

***Klebsiella Pneumoniae* Visceral Organ Abscesses – Clinical Characteristics**

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Abstract

Introduction: In recent years, *Klebsiella pneumoniae* (KP) has emerged as the predominant cause of pyogenic liver abscess in Asia. KP—as the causative microorganism in other visceral organ abscesses—is less described. In this study, we sought to describe the clinical characteristics of KP visceral organ abscesses in our institution and evaluated the prescription practices of physicians with regard to antibiotic therapy. **Materials and Methods:** A retrospective analysis of patients with culture positive (blood or abscess aspirate) KP visceral organ abscesses from May 2014 to April 2016 requiring hospitalisation in Changi General Hospital was conducted. **Results:** A total of 140 adult patients with KP visceral organ abscesses were identified. The commonest site of involvement was the liver (77.9%), followed by genitourinary tract (20.7%). Diabetic patients were more likely to have liver abscesses, genitourinary abscesses, abscesses in 2 or more organs, genitourinary disease with abscess formation outside of the genitourinary tract, and endovascular infection. Patients with extended spectrum beta-lactamase producing KP, were more likely to have an obstructive lesion related to the site of the abscess. Overall mortality rate was 7.1%. Amongst survivors, the mean total duration of parenteral antimicrobial therapy was 2.5 weeks before switching to oral antimicrobial agents. **Conclusion:** Genitourinary tract is the commonest extra-hepatic site for visceral organ abscess in KP infections. Parenteral to oral switch of antimicrobial agents appears to be a safe and effective treatment option.

Ann Acad Med Singapore 2019;48:48-54

Key words: Disseminated infection, Genitourinary abscess, Liver Abscess

Introduction

Klebsiella pneumoniae (KP) liver abscesses were first described in the 1980s in Taiwan.¹ Consequently, KP emerged as the predominant cause of pyogenic liver abscess in various other countries in East and Southeast Asia. Metastatic infections involving the lung, eye, central nervous system, musculoskeletal system and urinary system have been described.²⁻⁴ Diabetes mellitus is a major risk factor for the development of KP liver abscesses and is associated with metastatic complications especially for non-K1/K2 strains.^{5,6} KP—as the causative microorganism in other visceral organs—is less described despite its propensity for tissue invasion.

In this study, we sought to describe the clinical characteristics of patients with KP visceral organ abscesses (VOA) in our institution, with an emphasis on the influence of diabetes mellitus, and evaluated antibiotic prescription practices of managing physicians.

Materials and Methods

A list of patients with blood or abscess aspirate cultures positive for KP received from 1 May 2014 to 30 April 2016 was obtained from the Department of Laboratory Medicine, Changi General Hospital. We included all patients seen at our hospital, with blood and/or abscess aspirate cultures positive for KP, in whom concomitant imaging evidence of

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VOA was demonstrated through either ultrasound, computed tomography or magnetic resonance imaging. The case records of these patients were then retrospectively analysed to evaluate their clinical characteristics and outcomes.

Statistical analysis was performed using the SPSS version 25 statistical software package. Chi-squared test and Fisher's exact test were used to test for associations in categorical variables whereas the Mann-Whitney U test was used to test for differences in continuous variables. $P < 0.05$ was considered to be statistically significant. The confidence intervals (CIs) are reported with 95% confidence level.

The study was approved by the SingHealth Centralised Institutional Review Board.

Results

Between 1 May 2014 and 30 April 2016, a total of 140 adult patients with *KP* VOA were identified and included in this study. During this study period, we screened a total of 475 *KP*-positive blood cultures from unique patients as well as 1017 non-urine *KP* culture isolates from unique patients. Eighty-four (60.0%) were males. The mean age was 63.6 years (range, 22 to 98 years). Majority were Chinese ($n = 106$; 75.7%). The majority of *KP* VOA were liver abscesses (109 patients, 77.9%), followed by genitourinary abscesses (29 patients, 20.7%). Amongst the 29 patients with genitourinary abscesses, 1 had mycotic aneurysm, 1 had infective endocarditis, 1 had meningitis and 2 had endophthalmitis.

Seventy-seven (55.0%) patients were diabetics. Table 1 compares between diabetic and non-diabetic patients with *KP* VOA. Diabetic patients were more likely to present with liver abscesses, genitourinary abscesses, abscesses in 2 or more organs, genitourinary disease with abscess formation outside of the genitourinary tract, and endovascular infection.

Amongst the diabetic patients, 10 (13.0%) were newly diagnosed. Sixty-seven (87.0%) patients had known diabetes mellitus, with treatment history available for 63 (81.8%) patients. With regard to their treatment history, 4 (5.2%) patients were on diet control, 41 (53.2%) were on oral hypoglycaemic agents (OHGAs), 6 (7.8%) were on insulin and 8 (10.4%) were on both OHGA and insulin. Four (5.2%) patients were non-compliant to diabetic treatment. Six (14.6%) patients presented with hyperglycaemic crises (4 with diabetic ketoacidosis, 2 with hyperosmolar hyperglycaemic state). Data on glycated haemoglobin (HbA1c) was available for 56 patients. The mean HbA1c value was 9.3% (range, 5.2% to 13.5%). Nine patients had HbA1c $< 7.0\%$, 25 patients had HbA1c ranging 7.0% to 9.9% and 22 patients had HbA1c $\geq 10.0\%$. Data analysis on these 3 distinct groups of patients did not reveal any significant differences in terms of metastatic complications, systemic complications, recurrence or mortality.

Amongst the patients with non-extended spectrum beta-lactamase (ESBL)-producing *KP* isolates, 35/132 (26.5%) were tested non-susceptible to cefuroxime by

Table 1. Demographic, Clinical, Laboratory, Microbiological Features of Diabetic and Non-Diabetic Patients

	All (n = 140)	Diabetics (n = 77)	Non-Diabetics (n = 63)	P Value
Mean age (years)	63.6 $\pm$ 14.6	63.1 $\pm$ 13.1	64.3 $\pm$ 16.3	0.61
Male gender	84 (60.0%)	49 (63.6%)	35 (55.6%)	0.33
Chinese	106 (75.7%)	54 (70.1%)	52 (82.5%)	0.088
Malay	29 (20.7%)	20 (26.0%)	9 (14.3%)	0.090
Indian	2 (1.4%)	2 (2.6%)	0 (0.0%)	0.50
Comorbidities				
Underlying cancer	10 (7.1%)	8 (10.4%)	2 (3.2%)	0.19
Chronic liver disease	9 (6.4%)	7 (9.1%)	2 (3.2%)	0.19
Structural hepatobiliary disease*	30 (21.4%)	13 (16.9%)	17 (27.0%)	0.15
Intestinal pathology†	2 (1.4%)	1 (1.3%)	1 (1.6%)	1.00
Structural urinary abnormality‡	6 (4.3%)	5 (6.5%)	1 (1.6%)	0.22
Fever	111 (79.3%)	58 (75.3%)	53 (84.1%)	0.20
Haemoglobin (g/dL)	12.5 (7.5 – 18.5)	12.4 (7.5 – 18.5)	12.7 (7.7 – 18.1)	0.59
White blood cell count ($\times 10^9/L$)	15.1 (1.9 – 38.4)	15.2 (2.2 – 38.4)	15.0 (1.9 – 32.4)	0.91
Platelet count ($\times 10^9/L$)	235 (18 – 642)	244 (20 – 642)	224 (18 – 621)	0.23

ESBL: Extended spectrum beta-lactamase

*Includes pancreatic cancer, periampullary carcinoma, cholangiocarcinoma, hepatocellular carcinoma, liver metastasis, biliary stricture, cholecystitis, cholangitis, choledochocyst, previous biliary stenting, previous biliary surgery.

†Includes known colon cancer, diverticular disease.

‡Includes urolithiasis, benign prostate hypertrophy, polycystic kidney disease.

Table 1. Demographic, Clinical, Laboratory, Microbiological Features of Diabetic and Non-Diabetic Patients (Cont'd)

	All (n = 140)	Diabetics (n = 77)	Non-Diabetics (n = 63)	P Value
C-reactive protein (mg/L)	220 (3 missing) (1.6 – 380)	218 (2 missing) (1.6 – 380)	222 (1 missing) (4.4 – 380)	0.68
Procalcitonin (µg/L)	33.6 (17 missing) (0.19 – 100)	33.8 (10 missing) (0.37 – 100)	33.4 (7 missing) (0.19 – 100)	0.80
Bacteraemia	96 (68.6%)	56 (72.7%)	40 (63.5%)	0.26
Abscess location				
Liver	109 (77.9%)	54 (70.1%)	55 (87.3%)	0.015
Right lobe	61 (43.6%)	31 (40.3%)	30 (47.6%)	0.76
Left lobe	24 (17.1%)	9 (11.7%)	15 (23.8%)	0.18
Both lobes	24 (17.1%)	14 (18.2%)	10 (15.9%)	0.33
Genitourinary	29 (20.7%)	22 (28.6%)	6 (9.5%)	0.050
Kidney	12 (8.6%)	11 (14.3%)	1 (1.6%)	0.080
Prostate	17 (12.1%)	13 (16.9%)	4 (6.3%)	0.058
Lung	5 (3.6%)	2 (2.6%)	3 (4.8%)	0.66
Brain	4 (2.9%)	4 (5.2%)	0 (0.0%)	0.13
Solitary abscess	75 (53.6%)	38 (50.7%)	37 (49.3%)	0.27
Abscess size ≥5 cm	65 (46.4%)	36 (55.4%)	29 (44.6%)	0.94
Abscess formation in ≥2 organs	9 (6.4%)	8 (10.4%)	1 (1.6%)	0.041
Other sites of involvement without abscess formation				
None	97 (69.3%)	51 (66.2%)	46 (73.0%)	0.39
Lung	16 (11.4%)	12 (15.6%)	4 (6.3%)	0.09
Genitourinary	9 (6.4%)	8 (10.4%)	1 (1.6%)	0.041
Musculoskeletal	5 (3.6%)	5 (6.5%)	0 (0.0%)	0.06
Endovascular	10 (7.1%)	2 (2.6%)	8 (12.7%)	0.043
Septic thrombus	8 (5.7%)	2 (2.6%)	6 (9.5%)	0.14
Eye	7 (5.0%)	3 (3.9%)	4 (6.3%)	0.70
Meninges	3 (2.1%)	3 (3.9%)	0 (0.0%)	0.25
Abscess rupture with locoregional extension	7 (5.0%)	3 (3.9%)	4 (6.3%)	0.70
Disseminated disease involving ≥2 organs	28 (20.0%)	19 (24.7%)	9 (14.3%)	0.13
Systemic complications	74 (52.9%)	43 (55.8%)	31 (49.2%)	0.43
Septic shock	30 (21.4%)	14 (18.2%)	16 (25.4%)	0.30
Respiratory failure	12 (8.6%)	6 (7.8%)	6 (9.5%)	0.71
Acute kidney injury	61 (43.6%)	34 (44.2%)	27 (42.9%)	0.88
Myocardial infarction	18 (12.9%)	10 (13.0%)	8 (12.7%)	0.96
Atrial fibrillation with rapid ventricular response	5 (3.6%)	3 (3.9%)	2 (3.2%)	1.0
Disseminated intravascular coagulopathy	5 (3.6%)	4 (5.2%)	1 (1.6%)	0.38
Recurrence	6 (4.3%)	4 (5.2%)	2 (3.2%)	0.69
28-day mortality	10 (7.1%)	8 (10.4%)	2 (3.2%)	0.19
Antimicrobial resistance				
Second generation cephalosporin resistance	43 (30.7%)	25 (32.5%)	18 (28.6%)	0.62
Beta-lactam-beta-lactamase inhibitor resistance	11 (7.9%)	8 (10.4%)	3 (4.8%)	0.35
Fluoroquinolone resistance	9 (6.4%)	7 (9.1%)	2 (3.2%)	0.19
ESBL-producing strain	8 (5.7%)	6 (7.8%)	2 (3.2%)	0.30
Polymicrobial growth	12 (8.6%)	9 (11.7%)	3 (4.8%)	0.15

ESBL: Extended spectrum beta-lactamase

*Includes pancreatic cancer, periampullary carcinoma, cholangiocarcinoma, hepatocellular carcinoma, liver metastasis, biliary stricture, cholecystitis, cholangitis, choledochocyst, previous biliary stenting, previous biliary surgery.

†Includes known colon cancer, diverticular disease.

‡Includes urolithiasis, benign prostate hypertrophy, polycystic kidney disease.

the disk diffusion method, majority being of intermediate resistance. Of these, 29/35 (82.9%) patients did not have recent hospital contact.

Patients with ESBL-producing *KP* were more likely to have an obstructive lesion related to the site of the abscess (i.e. biliary obstruction for liver abscess, obstructive uropathy for genitourinary abscess) ($P < 0.001$). Amongst the 8 cases of ESBL-producing *KP*, 2 were community-acquired whilst 6 had the *KP* isolated either within 3 months of a recent hospitalisation or after 48 hours of a hospital admission.

Forty-five out of 140 (32.1%) patients had their abscesses conservatively managed with systemic antimicrobial therapy alone whilst 95/140 (67.9%) patients had both abscess drainage and systemic antimicrobial therapy. Amongst the 95 patients who underwent abscess drainage, the majority (93.7%) were performed through radiological guidance; 7.4% needed surgical intervention. The most commonly drained abscess was from the liver ($n = 86$), followed by the prostate ($n = 12$) and the kidney ($n = 3$).

Overall mortality rate was 7.1%. Amongst survivors, 129/130 (99.2%) patients had data of antibiotic duration available for analysis. These patients had a mean total duration of systemic antibiotics, parenteral antibiotics and oral antibiotics of 8.6 weeks, 2.5 weeks and 6.2 weeks, respectively; 6/129 (4.6%) survivors received parenteral antibiotics throughout the treatment course despite having oral antibiotic options.

Table 2 shows the predictive value of biomarkers for various clinical features and complications of patients with *KP* VOA. A higher leucocyte count is predictive of disseminated disease ($P = 0.028$), abscess formation in ≥ 2 sites ($P = 0.032$), lung abscess ($P = 0.002$), genitourinary involvement without abscess formation ($P = 0.009$), respiratory failure ($P = 0.002$) and polymicrobial infection ($P = 0.048$). A lower leucocyte count is predictive of liver abscess ($P = 0.004$). A lower platelet count is predictive of acute kidney injury ($P = 0.001$) (data not shown). A higher C-reactive protein is predictive of abscess ≥ 5 cm ($P < 0.001$). A higher procalcitonin is predictive of bacteraemia ($P = 0.008$), prostate abscess ($P = 0.030$) and systemic complications ($P = 0.002$).

Table 3 shows the factors predictive of mortality in our patient cohort. We found that having a lung abscess, presenting with respiratory failure, acute kidney injury and atrial fibrillation with rapid ventricular response, as well as having a polymicrobial infection are predictors of mortality. Presenting with fever or having a liver abscess appears to be protective.

In addition, having a polymicrobial infection appears predictive of likelihood of recurrence, with a trend towards significance (odds ratio 6.20, 95% CI 1.01–38.1; $P = 0.083$).

Discussion

In this single-centre retrospective study in Singapore, we found that liver and genitourinary sites were the predominant visceral organs involved in *KP* VOA. The presence of diabetes mellitus is predictive of abscess formation in the liver, genitourinary tract, multi-organ abscesses and endovascular involvement.

Although a previous study showed that glycaemic control in diabetic patients is an important determinant in predicting the presence of metastatic complications in liver abscess,⁷ our study failed to demonstrate a similar association for *KP* VOA. However, we showed that the presence of diabetes mellitus significantly increases the risk of dissemination, evidenced by the increased risk of multi-organ abscess and endovascular complications.

While *KP* pyogenic liver abscesses are well described in the literature, the phenomenon of *KP* genitourinary abscesses is less commonly reported. *KP* has been reported to be the predominant cause of prostatic abscesses in some centres, but available case series are small. In 2 centres in Southern Taiwan, 10/17 prostatic abscesses diagnosed during a 11-year period were due to *KP*.⁸ A Korean single-centre study over 7 years identified 6/14 cases of prostatic abscesses to be due to *KP*.⁹ The largest series of *KP* renal abscess came from Taiwan, which reported a total of 24 cases identified over 17 years.¹⁰ Our series identified 17 *KP* prostatic abscesses and 12 *KP* renal abscesses across a 2-year period, with at least 5/29 patients exhibiting features of complicated, difficult-to-treat infections (mycotic aneurysm, infective endocarditis, meningitis and endophthalmitis), otherwise rarely reported in the literature.^{11–14} Of note, in 2 Singaporean studies of 101 and 129 cases of *KP* bacteraemia (the latter study is also from our centre), 17% and 16% of cases were found associated with pyogenic liver abscesses, respectively.^{15–16} No mention was made, however, of any association with other VOA in both series. Our study strengthens the case in point about *KP* genitourinary abscesses as an emerging clinical entity.

In our study, we find that the majority of our abscess-forming *KP* isolates are susceptible to most of the commonly prescribed antibiotics ($< 10\%$ resistance to fluoroquinolones and third generation cephalosporins). A significant percentage of resistance to cefuroxime (30.7%) is observed, however, limiting the empiric use of this agent in patients with VOA without microbiological diagnosis. The optimal duration and mode of antimicrobial administration in the management of *KP*-associated abscesses remain unknown. Most experts would opt for a combination of percutaneous drainage coupled with several weeks of parenteral antibiotics. As demonstrated in our study, percutaneous drainage appears to be the preferred modality for source control over surgery in our centre. In our cohort, only a small

Table 2. Relation between White Blood Cell Count, C-Reactive Protein, Procalcitonin and Various Clinical Parameters

Parameter	Category	Total, n (%)	White Blood Cell Count (x10 ⁹ /L)		C-Reactive Protein (mg/L)		Procalcitonin (µg/L)	
			Median (Q1 – Q3)	P Value	Median (Q1 – Q3)	P Value	Median (Q1 – Q3)	P Value
Bacteraemia	Yes	96 (68.6)	13.7 (10.4 – 19.5)	0.96	234.5 (162.9 – 279.4)	0.85	24.5 (3.3 – 91.3)	0.008
	No	44 (31.4)	15.2 (10.7 – 18.4)		224.0 (141.4 – 290.5)		5.9 (1.4 – 35.8)	
Abscess								
Size ≥5 cm*	Yes	65 (46.4)	14.0 (9.7 – 17.9)	0.68	259.4 (196.1 – 328.7)	<0.001	16.1 (2.0 – 75.7)	0.91
	No	64 (45.7)	13.7 (10.6 – 19.3)		192.9 (119.2 – 263.4)		17.4 (2.1 – 45.4)	
Location ≥2 organ sites	Yes	9 (6.4)	17.5 (16.4 – 29.1)	0.032	224.3 (187.9 – 347.6)	0.54	5.2 (6.7 – 29.1)	0.15
	No	131 (93.6)	13.2 (10.4 – 19.0)		235.5 (156.2 – 284.1)		16.7 (2.1 – 60.4)	
Liver	Yes	109 (77.9)	13.2 (10.2 – 17.8)	0.004	242.1 (163.8 – 290.2)	0.11	16.8 (2.0 – 57.0)	0.94
	No	31 (22.1)	17.5 (10.7 – 23.7)		197.5 (135.8 – 252.6)		11.8 (3.4 – 49.4)	
Kidney	Yes	12 (8.6)	17.3 (12.6 – 21.8)	0.15	224.0 (177.9 – 278.2)	0.88	10.2 (6.4 – 65.3)	0.98
	No	128 (91.4%)	14.1 (10.4 – 19.2)		234.5 (161.6 – 285.7)		16.7 (2.0 – 56.4)	
Prostate	Yes	17 (12.1)	17.5 (12.7 – 21.5)	0.97	192.9 (128.2 – 221.8)	0.60	2.6 (1.0 – 15.8)	0.030
	No	123 (87.9)	13.2 (10.3 – 18.5)		241.9 (162.8 – 289.6)		16.9 (2.8 – 63.9)	
Systemic complications†	Yes	74 (52.9)	15.3 (10.0 – 21.2)	0.33	240.9 (164.7 – 292.9)	0.14	25.6 (7.5 – 98.1)	0.002
	No	66 (47.1)	13.2 (10.6 – 17.6)		211.8 (145.3 – 269.3)		4.42 (1.53 – 31.0)	
Polymicrobial infection	Yes	12 (8.6)	20.9 (11.1 – 26.4)	0.048	211.8 (107.2 – 263.0)	0.42	8.7 (1.6 – 63.9)	0.46
	No	128 (91.4)	13.6 (10.4 – 18.1)		236.9 (163.3 – 285.7)		16.8 (2.0 – 55.7)	
Outcomes								
Recurrence	Yes	6 (4.3)	17.8 (9.3 – 22.0)	0.52	168.9 (111.6 – 229.9)	0.18	30.7 (14.8 – 65.5)	0.34
	No	134 (95.7)	14.4 (10.4 – 19.1)		238.2 (163.2 – 285.4)		16.3 (2.0 – 56.4)	
28-day mortality	Yes	10 (7.1)	19.5 (10.4 – 26.3)	0.18	209.5 (151.8 – 259.0)	0.67	24.6 (3.3 – 36.5)	0.85
	No	130 (92.9)	14.4 (10.4 – 18.6)		235.5 (163.1 – 286.7)		16.2 (2.0 – 56.9)	

Q: quartile

*11 abscesses not measured.

†Includes shock, respiratory failure, acute kidney injury, myocardial infarction, disseminated intravascular coagulopathy.

Table 3. Factors Predictive of Mortality in Patients with Visceral Abscess

	Odds Ratio (95% CI)	P Value
Fever as presenting complaint	0.143 (0.0370 – 0.549)	0.006
Liver abscess	0.25 (0.0670 – 0.928)	0.043
Lung abscess	10.6 (1.54 – 72.7)	0.041
Respiratory failure	10.2 (2.38 – 43.5)	0.005
Acute kidney injury	5.8 (1.19 – 28.5)	0.021
Atrial fibrillation with rapid ventricular response	10.6 (1.54 – 72.7)	0.041
Polymicrobial infection	5.76 (1.27 – 26.1)	0.041

number of patients (4.6%) received parenteral antibiotics throughout the course of their treatment despite having oral antibiotic options. The mean parenteral treatment duration of 2.5 weeks amongst survivors, followed by oral switch and a low recurrence rate of 4.3% seem to support early use of oral antibiotics as a therapeutic option. Indeed, Chen et al, reported safe and efficacious use of oral antibiotics in an open-label randomised controlled trial in a group of patients with liver abscesses, predominantly due to *KP*.¹⁷ ESBL-producing strains causing invasive *KP* VOA appears low at 5.7% in our cohort. Many of our patients in this cohort presented as community-acquired infections and over half presented with systemic complications such as organ failure. Our finding of ESBL-producing *KP* infections being significantly associated with an obstructive lesion related to the site of the abscess, may potentially allow clinicians to make early informed decisions about ESBL coverage in their empiric antimicrobial regimen. This observation is also consistent with Shi et al's study of 817 pyogenic liver abscess patients, where ESBL-producing *Enterobacteriaceae* occurred mainly in individuals with biliary disorders.¹⁸

Our results show that presence of fever and having a liver abscess was protective. We postulate that patients with fever tended to present earlier, have blood cultures performed and also received antibiotics more promptly. Several other studies have highlighted lower mortality in septic patients with higher body temperature,¹⁹⁻²¹ possibly enhancing immune-cell function and promoting antimicrobial activity.²²⁻²³ It is plausible that patients with liver abscess tend to have drainage performed more promptly, allowing better source control, hence improving mortality. Indeed 86/109 (78.9%) of the liver abscesses in our study were drained compared to 15/29 (51.7%) of genitourinary abscess, which is the second most common site of involvement for abscesses.

Our study is one of the largest series of patients with *KP* VOA with their clinical outcomes described. We

acknowledge several limitations. This is a retrospective single-centre study, which may give rise to selection bias in our patient population. There is also a lack of serotyping and identification of genotypic virulent factors in our clinical isolates. The actual number of *KP* VOA is possibly even higher, given that there were bacteraemic patients who were too ill to undergo abdominal imaging and demised early in their clinical course.

Conclusion

Our study concludes that the genitourinary tract is the commonest extra-hepatic site for VOA in *KP* infections, with diabetes mellitus as a clear risk factor for both hepatic and genitourinary abscesses in this series. Early parenteral to oral switch of antimicrobial agents appears to be a safe and effective treatment option.

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