

Emerging Severe and Fatal Infections Due to *Klebsiella pneumoniae* in Two University Hospitals in France[∇]

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Severe infections caused by hypermucoviscous *Klebsiella pneumoniae* have been reported in Southeast Asian countries over the past several decades. This report shows their emergence in France, with 12 cases observed during a 2-year period in two university hospitals. Two clones (sequence type 86 [ST86] and ST380) of serotype K2 caused five rapidly fatal bacteremia cases, three of which were associated with pneumonia, whereas seven liver abscess cases were caused by K1 strains of ST23.

Klebsiella pneumoniae is responsible for hospital-acquired urinary tract infections, septicemia, pneumonia, and intra-abdominal infections. In addition, since the mid-1980s, a distinct clinical syndrome of liver abscess and metastatic infections due to *K. pneumoniae* has emerged, with a predominance of cases in Taiwan (4, 9, 14). In addition, *K. pneumoniae* can cause severe pneumonia, bacteremia, and meningitis (9). These severe infections are usually community acquired with host risk factors, including diabetes mellitus and possibly an Asian ancestry. The *K. pneumoniae* isolates from severe invasive infections are often hypermucoviscous and frequently belong to the capsular serotype K1 or K2 (10, 15). Two of the most extensively studied genes associated with invasive infections are mucoviscosity-associated gene A (*magA*) and regulator of mucoid phenotype A (*rmpA*) (7, 16, 18). The *magA* gene actually corresponds to the capsular polysaccharide synthesis (*cps*) gene *wzy* of *K. pneumoniae* isolates of serotype K1 (15). The *rmpA* gene is a plasmid-mediated regulator of extracellular polysaccharide synthesis, and *rmpA*-carrying strains were associated with the hypermucoviscosity phenotype (12). In addition, two chromosomal virulence genes, *kfu* (responsible for an iron uptake system) and *allS* (associated with allantoin metabolism), correlate strongly with *K. pneumoniae* isolates from liver abscess (5).

Until recently, invasive infections due to *K. pneumoniae* were geographically confined to Southeast Asia and South Africa. However, some clinical cases have been reported recently in Western countries (7, 8, 11). Here, we describe 12 cases of invasive infections due to *K. pneumoniae*, including five rapid and fatal bacteremia cases and seven liver abscesses, observed over a 2-year period in two university hospitals in France.

Case reports and bacterial investigation. The clinical features and characteristics of the *K. pneumoniae* isolates are reported in Table 1. Five isolates were associated with fatal bacteremia within 48 to 72 h, whereas seven isolates were responsible for liver abscesses. The 12 isolates were identified according to standard microbiological methods. On blood agar, all isolates grew as hypermucoviscous colonies and displayed a positive string test (7). All isolates harbored the usual resistance phenotype of the species *K. pneumoniae*, i.e., resistance to amoxicillin and ticarcillin. The presence of known virulence factors (*rmpA*, *allS*, and *kfu*) associated with severe infections, as well as K1 (*magA*) and K2 *wzy*-specific sequences, was determined by PCR using primers described elsewhere (1, 14, 19). Two reference strains of capsular serotypes K1 (NTUH K2044) and K2 (CG43) were used as controls (2, 7). Multilocus sequence typing (MLST) was performed using the international MLST scheme of the Institut Pasteur, Paris, France (<http://www.pasteur.fr/mlst>).

Our observations (Table 1) are in accordance with the fact that the hypermucoviscous phenotype is highly associated with severe community-acquired *K. pneumoniae* infections, including bacteremia and liver abscess (7, 10). All isolates recovered from patients with liver abscess were of serotype K1 and were positive for the presence of *magA*, *rmpA*, *kfu*, and *allS* genes. The last gene has been reported to be strongly associated with strains recovered from liver abscess (5). In addition, all 7 isolates as well as reference strain NTUH-K2044 belonged to sequence type 23 (ST23), which is one of the major clonal complexes (CC23-K1) that includes only K1 isolates (1, 13). During the past several decades, more than 900 cases of liver abscess due to *K. pneumoniae* have been reported in East and South Asia and in Taiwan, compared to only 50 cases in other parts of the world. In addition, case reports and small series from South Korea, Singapore, Japan, India, and Thailand have been published. Recent studies suggest that the incidence of *K. pneumoniae* liver abscess is increasing and that capsular serotype K1 is significantly associated with these infections (11, 17). All 7 patients were successfully treated: 6 received an extend-

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TABLE 1. Patient characteristics, clinical features, and virulence factors associated with strains recovered from 12 cases

Case (hospital) ^a	Patient characteristics and clinical features	K1 serotype <i>magA</i> gene	K2 serotype	<i>rmpA</i>	<i>allS</i>	Sequence type
1 (SA)	Caucasian, 50 years old, previous travel to Thailand (return for 1 week before admission); blood and pulmonary sputum isolate; fatal	–	+	+	–	ST86
2 (SA)	Asian origin, 60 years old, diabetes mellitus, no recent travel; blood isolate; fatal	–	+	+	–	ST380
3 (T)	African, 47 years old, return from Ivory Coast 24 h prior to symptoms; blood and cerebrospinal fluid isolate; fatal	–	+	+	–	ST86
4 (SA)	Caucasian, 60 years old, no recent travel; blood and sputum isolate; fatal	–	+	+	–	ST380
5 (SA)	Caucasian, 35 years old, no recent travel; blood isolate; fatal	–	+	+	–	ST380
6 (SA)	Caucasian, 60 years old, diabetes mellitus, no recent travel; liver abscess	+	–	+	+	ST23
7 (SA)	Asian origin, 60 years old, no recent travel; liver abscess	+	–	+	+	ST23
8 (SA)	Asian origin, 45 years old, no recent travel; liver abscess	+	–	+	+	ST23
9 (T)	Asian origin, 52 years old, diabetes mellitus, no recent travel; liver abscess	+	–	+	+	ST23
10 (T)	Asian origin, 80 years old, no recent travel; liver abscess	+	–	+	+	ST23
11 (T)	Asian origin, 75 years old, diabetes mellitus, return from Cambodia 24 h prior to symptoms; liver abscess	+	–	+	+	ST23
12 (T)	Caucasian, 60 years old, no recent travel; liver abscess	+	–	+	+	ST23

^a SA, Saint-Antoine University Hospital; T, Tenon University Hospital.

ed-spectrum cephalosporin (e.g., cefotaxime or ceftriaxone) associated with a 2-day course of gentamicin. For the seventh patient, treatment included amoxicillin-clavulanic acid associated with gentamicin.

In contrast, the isolates from the five fatal cases (patients 1 to 5) were all of capsular serotype K2; they also possessed the *rmpA* gene. Capsular serotype K2 also plays an important role in determining virulence and metastatic complications in *K. pneumoniae* infections (7). Two isolates belonged to ST86, as did the highly virulent clinical isolate CG43, from which the virulence plasmid pLVPK was identified (2). The three other isolates belonged to a novel ST, ST380. Three cases (one ST86 and two ST380) corresponded to bacteremic pneumonia complicated by septic shock (cases 1, 2, and 4). Historically, *K. pneumoniae* has been a recognized pulmonary pathogen associated with dramatic clinical presentation and alcoholism as a risk factor. Even if the incidence of community-acquired *K. pneumoniae* pneumonia has apparently declined, severe cases are encountered in Asia and South Africa (9). Fatal case 3 (ST86) had sustained bacteremia without a clear source, although the cerebrospinal fluid recovered just after death yielded a positive culture. In a worldwide collaborative study initiated to elucidate the clinical patterns of *K. pneumoniae*, Ko et al. (9) underlined the preponderance of this species as a cause of community-acquired bacterial meningitis in adults, particularly in Taiwan, even in the absence of other sites of infections. In their report, among the seven cases included, five were in Taiwanese patients and two were in African patients, as was case 3. Upon admission, patient 1 was treated with amoxicillin-clavulanic acid and rovamycin and then cefotaxime and gentamicin. Other patients received cefotaxime and gentamicin.

In addition to the characteristics of the strains, host risk factors for invasive *K. pneumoniae* infections include diabetes mellitus and possibly an Asian ancestry. Indeed, the majority of invasive infections with hypermucoviscous *K. pneumoniae* have

been reported in Asia and in Asian patients living abroad. In our series, 6 patients were of Asian origin. The basis for the apparent ethnic specificity remains unknown. Host genetic susceptibility, limited geographical distribution of particular strains, or contamination with unique dietary elements may play a role in the epidemiology of these invasive infections. The history of travel to Thailand in our first case, prior to presentation of the infection, raises the possibility of acquisition of the *K. pneumoniae* isolate in this country. However, cases with no history of travel to Asia have been documented, demonstrating that highly virulent strains are present outside Asia (11).

Although diabetes mellitus has been recognized as an important risk factor for *K. pneumoniae* liver abscess, more than half of the patients did not have diabetes, both in Western and in Asian countries (6). In our series, diabetes mellitus was present in 4 patients (3 of 7 with liver abscesses). Finally, the source of the invasive strain in individual patients usually remains unknown. In most cases, including the Taiwanese patients with *K. pneumoniae* liver abscess, there was no history of hepatobiliary disease (3).

In conclusion, infections caused by hypermucoviscous *K. pneumoniae* isolates have been reported in France for the first time. Our 12 *K. pneumoniae* isolates appear similar to those reported in Asia with respect to capsular serotype, genes *magA*, *rmpA*, *allS*, and *kfu*, and *in vitro* susceptibility. In agreement with previous reports (1, 13), our data show that the K1 isolates from liver abscesses in France belong to ST23. In contrast, K2 isolates responsible for invasive infections belong to at least two unrelated STs, ST86 and ST380. It remains to be determined whether the emergence of severe K2 *K. pneumoniae* infections in Asia and elsewhere is also multiclonal and due to the same genotypes. Genotyping with the standardized MLST method should help in deciphering the contributions of clonal spread and multiple emergence to the global occurrence of severe *K. pneumoniae* infections.

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