J Microbiol Immunol Infect.
2008;41:311-317

Original Article

Clinical spectrum and molecular characteristics of *Klebsiella pneumoniae* causing community-acquired extrahepatic abscess

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Received: May 12, 2007 Revised: June 4, 2007 Accepted: July 26, 2007

Background and Purpose: *Klebsiella pneumoniae* causes a wide spectrum of infections, including abscess and non-abscess formation. This study investigated the clinical spectrum and molecular characteristics of community-acquired *Klebsiella* infection with primary extrahepatic abscess.

Methods: From April 2004 through March 2007, a total of 18 strains of *K. pneumoniae*, 11 from blood and 7 from focal purulent specimens, were recovered from a medical center in southern Taiwan. The clinical data were collected from medical records. Hypermucoviscosity phenotype was defined as positive string test. The virulence genes, including *rmpA* (regulator of mucoid phenotype), *magA* (specific to K1 capsule serotype), k_2A (specific to K2 capsule serotype), and *kfu* (an iron uptake system) were amplified by polymerase chain reaction using specific primers.

Results: Twelve men and 6 women with ages ranging from 37 to 74 years were enrolled. Fifteen patients had underlying diabetes mellitus. The duration of hospitalization ranged from 1 to 96 days. Three patients died by the end of treatment. All of the *K. pneumoniae* strains carried *rmpA* and 16 strains showed the hypermucoviscosity phenotype. Of the 18 strains, 7 strains were positive for k_2A and 4 strains carried *magA*. *kfu* was identified in 4 *magA*-positive strains and 2 *magA*-negative/k_2A-negative strains.

Conclusion: Diabetes mellitus was the most frequent underlying disease among our patients. The *rmpA* and/or hypermucoviscosity phenotype were the most common virulence factors in *K. pneumoniae* isolates causing extrahepatic abscesses, among which K2 capsule serotype (k_2A^+) was more prevalent than K1 capsule serotype ($magA^+$).

Key words: Bacterial capsules; Bacterial proteins; Comorbidity; *Klebsiella pneumoniae*; Liver abscess; Virulence factors

Introduction

A wide spectrum of *Klebsiella pneumoniae* infection has been reported, including septicemia, pneumonia, urinary tract infection, meningitis, and purulent abscess at various sites [1,2]. The search for the pathogenic mechanism of *Klebsiella* infections has identified a number of virulence factors that contribute to the pathogenesis of these bacteria, including hypermucoviscosity, capsular serotype, especially K1 or K2, and virulence-associated genes, such as *wabG*, *uge* (UDP-glucose 4-epimerase), *kfu* (an iron uptake system), *fimH*, *rmpA* (regulator of mucoid phenotype) and *magA* (specific to K1 capsule serotype) [3-10].

In the past two decades, *K. pneumoniae* has emerged in Taiwan as an invasive pathogen in community-acquired pyogenic liver abscess [11,12], which has been documented to be associated with virulence factors including *kfu* [5], capsule serotypes K1 or K2, *magA*, *rmpA*, and hypermucoviscous phenotype [7-10]. Later, *magA* and k_2A (specific to K2 capsule serotype)

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were found to be specific to the capsule gene clusters of K1 and K2 serotype, respectively [13,14]. However, data on the pathogenesis of purulent infections at non-hepatic sites are relatively limited.

We performed a large-scale study of virulence gene distribution and clinical syndromes caused by *K. pneumoniae*, and found that there was no statistically significant difference in the prevalence of hypermucoviscosity phenotype, *rmpA* and *magA* between the causative isolates of liver abscess and non-hepatic abscess [9]. However, detailed information about the distribution of capsular K serotypes of causative organisms and the clinical characteristics of patients with *K. pneumoniae* extrahepatic abscesses and their interrelationships were not described. We investigated the seroepidemiology, demographic and laboratory data, disease outcomes and clinical relevance of community-acquired purulent *K. pneumoniae* infections outside the liver.

Methods

Primary organisms studied

K. pneumoniae isolates were collected from patients with primary extrahepatic abscess with or without bacteremia at a medical center in southern Taiwan from April 2004 through March 2007. Each isolate was recovered from a different patient. Cases of mixed infection or metastatic infection originating from *K. pneumoniae* liver abscess were excluded.

The isolates were identified by routine microbiological methods, and species identification was confirmed using the Phoenix system (Becton Dickinson Company, Baltimore, MD, USA) and API 20E system (bioMérieux Company, Marcy l'Etoile, France). All isolates were subcultured and frozen at –70°C until used in the study. All strains were recovered from patients with community-acquired infection. Of these, there were 11 cases of bacteremia, due to renal abscess (n = 2), mycotic aneurysm (n = 2), meningitis (n = 2), paraspinal abscess/infective spondylitis (n = 2), deep neck abscess (n = 1), pyomyositis (n = 1), lung abscess (n = 1) and septic arthritis (n = 1); one of the bacteremic patients had simultaneous mycotic aortic aneurysm and pyomyositis. The remaining 7 infections without bacteremia were lung abscess/empyema (n = 2), deep neck abscess (n = 2), parotid gland abscess (n = 1), subdural empyema (n = 1) and mycotic aortic aneurysm (n = 1). Purulent specimens were obtained either at surgery (n = 5) or by needle aspiration (n = 2).

Antimicrobial susceptibility testing

Antimicrobial susceptibilities were determined by the Kirby-Bauer disk diffusion test on Mueller-Hinton agar (BBL Microbiologic System, Cockeysville, MD, USA) with the following antibiotics: ampicillin (30 μg), amikacin (30 μg), gentamicin (10 μg), cefazolin (30 μg), cefuroxime (30 μg), ceftazidime (30 μg), cefpirome (30 μg), flomoxef (30 μg), ciprofloxacin (30 μg), lomefloxacin (10 μg), amoxicillin-clavulanate (20/10 μg), piperacillin (100 μg), and piperacillin-tazobactam (100/10 μg). Interpretations were performed according to the guidelines of the Clinical Laboratory Standards Institute (CLSI) [15].

Definition of hypermucoviscosity of the bacteria and clinical syndrome

To determine hypermucoviscosity phenotype, a standard bacteriologic loop was used to stretch a mucoviscous string from the colony. Strains were defined as positive hypermucoviscosity phenotype when the viscous strings were >5 mm (a positive string test result) [10]. Each infectious syndrome was defined as described elsewhere [2].

Detection of virulence-associated genes

With genomic DNA used as the template, polymerase chain reaction was performed to amplify *rmpA*, *magA*, k_2A, and *kfu* as previously described [9,14]. Specific primers used to detect the alleles of the target gene sequences are shown in Table 1.

Results

A total of 18 *K. pneumoniae* isolates were collected from patients with community-acquired extrahepatic

Table 1. Specific primers used for amplification of the target alleles of various virulence genes of *Klebsiella pneumoniae*

Target gene (reference)	Primer
magA [10]	
Forward	5'-GGTGCTCTTTACATCATTGC-3'
Reverse	5'-GCAATGGCCATTTGCGTTAG-3'
rmpA [9,21]	
Forward	5'-ACTGGGCTACCTCTGCTTCA-3'
Reverse	5'-CTTGCATGAGCCATCTTTCA-3'
kfu [present study]	
Forward	5'-AGAACCTTCCTCGCTGAACA-3'
Reverse	5'-ATAGTAGGCGAGCACCGAGA-3'
k_2A [14]	
Forward	5'-CAACCATGGTGGTCGATTAG-3'
Reverse	5'-TGGTAGCCATATCCCTTTGG-3'

purulent infections. The clinical characteristics of the enrolled patients are shown in Table 2. There were 12 men and 6 women, aged from 37 to 74 years (mean, 60.6 years). Most patients had serious underlying disease, most commonly diabetes mellitus (n = 15), in addition to liver cirrhosis (n = 3), chronic renal failure (n = 3), malignancy (n = 2), and adrenal insufficiency (n = 2). Eight patients had more than one comorbid disease while 2 patients had no comorbidity. A wide range of laboratory data were collected, including white blood cell count (range, 2700-46,900/U; mean, 14.9 × 10^3/U), platelet count (range, 20-391 × 10^3/U; mean, 199.8 × 10^3/U), serum creatinine (range, 0.2-3.6 mg/dL; mean, 1.6 mg/dL), aspartate aminotransferase (range, 6-144 IU/L; mean, 43.8 IU/L), alanine aminotransferase (range, 8-230 IU/L; mean, 57.7 IU/L) and C-reactive protein (range, 2->250 mg/L). The duration of hospitalization ranged from 1 to 96 days (mean, 34.6 days). Three patients died, including one patient who developed both mycotic aneurysm and anterior-tibia pyomyositis (died of nosocomial complications), and 2 patients who developed progressive disease involving mycotic aneurysm and renal abscess with septic shock and multiple organ failure.

Table 2. Clinical characteristics of 18 patients with extrahepatic abscess

Clinical characteristic	Number of patients
Age (years; range) [mean]	37-74 (60.6)
Gender (male:female)	12:6
Underlying disease	
Diabetes mellitus	15
Liver cirrhosis	3
Malignancy	2
Chronic renal failure	3
Adrenal insufficiency	2
No underlying disease	2
Laboratory data (range) [mean][a]	
White blood cell count (× 10^3/U)	2.7-46.9 (14.9)
Platelet count (× 10^3/U)	20-391 (199.8)
Serum creatinine (mg/dL)	0.2-3.6 (1.6)
CRP (mg/L)[b]	2->250
AST (IU/L)[c]	6-144 (43.8)
ALT (IU/L)	8-230 (57.7)
Duration of hospitalization (days; range) [mean]	1-96 (34.6)
Mortality	3

Abbreviations: CRP = C-reactive protein; AST = aspartate aminotransferase; ALT = alanine aminotransferase

[a]Laboratory values were collected at the first visit.

[b]Seven patients had no CRP data collected.

[c]One patient had no AST data collected.

Table 3. Sites of purulent extrahepatic infection

Infection site	Number
Renal abscess	2
Deep neck abscess	3
Pyomyositis[a]	1
Mycotic aortic aneurysm[a]	3
Paraspinal abscess/infective spondylitis	2
Subdural empyema	1
Lung abscess/empyema	3
Parotid gland abscess	1
Septic arthritis	1
Meningitis	2

[a]One patient had simultaneous *Klebsiella pneumoniae* mycotic aortic aneurysm and pyomyositis of anterior tibia.

Various sites of purulent *K. pneumoniae* infections were documented in this study (Table 3 and Fig. 1), including renal abscess (n = 2), mycotic aortic aneurysm (n = 3), meningitis (n = 2), paraspinal abscess/infective spondylitis (n = 2), deep neck abscess (n = 3), pyomyositis (n = 1), lung abscess/empyema (n = 3), septic arthritis (n = 1), parotid gland abscess (n = 1), and subdural empyema (n = 1). Eleven patients had secondary bacteremia, and one of these patients acquired both mycotic aortic aneurysm and pyomyositis of the anterior tibia.

Among the tested antimicrobial agents, all except one strain of *K. pneumoniae* were resistant to ampicillin. Of the 18 strains of *K. pneumoniae*, 2 isolates showed resistance to lomefloxacin, one was resistant to gentamicin or piperacillin, and one showed intermediate resistance to either amoxicillin-clavulanate or ciprofloxacin.

Hypermucoviscosity phenotype and other virulence-associated genes were detected by positive string test and polymerase chain reaction methods, respectively (Table 4). All of the *K. pneumoniae* isolates carried *rmpA*, and 16 isolates showed hypermucoviscosity phenotype. Seven strains carried k_2A and 4 strains were *magA*-positive. *kfu* was detected in 7 strains, including 4 *magA*-positive strains and 2 strains negative to both *magA* and k_2A (non-K1/K2 isolates). The clinical spectrum and abscess sites seemed similar among various serotypes of *K. pneumoniae*, except that all 3 non-surviving patients had K1/K2 isolates (Table 5).

Discussion

Studies of primary community-acquired purulent *K. pneumoniae* infections affecting sites other than the liver have been relatively infrequent in the literature. Here, we analyzed the clinical characteristics and

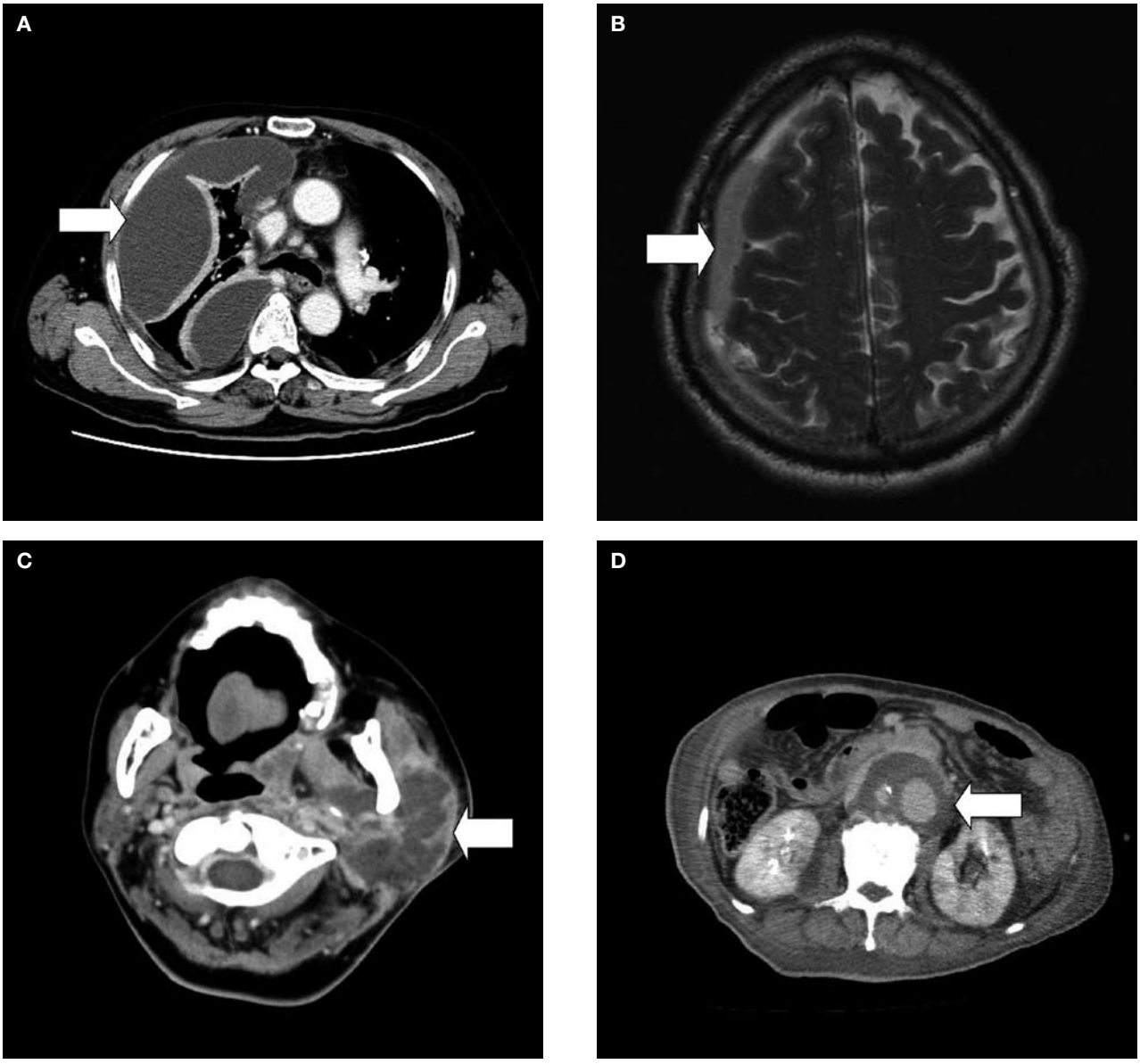

Fig. 1. Radiographic images of several cases of primary *Klebsiella pneumoniae* extrahepatic purulent infections (white arrow). (A) Computed tomography: thoracic empyema, right. (B) Brain magnetic resonance imaging (T2I): subdural empyema, right. (C) Computed tomography: parotid abscess, left. (D) Computed tomography: mycotic aneurysm of infrarenal aorta.

possible virulence-associated factors of non-hepatic purulent *K. pneumoniae* infections.

K. pneumoniae can cause infections in all age groups, especially in the extremes of age, and in those whose immune systems are compromised [16,17]. In the present study, most of the enrolled patients were elderly (mean age, 60.6 years) with underlying diseases. Limited correlation was found between the mortality of *K. pneumoniae* infections and the selected laboratory data, including serum creatinine, C-reactive protein, aspartate aminotransferase, alanine aminotransferase, and white blood cell and platelet counts, due to the limited number of patients. Not surprisingly, diabetes mellitus was the most common concomitant condition, in agreement with results documented elsewhere [2,16,17], less frequent disorders being liver cirrhosis, chronic renal failure, malignancy and adrenal insufficiency. All community-acquired strains of *K. pneumoniae* showed good susceptibility to tested antibiotics except ampicillin.

The possible pathogenesis of diabetes mellitus in *K. pneumoniae* infections has been investigated. The role of neutrophils in the innate immunity against bacterial infection is well established. Neutrophil

Table 4. Distribution of hypermucoviscosity phenotype and virulence-associated genes among *Klebsiella pneumoniae* isolates causing extrahepatic abscess

Virulence factor	Number of isolates (n = 18)
Hypermucoviscosity phenotype	16
Hypermucoviscosity-associated gene (*rmpA*)	18
Capsule K serotype-specific gene	
magA (K1 serotype)	4
k_2A (K2 serotype)	7
Iron uptake system (*kfu*)	7

bactericidal function in type 2 diabetes mellitus is positively associated with good blood glucose control, and impaired neutrophil activity is partly responsible for the increased susceptibility to infection in diabetic patients [18,19]. Furthermore, poor glycemic control in type 2 diabetes mellitus played a role in impaired phagocytic resistance against K1 or K2 *K. pneumoniae* but not non-K1/K2 *K. pneumoniae* [20]. However, in the present study, diabetes mellitus appeared to be a contributing factor to infection among K1, K2 and even non-K1/K2 isolates. In addition, we found that patients with diabetes mellitus were prone to extrahepatic abscess, although the foci were not limited to liver abscess formation.

Various human pathogens express the mucoid phenotype and related pathogenic mechanisms have been demonstrated. In general, *K. pneumoniae* with mucoid phenotypes are more resistant to phagocytosis, less sensitive to serum killing, and thus more virulent in animal studies [8-10,21]. Clinical *K. pneumoniae* strains usually form glistening mucoid colonies with viscid consistency on the culture plate, and such hypermucoviscosity phenotype was demonstrated to be virulent and more likely to cause the distinctive invasive syndrome [8,9]. The findings here were consistent with these properties. Sixteen out of 18 strains of pathogenic *K. pneumoniae* in this study isolated from patients with or without bacteremia showed the presence of hypermucoviscosity phenotype.

To further understand the phenotype of hypermucoviscosity, the possible responsible genetic elements have been investigated previously, including *magA*, *cps* (capsular polysaccharide synthesis), *rmpA*, $rmpA_2$ and *wb* [8,21]. *magA* has been thought to be responsible for the expression of hypermucoviscosity in liver-invasive strains [10]. However, the present study revealed that most non-liver pyogenic organisms were *magA*-negative, but all were *rmpA*-positive, in accordance with previous studies that have documented the association of *rmpA* with the mucoid phenotype of *K. pneumoniae* regardless of the capsular serotypes and with various purulent infections [9,21]. Until now, the most frequently documented genetic correlation with mucoidity was *rmpA* in addition to *magA* [8,9,14]. Two strains that were positive for *rmpA* but negative for the hypermucoviscosity phenotype may possibly be explained by their lacking full genetic expression of *rmpA* [9,21].

Klebsiellae usually develop prominent capsules which are essential for virulence. The capsules of K1 and K2 serotypes in particular can protect the bacteria from phagocytosis by polymorphonuclear granulocytes and prevent killing by bactericidal serum

Table 5. Clinical spectrum of extrahepatic abscess caused by *Klebsiella pneumoniae* according to K capsule serotype

Variable	Capsule serotype		
	K1 (n = 4)	K2 (n = 7)	Non-K1/K2 (n = 7)
WBC count (× 10^3/U; range) [mean]	8.5-30.3 (17.2)	2.7-46.9 (18.3)	3.4-15.2 (10.3)
CRP (mg/L; range)	>150[a]	2.0->250[b]	27.6->250[d]
Platelet (× 10^3/U; range) [mean]	119-306 (201.3)	20-391 (248.9)	62-249 (149.9)
Abscess site (no.)	Mycotic aneurysm (1); lung (3)	Subdural empyema (1); mycotic aneurysm (2)[c]; paraspinal (1); kidney (1); neck (1); meningitis (1); pyomyositis (1)[c]	Kidney (2); neck (1); parotid gland (1); meningitis (1); arthritis (1); paraspinal (1)
Diabetes mellitus (no.)	3	6	6
Mortality (no.)	1	2	0

Abbreviations: WBC = white blood cell; CRP = C-reactive protein

[a]Two patients had no CRP data.

[b]Three patients had no CRP data.

[c]One patient had simultaneous mycotic aneurysm and pyomyositis of the anterior tibia.

[d]One patient had no CRP data.

factors [1]. Capsular serotypes K1 and K2 are generally considered to be the predominant virulent strains of *K. pneumoniae* [7], and thus may contribute to all mortality cases in the present study. Furthermore, K1 has been documented as the most common serotype isolated from patients with *K. pneumoniae* liver abscess [22], and *magA* is specifically restricted to the gene cluster of capsular serotype K1 strains but not in non-K1 serotype [13]. In addition, k_2A, in the *cps* gene clusters of K2 may play a role in the genetic determination of the K2 capsular serotype [14]. In this study, k_2A seemed more prevalent than *magA* in *Klebsiella* isolates from extrahepatic abscesses. Due to the limited number of cases, however, further investigation is required to document the seroepidemiology. Similarly, further studies are necessary to identify the pathogenetic role of *kfu* in purulent non-hepatic infections, which is involved in causing liver abscess via coexistence with *magA* [5].

In conclusion, diabetic mellitus is mostly associated with invasive *K. pneumoniae* infection, such as in extrahepatic abscess. Regardless of K capsule serotype, the *rmpA*-associated hypermucoviscosity was the most common virulence factor among causative *Klebsiella* isolates of extrahepatic abscesses. In addition, unlike primary *Klebsiella* liver abscess that has been predominantly caused by K1 isolates, the expression of k_2A (implying K2 serotype) seems more prevalent than *magA* (implying K1 serotype) in *K. pneumoniae* causing purulent infections outside the liver.

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