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Review Article

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Klebsiella pneumoniae Liver Abscess

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Conflict of Interest
No conflicts of interest.

ABSTRACT

Since the mid 1980s, the prevalence of liver abscess caused by hypervirulent *Klebsiella pneumoniae* strain has increased in Asia, particularly in Taiwan and Korea. This strain is mostly K1 or K2 serotype, and has hypercapsular and hypermucoid phenotypes. Most infections are community acquired, and patients rarely have a hepatobiliary disease prior to infection. Clinical manifestations are characterized by fever and high C-reactive protein, and metastatic infections, such as septic emboli in the lung and endophthalmitis and meningitis are frequently observed. Antibiotic resistance is rare. Antibiotic treatment and abscess drainage are needed, and early diagnosis and treatment of endophthalmitis is also important.

Keywords: Liver Abscess; *Klebsiella pneumoniae*; C-reactive protein

INTRODUCTION

In the mid-1980s, investigators in Taiwan first noted a distinctive syndrome of monomicrobial *Klebsiella pneumoniae* pyogenic liver abscess in individuals who were often diabetic but had no biliary tract disorders [1-3]. Subsequently, community-acquired *K. pneumoniae* liver abscess has become a major health problem in parts of Asia, accounting for 80% of all cases of pyogenic liver abscess in Taiwan and Korea, and has been reported sporadically elsewhere in Asia, North America, Europe, and Australia [4-6].

Infections are primarily caused by hypermucoid strains of *K. pneumoniae* of the capsular K1 (or occasionally K2) serotype. The mortality rate is approximately 5%, which is not much different than non-*K. pneumoniae* liver abscess [5], but metastatic infections, such as endophthalmitis and meningitis, have been reported in approximately 10-16% of cases [7].

ROUTE OF HEPATIC INVASION

Pyogenic liver abscess occurs whenever the initial inflammatory response fails to clear an infectious insult to the liver. Pyogenic liver abscesses are usually classified by presumed route of hepatic invasion: (1) biliary tree, (2) portal vein, (3) hepatic artery, and (4) direct extension from contiguous focus of infection (**Fig. 1**) [8]. The most common etiologies

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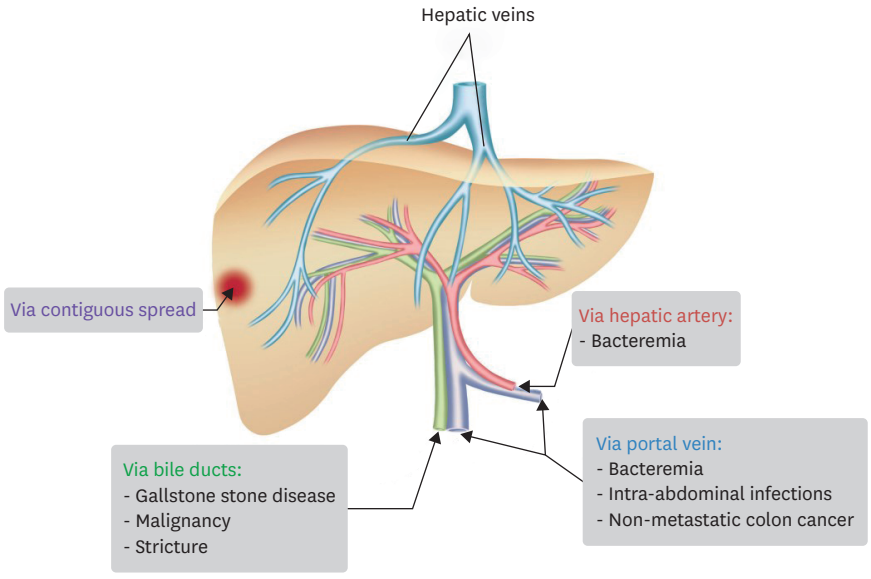

Figure 1. Routes of Infection (adapted from reference 8).

are unknown cryptogenic (primary) origin and infection by biliary route [9, 10]. Biliary infections are associated mostly with stricture subsequent to gallstone disease, malignancy, or hepaticojejunostomy, which is believed to involve bacterial proliferation in the bile duct that causes ascending cholangitis and invasion of the liver parenchyma [11, 12]. Portal venous route may originate from an abdominal infection, where appendicitis, diverticulitis, colorectal cancer, and inflammatory bowel disease may be the cause [7]. Hepatic arterial route usually involves bacteremia caused by *Staphylococcus aureus,* leading to secondary liver abscess [7].

Compared to non-*K. pneumoniae* liver abscess, *K. pneumoniae* liver abscess rarely have biliary or portal vein route of infection involving hepatobiliary disease, history of hepatobiliary surgery, history of intra-abdominal trauma or surgery, or malignancy [4, 13]. An animal study using a mouse model reported that *K. pneumoniae* crosses the intestinal barrier to cause liver abscess [14].

EPIDEMIOLOGY AND RISK FACTOR

The cause in most patients was community-acquired infections, being reported predominantly in Asian countries, including Taiwan and Korea, while even the 2 case series reported in the US showed that the ethnic origin of half of the patients was Asian [5]. Studies have yet to identify any host genetic factors that can explain such high prevalence among Asians. Previous studies reported that the prevalence of *K. pneumoniae* in healthy adults in Asian countries was up to 75%, and that 23% of typeable stains in Taiwan were K1 or K2 serotype [15]. In a Korean study, *K. pneumoniae* was isolated from 248 of 1,175 stool samples (21.1%) and 23% (57/248) of *K. pneumoniae* isolates were K1 serotype [16]. In contrast, a European study with small sample size reported that the prevalence of *K. pneumoniae* in fecal samples was only about 10-19% [17, 18]. While there is the limitation that the environmental reservoir of *K. pneumoniae* has not been identified, it is believed that an association between incidence of liver abscess and high prevalence of virulent *K. pneumoniae* strains among Asians does exist. In other words, it is suspected that after gastrointestinal colonization of *K. pneumoniae* through environmental exposure or fecal to oral transmission in Asian, the bacteria can cross the intestinal barrier to invade the liver.

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Diabetes mellitus (DM) is believed to be one of the risk factors of *K. pneumoniae* liver abscess [13]. Compared to 5–33% of non-*K. pneumoniae* liver abscess patients having DM, up to 63% of the patients in the Taiwanese case series were reported to have DM [3, 19, 20]. Although the definitive mechanism associated with this has not been identified, but it has been reported that poor glycemic control may impair neutrophil phagocytosis of K1 and K2 capsular serotypes [21]. In patients with endophthalmitis, it has been reported to be associated with poor visual outcome [22]. In addition, others have reported that incidence of *K. pneumoniae* liver abscess is associated with history of antibiotics use, such as ampicillin and amoxicillin, within 30 days. In an accompanying animal study, ampicillin administration predisposed *K. pneumoniae*-colonized mice to increased liver abscess formation [23].

VIRULENCE FACTORS

"Classical" *K. pneumoniae* generally causes nosocomial acquired pneumonia, urinary tract infection, or bacteremia in immunocompromised patients, such as those with DM or malignancy [24]. Hypervirulent strains that have become more common around Asia in recent times have community origin and can often cause infection in even healthy and immunosufficient people [24]. Moreover, they characteristically cause pyogenic liver abscess and have hematogenous metastatic spread. Antibiotic resistance is a phenomenon associated primarily with classical *K. pneumoniae*. Although there have been reports of hypervirulent *K. pneumoniae* strains that carry extended-spectrum beta-lactamases (ESBLs) or carbapenemases, it is a rare occurrence [25]. An overview of the difference between classical and hypervirulent *K. pneumoniae* strain can be found in **Table 1**.

To date, there are four major classes of virulence factors that have been well characterized in *K. pneumoniae*. These virulence factors consist of capsule, including the production of hypercapsule in hypervirulent strains; lipopolysaccharide (LPS); siderophores; and fimbriae, also known as pili. Differences between classical and hypervirulent strains that have been identified in studies to date include serotype K1 or K2 serotype being hypercapsular and greater expression of siderophores, such as yersiniabactin, salmochelin, and aerobactin [24].

Capsule is an extracellular polysaccharide matrix that envelops the bacteria. Both classical capsule and hypervirulent hypercapsule are made up of strain-specific polysaccharides termed K antigen (*i.e.*, K1 and K2, up through K78). The genes needed for the production of capsule are located on a chromosome operon, *cps*. K antigens have been traditionally

Table 1. Characteristics of classical and hypervirulent *Klebsiella pneumoniae* strains

Parameter	Characteristics for strain type	
	Classical	Hypervirulent
Common types of infection	Pneumonia, UTI, bacteremia	Pyogenic liver abscess, bacteremia, pneumonia, necrotizing fasciitis, myositis, meningitis, endophthalmitis
Susceptible population	Immunosuppressed (diabetics, patients with malignancies)	Diabetics, healthy people
Capsule type	Capsule serotypes K1-K78	Hypercapsular serotype K1 (93%) or K2
Siderophores (% of strains expressing siderophore)	Enterobactin (100), yersiniabactin (17–46), salmochelin (2–4), aerobactin (6)	Enterobactin (100), yersiniabactin (90), salmochelin (>90), aerobactin (93–100)
Primary acquired infection type	Nosocomial	Community acquired
Geographic concentration	Worldwide	Primarily Taiwan, Korea, and Southeast Asia
Frequency of reports of antibiotic resistance	Frequent (ESBL and carbapenemase producing)	Infrequent

UTI, urinary tract infections; ESBL, extended-spectrum beta-lactamases.

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assigned by using serologic methods [26]. Recently however, K-antigen typing is often performed by sequencing of the *wzi* locus [27]. This locus is present in all capsular types of *K. pneumoniae*, and different *wzi* locus sequences are strongly associated with specific K antigens. Classical *K. pneumoniae* strainis produce a capsule that can be of any of the serotypes K1 to K78. Hypervirulent strains make a hypercapsule, which amplifies the production of capsular material, resulting in a relatively larger capsule, and are predominantly of the K1 serotype, while the remaining strains are of serotype K2. One study characterizing hypervirulent *K. pneumoniae* strains isolated from 4 different continents found that these strains were almost exclusively K1 strains (93%), while the remaining minority were K2 strains [28]. The hypercapsule phenotype showed enhanced resistance to a variety of humoral defenses, including complement killing and phagocytosis by human neutrophils and macrophages compared to a number of classical strains [29].

Hypervirulent *K. pneumoniae* shows a mucoid phenotype and the genes associated with this include regulator of mucoid phenotype A (*rmp*A) and *rmp*A2, mucoviscosity-associated gene A (*mag*A), which increases capsule production. When colonies of mucoid phenotype were touched with a loop and the loop lifted vertically from the surface of the agar plate, mucoid isolates adhered to the loop as it was lifted from the plate (**Fig. 2**) [30]. In fact, 55% to 100% of hypervirulent *K. pneumoniae* strains express at least one copy of *rmp*A or *rmp*A2, compared to 7–20% of non-hypervirulent *K. pneumoniae* strains [31]. Gene *mag*A is actually specific to K1 stains.

K. pneumoniae, like many other bacterial pathogens, must employ tactics to acquire iron from the host in order to survive and propagate during mammalian infection. The predominant tactic used by many pathogens, including *K. pneumoniae*, to acquire iron is through the secretion of siderophores, which are molecules that possess a higher affinity for iron than host transport proteins do. Siderophores can steal iron from host iron-chelating proteins or scavenge it from the environment [32]. Several siderophores are expressed in *K. pneumoniae*, including enterobactin, yersiniabactin, salmochelin, and aerobactin. Enterobactin expression is almost ubiquitous among both classical and hypervirulent *K. pneumoniae* strains and is therefore considered to be the primary iron uptake system utilized by *K. pneumoniae*. In contrast, expression levels of yersiniabactin, salmochelin, and aerobactin are much higher in hypervirulent *K. pneumoniae* strain than in classical strain. Yersiniabactin has been observed in only 18% of classical but 90% of hyperevirulent *K. pneumoniae* clinical isolates [24]. Salmochelin is present in only about 2 to 4% of nosocomial *K. pneumoniae* strains but is much more prevalent in hypervirulnet *K. pneumoniae* strains, with one study reporting its presence in 90% of hypervirulent *K. pneumoniae* strains associated with pyogenic liver abscess. Aerobactin

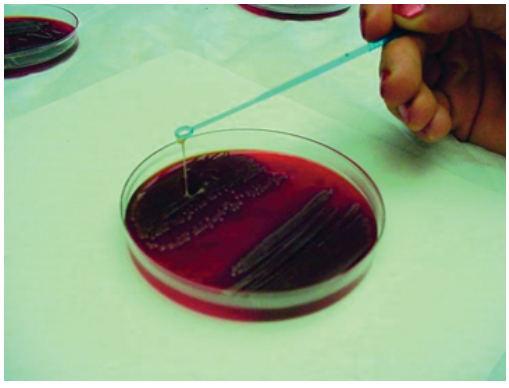

Figure 2. Mucoid phenotype of *Klebsiella pneumoniae* (adapted from reference 30).

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is found in only about 6% of classical strains, yet is present in 93 to 100% of hypervirulent *K. pneumoniae* isolates. The presence of aerobactin is always associated with a hypercapsule, although not all hypercapsulated strains possess this siderophore [24].

CLINICAL MANIFESTATION AND DIAGNOSIS

The most common clinical manifestations in patients with *K pneumoniae* liver abscesses are fever, chills, and abdominal pain [19, 20, 33, 34]. Leukocytosis, thrombocytopenia, increased concentrations of C-reactive protein and glucose in blood, and abnormal results of liver function tests were common. The mean value of C-reactive protein level that tends to be elevated in most patients is ≥20 [34].

Diagnosis of pyogenic liver abscess requires abdominal imaging study, such as ultrasonography or computed tomography (CT). Since it has been reported that imaging by ultrasonography offers poorer sensitivity than abdominal CT (85.8% *vs.* 100%), abdominal CT is recommended for diagnosis, whenever possible [35]. In the CT findings, *K. pneumoniae* liver abscesses were more likely than non-*K. pneumoniae* liver abscesses to show a single abscess, unilobar involvement, solid rather than cystic appearance, multilocular rather than unilocular septation, and greater association with thrombophlebitis of portal or hepatic vein [36]. Pigtail drainage of abscess during diagnosis is often difficult due to the solid appearance and multilocular characteristics of the abscesses. Thrombophlebitis of portal or hepatic vein was associated with hematogenous septic complications [36, 37].

Mortality rate was about 5%, which did not differ much from that of non-*K. pneumoniae* liver abscesses [5]. Meanwhile, metastatic infections, such as endophthalmitis or meningitis, was reported in approximately 10–16% of cases, with the lungs, eyes, and central nervous system being the common sites of such infections [5]. Presence of metastatic infection is associated with higher frequency of intensive care unit (ICU) admission and in-hospital mortality [13]. The frequency of meningitis was higher in Taiwan than in Korea [5]. Endophthalmitis tends to be more prevalent during winter, and if the initial vision is counting fingers level and below, it may be associated with poor visual outcome [22]. It has been reported that Gram negative bacilli account for most cases of endogenous endophthalmitis in Asia, while *K. pneumoniae* has been reported to account for up to 60% [38-40]. Diabetes is a significant risk factor for the development of endogenous endophthalmitis and poor visual outcome in patients with *K. pneumoniae* liver abscess [22].

MANAGEMENT

Clinical isolates are characteristically highly drug sensitive and cephalosporin are the antibiotic mainstay of treatment for *K. pneumoniae* abscess [5]. A third-generation cephalosporin is preferable to a first-generation cephalosporin [41]. Many favor use of first-generation cephalosporins given their relative low cost and apparent efficacy with respect to rates of mortality, metastatic infection and complications [34]. However, others have reported higher metastatic infection rates among patients treated with cefazolin compared with those treated with a second- or third-generation cephalosporin [41]. Because ESBL-producing *K. pneumoniae* has been detected very rarely in patient with liver abscesses, antibiotics such as ampicillin-sulbactam, aztreonam, and a quinolone can also

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be used. Although aminoglycoside penetrate abscess cavities poorly, clinicians often add an aminoglycoside. In theory they may eradicate bloodstream organisms early in their course of infection, potentially decreasing risk for metastatic complications. However, this benefit is unproven and may be outweighed by the toxicity of aminoglycosides. Parenteral antibiotics are usually treated for 2 to 3 weeks, and a 4- to 6-week total course is completed with oral agents. Longer courses of treatment may be warranted for patients requiring subsequent drainage procedures or with persistent radiographic evidence of abscess. Abscess cavities usually resolve completely after therapy, but occasionally they persist despite prolonged courses of antibiotics. In such cases, patients should be observed closely. Recurrent symptoms such as fever or abdominal pain should prompt repeat imaging and possible reaspiration.

Adequate drainage of abscess is recommended for better clinical response. As mentioned above, *K. pneumoniae* abscess may not be amenable to immediate drainage, due to frequent multilocular and solid appearances. Two options are to postpone drainage and monitor closely until the abscess has matured and can then be drained or to insert the drain and retain the tubing so that the abscess can drain once it becomes liquefied. In a report, aggressive hepatic resection resulted in a better outcome than did conventional percutaneous drainage for those with more severe diseases [42].

Acute bacterial endophthalmitis is a medical emergency because delay in giving appropriate therapy may lead to irreversible loss of vision. Most patients with endophthalmitis present with acute decrease in vision and eye pain as the chief complaints. However, since patients whose conditions are severe enough to warrant ICU admission may not be able to express such symptoms, such patients should be checked for red eye, conjunctivitis, and hypopyon, followed by ophthalmic consultation. Automatic ophthalmic consultation may be considered for cases involving *K. pneumoniae* liver abscess. The prognosis for patients with endophthalmitis caused by *K. pneumoniae* is very poor; more than 85% of patients had a severe visual deficit. Prognosis for visual recovery is improved if a diagnosis is made early and the patient is given early antibiotic treatment [43, 44]. In addition to systemic antibiotics, intravitreal antibiotics and vitrectomy are usually required [33, 43, 44].

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