appropriate early empirical antibiotics has been repeatedly emphasised in the management of septic shock by the Surviving Sepsis Campaign 2016.⁶ Previously, we highlighted the importance of appropriate early antibiotics for

successful patient outcomes.⁴ To the best of our knowledge, risk factors for receiving inappropriate empirical antibiotics have not yet been explored. Therefore, in the present study, we aimed to evaluate the impact of appropriate empirical antibiotics on outcomes in patients with *K pneumoniae* bacteraemia; we also performed subgroup analysis on ICU patients with *K pneumoniae* bacteraemia.

Methods

Study design and data collection

We conducted a retrospective analysis of adult patients with *K pneumoniae* bacteraemia who were admitted to Pamela Youde Nethersole Eastern Hospital within the period from 1 January 2009 to 30 June 2017. Pamela Youde Nethersole Eastern Hospital is a 1700-bed hospital in Hong Kong which provides extensive services except cardiothoracic surgery, transplant surgery, and burns. Patients were excluded if they were aged <18 years or had incomplete information. Patient medical records were reviewed, as were data in clinical management and clinical information systems (IntelliVue Clinical Information Portfolio; Philips Medical, Amsterdam, The Netherlands). The clinical management system is a database that stores patients' demographics, laboratory results, and drug administration records for all public hospitals in Hong Kong. In the event of missing data, medical records were reviewed manually. Baseline demographics, clinical characteristics, and microbiological data for all included patients were identified from the above databases and medical records.

Disease severity was quantified using the maximum Sequential Organ Failure Assessment (SOFA) score.⁷ The following clinical outcome data were investigated: use of invasive organ supports (eg, inotropic use, mechanical ventilation, and renal replacement therapies), ICU and hospital lengths of stay (LOSs), ICU ventilator duration, and mortality. The primary outcome was 90-day all-cause mortality; secondary outcomes were ICU and hospital mortalities, ICU and hospital LOSs, and ICU ventilator duration.

Definitions

Klebsiella pneumoniae bacteraemia was defined as the growth of *K pneumoniae* in one or more blood cultures. If more than one positive blood culture result was recorded, only the first sample was included. Empirical antibiotic treatment was defined as the antibiotic used within 24 hours after a culture sample was collected. The empirical antibiotic treatment was considered appropriate if at least one of the antibiotic agents was consistent with the in vitro susceptibility results.⁸⁻¹⁰ Community-acquired infection was defined as *K pneumoniae*

identified in patients upon admission or within 48 hours after admission; hospital-acquired infection was defined as *K pneumoniae* identified in patients at >48 hours after admission.¹¹ Hepatobiliary sepsis comprised liver abscess, cholangitis, and cholecystitis; gastrointestinal sepsis comprised spontaneous bacterial peritonitis, peritonitis caused by bowel perforation, and intra-abdominal abscesses (excluding liver abscess). Medical co-morbidities (eg, diabetes mellitus, cirrhosis, congestive heart failure, chronic renal impairment, haematological malignancy and solid tumour) were defined in accordance with the International Classification of Disease coding. Prior steroid use was defined as oral or intravenous steroid consumption within 30 days before the index positive blood culture result. Chemotherapy use was defined as oral or intravenous infusion of biological agents or chemotherapy administered within 30 days before the index positive blood culture result. Any antibiotics usage within 30 days before the index hospital admission was regarded as prior antibiotics usage.

Microbiology

Blood cultures were incubated and processed. Blood culture results were considered negative if no positive growth occurred after 5 to 7 days. Susceptibility interpretation was based on Clinical and Laboratory Standards Institute interpretive criteria. The ESBL testing was based on Clinical and Laboratory Standards Institute testing criteria¹²⁻¹⁸ or the double-disk synergy test described by Jarlier et al.¹⁹ Regarding CR *K pneumoniae*, the isolates were sent to the Public Health Laboratory Centre of Hong Kong if further genetic testing was required to confirm carbapenemase production. Multiplex real-time polymerase chain reaction assays were performed to detect Classes A, B, and D carbapenemase gene targets.

Statistical analysis

We compared the characteristics and clinical parameters between patients treated with appropriate and inappropriate empirical antibiotics, as well as between 90-day survivors and non-survivors. Results are expressed as the median ± interquartile range (IQR) or as the number (percentage) of patients, as appropriate.

Categorical variables were compared by the Pearson Chi squared test or Fisher's exact test, as appropriate for univariate analysis. Continuous variables were compared by using the Mann-Whitney *U* test. Variables with $P < 0.2$ in univariate analysis or with clinical significance from previous studies were included in the multivariate analysis. Independent predictors for 90-day mortality were assessed by Cox regression analysis. Logistic regression analysis was used to assess independent predictors for receiving

appropriate and inappropriate empirical antibiotics. Post hoc analysis was performed for patients with chronic renal failure and resistant organisms.

The Statistical Package for Social Sciences (Windows version 24.0; IBM Corp, Armonk [NY], US) was used to perform statistical analyses.

Results

Baseline characteristics

During the 8.5-year study period, we identified 984 patients with *K pneumoniae* bacteraemia; of these, 686 (69.7%) and 298 (30.3%) received appropriate and inappropriate empirical antibiotics, respectively. Table 1 shows the baseline demographics of patients who received appropriate and inappropriate empirical antibiotics. The median patient age was 75 years (IQR=63-83 years). The most common types of infection were hepatobiliary tract infection (33.1%), urosepsis (24.4%), and respiratory tract infection (18.4%). The overall 90-day mortality was 32.7%, hospital mortality was 22.5%, and median hospital LOS was 10.68 days (5.38-22.81 days, $P < 0.001$).

Appropriateness of empirical antibiotics

Univariate analysis (Table 1) revealed that the risk factors for receiving inappropriate empirical antibiotics were age >65 years ($P = 0.044$), chronic renal impairment ($P < 0.001$), respiratory tract infection ($P = 0.002$), mechanical ventilation ($P = 0.001$), CR or ESBL-producing isolates (both $P < 0.001$), and higher total SOFA score ($P = 0.048$). Hepatobiliary sepsis was associated with a higher rate of appropriate empirical antibiotic treatment ($P = 0.009$).

Table 2 demonstrates the logistic regression analysis of the predictors for the appropriateness of empirical antibiotics for all patients and ICU subgroup. These include older patients ($P = 0.010$), chronic kidney disease ($P = 0.007$), mechanical ventilation ($P = 0.005$), respiratory tract infection ($P = 0.034$), and either carbapenem resistance or ESBL production ($P < 0.001$). Table 1 shows that the 90-day and hospital mortalities were significantly higher in patients with inappropriate empirical treatment (both $P < 0.001$). Moreover, the hospital LOS was shorter in patients who received inappropriate empirical antibiotics ($P < 0.001$).

Receipt of inappropriate empirical antibiotics was associated with higher hospital mortality; this finding was consistent in ICU subgroup (56% vs 23%). The absolute risk increases in mortality associated with the receipt of inappropriate empirical antibiotics were 18.3% and 33% in ICU subgroup. The number of inappropriate empirical antibiotics associated with each mortality was five in the ICU subgroup and three in all patients.

TABLE I. Clinical characteristics of adult patients with *Klebsiella pneumoniae* bacteraemia*

Parameters	All patients (n=984)	Received appropriate empirical antibiotics (n=686, 69.7%)	Received inappropriate or no empirical antibiotics (n=298, 30.3%)	P value
Age, y	75 (63-83)	74 (63-83)	76 (66-84)	0.075
Age >65 y	703 (71.4%)	477 (69.5%)	226 (75.8%)	0.044
Male sex	581 (59.0%)	404 (58.9%)	177 (59.4%)	0.883
Admitting department				0.841
Medicine	690 (70.1%)	481 (70.1%)	209 (70.1%)	
Surgery	221 (22.5%)	151 (22.0%)	70 (23.5%)	
Oncology	39 (4.0%)	29 (4.2%)	10 (3.4%)	
Others	34 (3.5%)	25 (3.6%)	9 (3.0%)	
Co-morbidities				
Diabetes mellitus	343 (34.9%)	240 (35.0%)	103 (34.6%)	0.899
Cirrhosis	29 (2.9%)	17 (2.5%)	12 (4.0%)	0.187
CHF	122 (12.4%)	77 (11.2%)	45 (15.1%)	0.090
CKD/ESRF	126 (12.8%)	69 (10.1%)	57 (19.1%)	<0.001
Haematological malignancy	50 (5.1%)	32 (4.7%)	18 (6.0%)	0.367
Solid tumour	339 (34.5%)	239 (34.8%)	100 (33.6%)	0.697
Steroid treatment (30D)	104 (10.6%)	74 (10.8%)	30 (10.1%)	0.736
Chemotherapy (30D)	39 (4.0%)	27 (3.9%)	12 (4.0%)	0.946
Source of sepsis				
Hepatobiliary	326 (33.1%)	245 (35.7%)	81 (27.2%)	0.009
Gastrointestinal	115 (11.7%)	80 (11.7%)	35 (11.7%)	0.970
Respiratory	181 (18.4%)	109 (15.9%)	72 (24.2%)	0.002
Urosepsis	240 (24.4%)	164 (23.9%)	76 (25.5%)	0.592
Musculoskeletal	20 (2.0%)	15 (2.2%)	5 (1.7%)	0.603
Neurological	2 (0.2%)	2 (0.3%)	0	1.000
Others or unknown	100 (10.2%)	71 (10.3%)	29 (9.7%)	0.768
Hospital-acquired infection	220 (22.4%)	134 (19.5%)	86 (28.9%)	<0.001
CVC usage	194 (19.7%)	129 (18.8%)	65 (21.8%)	0.276
Prior antibiotic use (30D)	772 (78.5%)	533 (77.7%)	239 (80.2%)	0.380
Septic shock	256 (26.0%)	174 (25.4%)	82 (27.5%)	0.479
Total SOFA score	3 (2.00-6.00)	3 (2.00-6.00)	4 (2.00-7.00)	0.048
Supportive treatment				
RRT	90 (9.1%)	60 (8.7%)	30 (10.1%)	0.509
Mechanical ventilation	151 (15.3%)	88 (12.8%)	63 (21.1%)	0.001
Vasopressor	164 (16.7%)	115 (16.8%)	49 (16.4%)	0.901
ICU care	205 (20.8%)	148 (21.6%)	57 (19.1%)	0.385
Resistance				
ESBL	113 (11.5%)	24 (3.5%)	89 (29.9%)	<0.001
Carbapenem	20 (2.0%)	3 (0.4%)	17 (5.7%)	<0.001
Outcome				
90-Day mortality	322 (32.7%)	183 (26.7%)	139 (46.6%)	<0.001
Hospital mortality	221 (22.5%)	116 (16.9%)	105 (35.2%)	<0.001
Hospital LOS, d	10.68 (5.38-22.81)	11.25 (6.02-23.5)	8.94 (3.25-20.12)	<0.001
Event-free LOS, d	11.43 (6.13-23.82)	11.43 (6.14-23.69)	11.58 (5.99-25.03)	1.000

Abbreviations: 30D = within preceding 30 days; CHF = congestive heart failure; CKD/ESRF = chronic kidney disease/end-stage renal failure; CVC = central venous catheter; ESBL = extended-spectrum beta-lactamase; ICU = intensive care unit; LOS = length of stay; RRT = renal replacement therapy (ie, intermittent or continuous replacement); SOFA = Sequential Organ Failure Assessment; Vasopressor = dopamine, adrenaline, and/or noradrenaline

* Data are shown as No. (%) or median (interquartile range), unless otherwise specified

TABLE 2. Independent predictors for receipt of inappropriate empirical antibiotics, according to logistic regression analysis*

Variables	All patients (n=984)		ICU subgroup (n=205)		
	Odds ratio (95% CI)	P value	Variables	Odds ratio (95% CI)	P value
Carbapenem or ESBL resistance	12.51 (7.886-19.487)	<0.001	CKD/ESRF	4.80 (1.563-14.759)	0.006
CKD/ESRF	1.81 (1.181-2.785)	0.007	ESBL or carbapenem resistance	4.34 (1.667-11.295)	0.003
Mechanical ventilation	1.79 (1.188-2.681)	0.005	Mechanical ventilation	4.07 (1.831-9.03)	0.001
Age >65 y	1.60 (1.120-2.295)	0.010	Solid tumour	0.38 (0.154-0.944)	0.037
Respiratory tract infection	1.50 (1.030-2.187)	0.034			

Abbreviations: 95% CI = 95% confidence interval; CKD/ESRF = chronic kidney disease/end-stage renal failure; ESBL = extended-spectrum beta-lactamase; ICU = intensive care unit; SOFA = Sequential Organ Failure Assessment

* Other factors included that did not reach statistical significance: cirrhosis, congestive heart failure, hepatobiliary sepsis, hospital-acquired infection, and total SOFA score (C index = 0.718; 95% CI = 0.681-0.755; Hosmer–Lemeshow goodness-of-fit test, $\chi^2 = 10.614$; degrees of freedom = 5; P = 0.060)

Multidrug-resistant *Klebsiella pneumoniae* infections

Antibiograms showing the proportions of non-susceptible *K pneumoniae* isolates are described in the Online Supplementary Table 1. Twenty (2.0%) patients had CR *K pneumoniae* bacteraemia, but molecular tests in the Public Health Laboratory Centre of Hong Kong revealed that none of them had CP strains. Overall, 113 (11.5%) patients had ESBL-producing infections.

Post hoc analysis revealed that patients with chronic renal failure were more likely to have ESBL infections (18.3% vs 10.5%; P=0.011) and CR infections (0.056% vs 0.015%; P=0.003).

Ninety-day mortality

The 90-day all-cause mortalities were 32.7% in all patients with *K pneumoniae* bacteraemia and 34.6% in the ICU subgroup. Univariate analysis (Table 3) showed that 90-day non-survivors were more likely to be aged >65 years (P<0.001), admitted through the Department of Medicine (P<0.001), have septic shock (P=0.005), have a higher total SOFA score (P<0.001), receive inappropriate or no empirical antibiotics (P<0.001 and P<0.001, respectively), have solid tumour (P<0.001), have respiratory tract infection (P<0.001), be mechanically ventilated (P<0.001), have gastrointestinal infections (P<0.001), and require renal replacement therapy (P=0.044). Patients with diabetes (P=0.001), hepatobiliary sepsis (P<0.001), and urosepsis (P<0.001) had lower 90-day mortalities.

Table 4 shows the Cox regression analysis of predictors for 90-day mortality. Independent predictors for increased 90-day mortality were respiratory tract infection (P<0.001), gastrointestinal infection (P<0.001), inappropriate empirical antibiotics (P<0.001), older age (P<0.001), solid tumour (P<0.001), patients admitted through the Department of Medicine (P=0.012), and higher total

SOFA score (P<0.001). Patients with diabetes had lower 90-day mortality (P=0.001). The Figure shows the Kaplan–Meier survival plot and according to log rank analysis, the results demonstrated a statistically significant improvement in survival among patients who received appropriate empirical antibiotics (P<0.001).

Intensive care unit subgroup analysis

Online Supplementary Table 2 shows the demographics for inappropriate empirical antibiotics by logistic regression analysis in ICU subgroup. Overall, 205 (20.8%) patients required intensive care; among them, 148 (72.2%) received appropriate empirical antibiotics, while 57 (27.8%) received inappropriate or no empirical antibiotics. The median patient age was 68 years (IQR=58-78 years). The commonest infection was hepatobiliary infections (42.9%), followed by respiratory tract (23.4%) and urosepsis (14.6%). Furthermore, 82.4% of the patients had septic shock, 33.2% received renal replacement therapy, 60% received mechanical ventilation, and 78.5% had vasopressor use. The ICU and overall 90-day mortalities were 18.5% and 34.6%, respectively. The receipt of inappropriate empirical antibiotics was significantly associated with higher 90-day mortality (59.6% vs 25.0%; P<0.001), higher ICU mortality (35.1% vs 12.2%; P<0.001), higher hospital mortality (56.1% vs 23.0%; P<0.001), and longer ventilator duration (2 d vs 1 d, P=0.026).

Cox regression analysis showed that the receipt of inappropriate or no empirical antibiotics (P<0.001; Table 4) was the strongest independent predictor of 90-day mortality in critically ill patients with *K pneumoniae* bacteraemia. Other independent predictors were congestive heart failure (P=0.02), admitted through the Department of Medicine (P=0.016), and a higher total SOFA score (P<0.001). Ninety-day non-survivors had longer hospital LOS (P<0.001).

TABLE 3. Clinical characteristics and risk factors associated with 90-day mortality*

Parameters	Total (n=984)	90-Day non-survivors (n=322, 32.7%)	90-Day survivors (n=662, 67.3%)	P value
Age, y	75.0 (63.0-83.0)	73.5 (62-82)	77.0 (67-85)	0.000
Age >65 y	703 (71.4%)	257 (79.8%)	446 (67.4%)	<0.001
Male sex	581 (59.0%)	185 (57.5%)	396 (59.8%)	0.479
Admitting department				<0.001
Medicine	690 (70.1%)	240 (74.5%)	450 (68.0%)	
Surgery	221 (22.5%)	48 (14.9%)	173 (26.1%)	
Oncology	39 (4.0%)	25 (7.8%)	14 (2.1%)	
Others	34 (3.5%)	9 (2.8%)	25 (3.8%)	
Co-morbidities				
Diabetes mellitus	343 (34.9%)	89 (27.6%)	254 (38.4%)	0.001
Cirrhosis	29 (2.9%)	12 (3.7%)	17 (2.6%)	0.313
CHF	122 (12.4%)	43 (13.4%)	79 (11.9%)	0.526
CKD/ESRF	126 (12.8%)	40 (12.4%)	86 (13.0%)	0.802
Haematological malignancy	50 (5.1%)	20 (6.2%)	30 (4.5%)	0.260
Solid tumour	339 (34.5%)	142 (44.1%)	197 (29.8%)	<0.001
Steroid (30D)	104 (10.6%)	35 (10.9%)	69 (10.4%)	0.831
Chemotherapy (30D)	39 (4.0%)	13 (4.0%)	26 (3.9%)	0.934
Source of sepsis				
Hepatobiliary	326 (33.1%)	73 (22.7%)	253 (38.2%)	<0.001
Gastrointestinal	115 (11.7%)	61 (18.9%)	54 (8.2%)	<0.001
Respiratory	181 (18.4%)	101 (31.4%)	80 (12.1%)	<0.001
Urosepsis	240 (24.4%)	53 (16.5%)	187 (28.2%)	<0.001
Musculoskeletal	20 (2.0%)	8 (2.5%)	12 (1.8%)	0.483
Neurological	2 (0.2%)	1 (0.3%)	1 (0.2%)	0.548
Others or unknown	100 (10.2%)	25 (7.8%)	75 (11.3%)	0.082
Hospital-acquired <i>Klebsiella pneumoniae</i>	220 (22.4%)	95 (29.5%)	125 (18.9%)	<0.001
CVC usage	194 (19.7%)	64 (19.9%)	130 (19.6%)	0.930
Prior antibiotic use (30D)	772 (78.5%)	259 (80.4%)	513 (77.5%)	0.292
Septic shock	256 (26.0%)	102 (31.7%)	154 (23.3%)	0.005
Total SOFA score	3.0 (2.00-6.00)	4.0 (2.00-8.00)	3.0 (2.00-5.00)	<0.001
Supportive treatment				
RRT	90 (9.1%)	38 (11.8%)	52 (7.9%)	0.044
Mechanical ventilation	151 (15.3%)	70 (21.7%)	81 (12.2%)	<0.001
Vasopressor	164 (16.7%)	66 (20.5%)	98 (14.8%)	0.025
ICU care	205 (20.8%)	71 (22.0%)	134 (20.2%)	0.512
Resistance				
ESBL	113 (11.5%)	43 (13.4%)	70 (10.6%)	0.199
Carbapenem	20 (2.0%)	7 (2.2%)	13 (2.0%)	0.826
Empirical treatment				
Appropriate	686 (69.7%)	183 (56.8%)	503 (76.0%)	<0.001
Failed	205 (20.8%)	76 (23.6%)	129 (19.5%)	<0.001
No antibiotic administered	93 (9.5%)	63 (19.6%)	30 (4.5%)	<0.001
Outcome				
Hospital mortality	221 (22.5%)	212 (65.8%)	9 (1.4%)	<0.001
Hospital LOS, d	10.68 (5.38-22.81)	11.43 (6.13-23.82)	8.80 (2.92-20.44)	<0.001

Abbreviations: 30D = within preceding 30 days; CHF = congestive heart failure; CKD/ESRF = chronic kidney disease/end-stage renal failure; CVC = central venous catheter; ESBL = extended-spectrum beta-lactamase; ICU = intensive care unit; LOS = length of stay; RRT = renal replacement therapy (ie, intermittent or continuous replacement); SOFA = Sequential Organ Failure Assessment; Vasopressor = dopamine, adrenaline, and/or noradrenaline

* Data are shown as No. (%) or median (interquartile range), unless otherwise specified

TABLE 4. Independent predictors for increased 90-day mortality according to Cox regression analysis*

Variables	All patients (n=984)		ICU subgroup (n=205)		
	Hazard ratio (95% CI)	P value	Variables	Hazard ratio (95% CI)	P value
Respiratory tract infection	2.94 (2.271-3.808)	<0.001	Inappropriate or no empirical antibiotics	3.00 (1.856-4.854)	<0.001
Gastrointestinal source	2.77 (2.055-3.744)	<0.001	Congestive heart failure	2.28 (1.141-4.561)	0.020
Inappropriate empirical antibiotics or no antibiotics	2.45 (1.928-3.124)	<0.001	Admitting department	1.94 (1.132-3.340)	0.016
Age >65 y	1.79 (1.356-2.371)	<0.001	Total SOFA score	1.17 (1.101-1.242)	<0.001
Solid tumour	1.77 (1.401-2.231)	<0.001	Diabetes mellitus	0.39 (0.221-0.696)	0.001
ESBL-producing or carbapenem-resistant isolates	1.64 (1.170-2.297)	0.004			
Admitting department	1.39 (1.076-1.800)	0.012			
Total SOFA score	1.09 (1.058-1.112)	<0.001			
Diabetes mellitus	0.65 (0.505-0.830)	0.001			

Abbreviations: 95% CI = 95% confidence interval; CKD/ESRF = chronic kidney disease/end-stage renal failure; ESBL = extended-spectrum beta-lactamase; ICU = intensive care unit; SOFA = Sequential Organ Failure Assessment

* Other factors included in analysis of all patients that did not reach statistical significance: hepatobiliary sepsis, urosepsis, renal replacement therapy, mechanical ventilation, hospital-acquired infection, and septic shock. Other factors included in ICU subgroup analysis that did not reach statistical significance: age >65 years, CKD/ESRF, hepatobiliary sepsis, gastrointestinal sepsis, respiratory tract infection, prior antibiotic use, septic shock, renal replacement therapy, mechanical ventilation, and vasopressor use

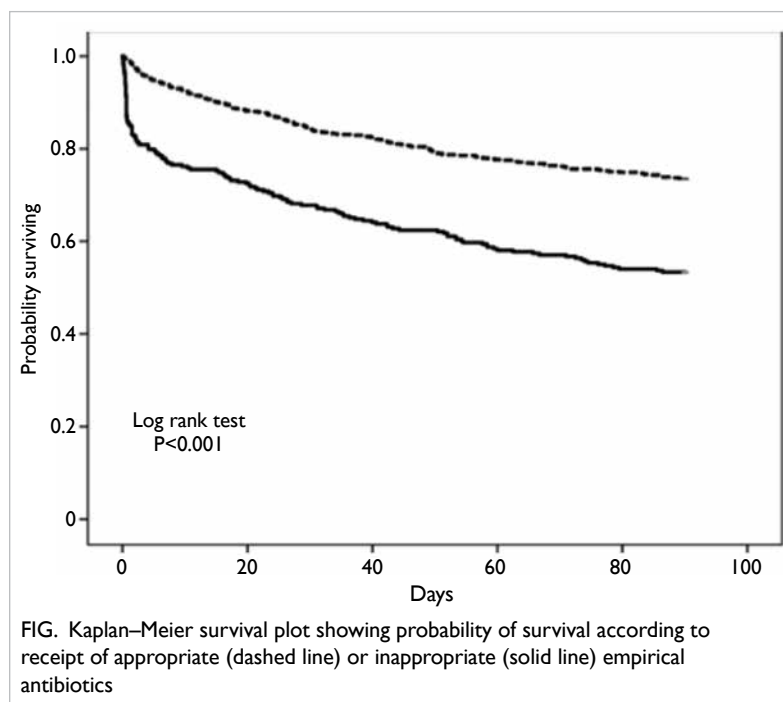
Discussion

Appropriateness of empirical antibiotics

Among all patients in this study, 686 (69.7%) received appropriate empirical antibiotics. Furthermore, 148 (72.2%) critically ill patients received appropriate empirical antibiotics. Importantly, 93 (9.5%) patients did not receive any empirical antibiotics. The median hospital LOS for these 93 patients was significantly shorter than the LOS for all patients in the study. We performed event-free survival analysis and found that the LOSs were similar in both groups; these findings suggested that patients who received inappropriate antibiotics had more severe disease and earlier death, leading to a shorter hospital LOS.

Micek et al²⁰ found that prior antibiotic exposure was a risk factor for inappropriate empirical therapy. Lautenbach et al²¹ described a positive correlation between the total cumulative dose of antibiotics and ESBL *K pneumoniae* infection. In our cohort, prior antibiotics exposure was not significantly correlated with inappropriate empirical antibiotic treatment; furthermore, prior antibiotics exposure was not associated with ESBL infections. We examined the presence of prior antibiotics use 30 days prior to positive blood culture results, but information regarding the total cumulative antibiotics exposure in terms of dosing and duration were not available. Other information was unavailable regarding antibiotics prescribed outside hospital settings.

Patients with chronic renal failure are reportedly more prone to developing resistant infections.²² They were at greater risk of receiving inappropriate antibiotics. Additionally, hospital-



acquired infection has been associated with a higher rate of inappropriate empirical antibiotic treatment and higher 90-day mortality.¹¹

Multidrug-resistant *Klebsiella pneumoniae* infections

The rates of CR and CP *K pneumoniae* bacteraemia were much lower than the rates reported in

other endemic countries.⁵ A study from Shanghai reported that approximately 22% of all patients with *K pneumoniae* bacteraemia had CR infections; moreover, approximately 59% of the isolates were CR infections in patients who required intensive care.²³

The prevalence of ESBL *K pneumoniae* bacteraemia in Hong Kong is low.⁴ The ESBL infection rate in our cohort was 11.5%, similar to previous local studies.^{1,24} Another study in China demonstrated a much higher rate of ESBL infections (approximately 39%).²⁵ Both ESBL and CR infections were not associated with increased mortality in our study in either the overall patient population or the ICU subgroup. However, ESBL and CR infections were significantly associated with longer hospital LOS.

The antibiotics sensitivity in our cohorts was comparable with the antibiogram data in the IMPACT guideline.¹ Ampicillin-sulbactam or amoxicillin-clavulanate is recommended as the drug of choice for treatment of *K pneumoniae* infections in local guidelines.¹ In our cohort, more than 80% of *K pneumoniae* isolates were susceptible to amoxicillin-clavulanate, indicating that it is a reasonable option for broad empirical coverage. Add-on therapy with aminoglycoside improves the coverage of this regimen, because more than 90% of the isolates in our cohort were sensitive to either gentamicin or amikacin. While combination therapy improves the chance of successful empirical therapy, routine use of combination therapy remains controversial.⁶

Ninety-day mortality

The 90-day all-cause mortalities in our study were comparable with the findings in previous studies.^{24,26} Respiratory tract infections and gastrointestinal infections have consistently been associated with a worse outcome and greater mortality.^{27,28} In contrast, urosepsis and hepatobiliary sepsis have repeatedly associated with better survival outcomes.²⁹ These sources of infections may be amendable to percutaneous, endoscopic, or surgical drainage, allowing more rapid and definitive control of sepsis, which leads to better survival.²⁸

A greater proportion of patients with respiratory tract infection did not receive any empirical antibiotics, which might explain the worse outcomes in these patients. The symptoms and signs of respiratory tract infection may overlap with other diseases (eg, heart failure) and treatment may be delayed while waiting for laboratory results and imaging. Given the greater proportion of patients with respiratory tract infections who did not receive any empirical antibiotics, there is a need for early consideration of empirical antibiotics in patients with signs and symptoms of respiratory tract infections.

Consistent with the findings of previous studies, we found that older age, solid tumour, and admission through the Department of Medicine were factors associated with higher 90-day mortality.^{30,31} Patients with these factors were more likely to have other pre-existing co-morbidities, worse pre-morbid functional status, and be institutionalised. They may also have received a more conservative approach to treatment overall.

Diabetes mellitus is well-known to predispose patients to infections, such that affected patients are reportedly 4.4-fold more likely to develop bloodstream infection.³² Similar to the findings by Peralta et al,³² we did not find increased mortality among patients with diabetes. In our cohort, diabetic patients were more likely to have urosepsis than respiratory tract infections. Greater frequency of urosepsis and smaller frequency of respiratory tract infection may have an overall positive effect on survival. Moreover, advances in diabetes care in recent decades (eg, newer generations of medication and integrated multidisciplinary care) have led to neutral effects of diabetes on short-term mortality in patients undergoing major operations and patients with sepsis.³³⁻³⁵ Glycaemic status, haemoglobin A1c levels, and diabetes severity were not available in the present study; thus, we could not delineate how diabetes control affected bacteraemia outcomes. Our results are limited to demonstrating that 90-day mortality and diabetes have a greater impact on long-term survival, although this conclusion may not be apparent in the current study.³³

In addition to mortality, we demonstrated that the inappropriate use of empirical antibiotics was associated with longer ICU ventilator duration, which leads to greater costs and more extensive use of ICU resources. A large retrospective cohort from the US regarding *Enterobacteriaceae* infections showed that each additional day without appropriate antibiotics was associated with an increased hospital expenditure of US\$750 and an increased risk of 30-day readmission.³⁶

To the best of our knowledge, the appropriateness of empirical antibiotics has consistently been identified as one of the strongest independent predictors of 90-day mortality in all affected patients and in critically ill patients.³⁷⁻³⁹ Kumar et al⁸ demonstrated a fivefold increase in mortality among patients with sepsis who received inappropriate initial antibiotics. In this study, we demonstrated a twofold increase in mortality in all patients with *K pneumoniae* bacteraemia, as well as a threefold increase in mortality in critically ill patients with *K pneumoniae* bacteraemia. Furthermore, receipt of inappropriate initial antibiotics was the strongest independent predictor of 90-day mortality in the ICU subgroup. Zilberberg et al⁴⁰ found that the detrimental effect of inappropriate empirical

antibiotic treatment could not be corrected despite subsequent targeted antibiotic treatments. A meta-analysis revealed a slower rate of bacterial clearance and increased treatment failure rate when patients were administered inappropriate empirical antibiotic therapy.⁴¹ Appropriate early antibiotics allow rapid reduction of bacterial load and modulate host defences, thus alleviating some organ dysfunction.⁴² A more pragmatic approach would be the early administration of broader-spectrum empirical antibiotics and timely de-escalation, according to bacterial sensitivity and the patient's clinical progression.

The chain of sepsis management begins during the first encounter in the Emergency Department and in general hospital wards, rather than in the ICU. Early administration of antibiotics within 3 hours of hospital admission and aggressive sepsis care (beginning in the Emergency Department) can improve survival.⁴² Another prospective observational study demonstrated that the adequate use of empirical antibiotics prior to ICU admission was the strongest independent factor associated with survival.²⁹ Extensive efforts are needed to facilitate early, appropriate use of empirical antibiotics, including the use of a current antibiogram, implementation of multidisciplinary sepsis management guidelines, and establishment of protocols among pharmacists, microbiologists, clinicians, and nurses.

Strengths

To the best of our knowledge, this is the largest study of *K pneumoniae* bacteraemia in Hong Kong and in the Asia-Pacific region. By including both ICU and general ward patients, we achieved clarity regarding the diverse characteristics of *K pneumoniae* bacteraemia. We also identified many potential predictors of *K pneumoniae* bacteraemia-related mortality, based on our extensive literature review and previous publications, then tested these predictors using real-world patient data. By evaluating 90-day mortality, hospital LOS, and ventilator duration, our study more comprehensively evaluated immediate and longer-term complications of bacteraemia; it also provided information for future studies of cost-effectiveness in terms of empirical antibiotics and resource utilisation. Finally, we used the maximum total SOFA score for severity assessment. This score has been repeatedly validated in determining disease severity and predicting mortality in critically ill patients.⁴³⁻⁴⁵

Limitations

This retrospective study was subject to potential confounding factors, including selection bias that could not be completely eliminated from the analysis.

Notably, the results of this single-centre study may not be generalisable to other countries with higher CR or CP *K pneumoniae* infections. Furthermore, this study encompassed a long duration, in which the definitions of sepsis or septic shock might have changed.⁴⁵ The care of patients with sepsis evolved over time, including advances in source control by percutaneous and endoscopic means that potentially improved patient survival. Nonetheless, the role of empirical antibiotics in patients with sepsis remains an essential sepsis consideration.

Antibiotic pharmacodynamics also has a fundamental role in bacteraemia treatment. In this study, we could not collect information regarding the timing of first-dose antibiotics, time to appropriate antibiotics, duration of antibiotics, or time to surgical treatments. Moreover, antibiotic stewardship and therapeutic de-escalation efforts, as well as their impacts on patient outcomes, were not assessed in the present study. Future studies may be needed concerning the prolonged infusion of beta-lactam antibiotics, use of combination therapies, duration of antibiotics, and serum monitoring of antibiotics.

Conclusion

The receipt of inappropriate empirical antibiotics led to twofold greater 90-day mortality in patients with *K pneumoniae* bacteraemia. In critically ill patients, inappropriate use of empirical antibiotics was the strongest independent predictor of mortality. Early identification of high-risk patients and administration of appropriate empirical antibiotics can improve patient outcomes.

Author contributions

Concept or design: MY Man, HP Shum.

Acquisition of data: MY Man, HP Shum.

Analysis or interpretation of data: MY Man, HP Shum.

Drafting of the manuscript: MY Man

Critical revision of the manuscript for important intellectual content: WW Yan.

All authors read and approved the final manuscript. All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

All authors have disclosed no conflicts of interest.

Declaration

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Ethics approval

This study was approved by the Hong Kong Easter Cluster Ethics Committee of the Hospital Authority (HKECREC-2018-018). The requirement for written informed consent was waived because of the retrospective nature of the study.

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