**Klebsiella pneumoniae** and the pyogenic liver abscess: implications and association of the presence of rpmA genes and expression of hypermucoviscosity

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*Klebsiella pneumoniae* is a common Gram-negative human opportunistic pathogen that causes both community and nosocomial infections primarily in immunocompromised hosts. This pathogen produces a wide range of infections including, pneumonia, bacteremia, urinary tract infection, meningitis, intra-abdominal infections, and community-acquired pyogenic liver abscess (PLA).1-5

Several virulence factors have been characterized clearly demonstrating their contribution to *K. pneumoniae* pathogenesis. The major virulence factors so far described are: a) the capsular polysaccharide (CPS), which confers the bacteria the ability to evade phagocytosis by immune cells and impedes bacterial killing by bactericidal complement serum;6 b) the LPS O-antigen, prevents complement protein deposition and complement-associated serum lytic activity;7 c) several pili or fimbrial adherence factors required for epithelial cell attachment and host colonization such as type 1 and type 3 pili, *K. pneumoniae* fimbrae 28 (KPF-28), the non-fimbrial adhesin CF29K, and the *E. coli* common pilus (ECP) have been described;2,8 d) enterobactin and aerobactin siderophores, are required for a pathogen to establish infection when entering the hosts and enhance iron uptake by *K. pneumoniae,*9 e) mucosity, a phenotype associated with a mucopolysaccharide network associated outside the capsule can facilitate mucosal colonization by *K. pneumoniae* and protects it from the interaction with antcapsule-specific antibodies to evade phagocytosis.10 Further, the hypermucoviscosity phenotype (HV) reported for certain strains are believed to increase the virulence of *K. pneumoniae.* The HV is regulated by the expression of 2 capsular polysaccharide genes: regulator of the mucoid phenotype gene (rpmA), a determinant controlling the CPS biosynthesis located in the chromosome or on the 180–220 Kb plasmid, and the plasmid-encoded transcriptional regulator of mucoid phenotype rpmA2. Iron-acquisition factors encoded on the same plasmid are also involved in regulation of the HV phenotype.11-13 Studies in animal models have shown that the HV-phenotype of *K. pneumoniae* isolates is one of the major virulence factors required to produce bacteremia in diabetic mice and that other factors could be involved in the systemic spread of bacteria.14 Another important point essential to the ability of *K. pneumoniae* to overcome antimicrobial therapies and to survive in demanding environments is multi-drug resistance, especially of isolates associated with nosocomial infections. One of the most common mechanisms of antimicrobial resistance of *K. pneumoniae* is the extended-spectrum β-lactamases (ESBL) production. ESBL-producing *K. pneumoniae* are rarely associated with community-acquired bacteremia and rarely express the HV phenotype.15 However, a recent report in China showed that antimicrobial resistance of *K. pneumoniae* HV variants has increased significantly.12

In 1986 a new invasive syndrome, primer pyogenic liver abscess (PLA), caused by *K. pneumoniae* was first described in Taiwan.16 In the last 3 decades, this syndrome has been reported in patients from many Asian countries, South Africa, Australia, Europe, and America.17,18 This community-acquired primary infection occurred primarily in healthy individuals and was associated with predisposing risk factors such as diabetes, malignancy, renal disease, and pneumonia.19 PLA was caused by HV variants of *K. pneumoniae*, and thus were designated as hypervirulent.13 These isolates exhibit the potential to cause nosocomial infections including pneumonia, meningitis, endophthalmitis, and may also cause metastatic infections.12

Several controversies have risen regarding the ability of *K. pneumoniae* to express the HV phenotype and its association with the prevalence of the rpmA/rmpA2 genes. Although some authors have
reported that *rmpA* is present in the vast majority of *HV* isolates, a small proportion of *HV* isolates do not possess these genes. Similarly, most of the *HV*-negative isolates do not carry *rmpA/rmpA2* but a small group of them may carry *rmpA* and/or *rmpA2*. Another point that remains unclear is whether the *HV* phenotype correlates with virulence. For instance, while the majority of isolates exhibiting the *HV* phenotype are considered more virulent, some *HV*-negative isolates show greater ability to cause bacteremia in the diabetes mouse model. Thus, it is apparent that virulence cannot be defined by the expression of *HV* alone. It is possible that *HV* is a key factor induced by specific host signals at different niches and could be important at certain stages during infection, for example during biofilm formation, particularly to evade the immune system and to colonize certain tissues within the host. This would explain, in part, the versatility of this pathogen to cause a myriad of human diseases.

In a recent issue of *Virusology*, Yu et al. investigated why some *rmpA*-positive *K. pneumoniae* were *HV*-negative. To this aim, they performed nucleotide sequencing analysis of the *rmpA* and *rmpA2* genes in *HV* and *HV* isolates. The comparative gene sequence analysis indicated the presence of frameshift mutations in *rmpA* or *rmpA2* genes in all of the *HV* isolates, but not in the *HV* isolates. The authors suggested that mutations in *rmpA/rmpA2* influenced negatively, to some extent, the level of virulence associated with the *HV* phenotype of *K. pneumoniae* and also that these mutations are responsible for the poor association of *HV* with ESBL-producing *K. pneumoniae* isolates.

The emergence and spread of ESBL-producing *K. pneumoniae* strains raise important questions regarding optimal therapies for serious infections caused by these microorganisms. *K. pneumoniae* causing nosocomial infections are ESBL-producing; however, hypervirulent *K. pneumoniae* variants causing PLA have been reported as non-ESBL-producing. The possibility that *K. pneumoniae* isolates causing PLA can increase resistance to antimicrobials is a potential public health problem and a continuous threat. Recent studies indicate that hypervirulent isolates continue to be highly susceptible but have increased their degree of antimicrobial resistance over time. Li et al. speculated why hypervirulent isolates exhibit low antimicrobial resistance, and suggested that these isolates perhaps cannot acquire resistance plasmids or may lose some resistance genes when they become hypervirulent. Yu et al. explained this controversy conducting conjugation experiments with ESBL-producing *K. pneumoniae* that exhibited the *HV* phenotype. They showed that the SHV-5 gene, one of the most prevalent ESBL genes and the *rmpA* gene are located on different plasmids. Based on their data they speculated that the ESBL-producing *K. pneumoniae* reduce genetic function of the *rmpA* system when the bacteria need to express ESBL genes during exposure to antibiotics. This is consistent with the general idea of bacterial metabolic economy to regulate gene expression in response to different host environment signals such as one under antibiotic selective pressure.

In sum, the epidemiological and molecular as well as experimental data from mouse models on infection indicate a strong correlation between the ability of PLA-causing *K. pneumoniae* strains to exhibit *HV* and to carry the *rmpA/rmpA2* genes. The studies discussed here highlight the need to deepen our understanding of the biological significance of *HV* as it relates to pathogenesis in the host. It is clear that further molecular and epidemiological characterization studies of potential factors that may contribute to virulence of *K. pneumoniae* causing PLA are needed. Chief to the clinical importance of the *HV* phenotype of *K. pneumoniae* strains worldwide is need to expand the number of ESBL- or non-ESBL-producing *K. pneumoniae* isolates originating from different geographic regions of the world and to determine the distribution of *rmpA* genes with or without genetic mutations in these strains. This opens an avenue for an interesting line of research on the genetics factors of the bacteria and/or the environmental cues that regulate *rmpA* gene function and the origin of its frameshift mutations. The investigation of the true role of the *rmpA* genes in expression of the *HV* phenotype and the virulence of PLA-causing strains calls for knock-out/complementation studies to fulfill molecular Koch’s Postulates. Of vital importance is the need to stand alert and increase the surveillance of antimicrobial resistance of these isolates, particularly in different regions the world where the syndrome is prevalent for earlier detection and optimal treatment of patients.

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No potential conflicts of interest were disclosed.

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