Hypervirulent (hypermucoviscous) *Klebsiella pneumoniae*

A new and dangerous breed

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**Abbreviations:** hvKP, hypervirulent *Klebsiella pneumoniae*; cKP, classic *Klebsiella pneumoniae*; CA-PLA, community-acquired pyogenic liver abscess; CP, capsular polysaccharide; CNS, central nervous system; DM, diabetes mellitus; EE, endogenous endophthalmitis; GNB, Gram-negative bacillus; IG, intra-gastric; IP, intra-peritoneal; LPS, lipopolysaccharide; NDM-1, New Delhi metallo-β-lactamase; ST, sequence type; UTI, urinary tract infection

A new hypervirulent (hypermucoviscous) variant of *Klebsiella pneumoniae* has emerged. First described in the Asian Pacific Rim, it is now increasingly recognized in Western countries. Defining clinical features are the ability to cause serious, life-threatening community-acquired infection in younger healthy hosts, including liver abscess, pneumonia, meningitis and endophthalmitis and the ability to metastasically spread, an unusual feature for enteric Gram-negative bacilli in the non-immunocompromised. Despite infecting a healthier population, significant morbidity and mortality occurs. Although epidemiologic features are still being defined, colonization, particularly intestinal colonization, appears to be a critical step leading to infection. However the route of entry remains unclear. The majority of cases described to date are in Asians, raising the issue of a genetic predisposition vs. geospecific strain acquisition. The traits that enhance its virulence when compared with “classical” *K. pneumoniae* are the ability to more efficiently acquire iron and perhaps an increase in capsule production, which confers the hypermucoviscous phenotype. An objective diagnostic test suitable for routine use in the clinical microbiology laboratory is needed. If/when these strains become increasingly resistant to antimicrobials, we will be faced with a frightening clinical scenario.

**Introduction**

The majority of infections due to *Klebsiella pneumoniae* in Western countries are due to “classical” *K. pneumoniae* strains. Friedlander, in 1882, described an encapsulated bacillus isolated from the lungs of patients who died of pneumonia. This predated the Gram stain technique, which was developed in 1884. It was initially named Friedlander’s bacillus but was changed to Klebsiella in 1886. In the pre-antibiotic era, *K. pneumoniae* was implicated as a cause of pneumonia, especially in alcoholics and diabetic patients. It was also an established uropathogen, and a cause of biliary tract infections, osteomyelitis and bacteremia. The epidemiology of *K. pneumoniae* infections has evolved in the antibiotic era, with most infections, particularly in developed Western countries, occurring in hospitals and long-term care facilities.1-4 Infections involving the urinary tract, lungs, abdominal cavity, intra-vascular devices, surgical sites, soft tissues and subsequent bacteremia were the most common clinical syndromes. Recently these “classical” *K. pneumoniae* (cKP) strains have received increased notoriety due to their propensity for acquiring antimicrobial resistance determinants. As a result, treatment has become more challenging. The spread of New Delhi metallo-β-lactamase (NDM-1)-containing strains from India associated with medical tourism and more recently the extreme drug-resistant *K. pneumoniae* outbreak at the Clinical Center Hospital on the National Institutes of Health campus have captured the attention of physicians, scientists and the lay press.5,6

A new hypervirulent variant of *Klebsiella pneumoniae* is emerging. In the mid-1980s and 1990s, reports from Taiwan described a unique clinical syndrome of community-acquired *K. pneumoniae* infections. Patients without a history of hepatobiliary disease presented with community-acquired pyogenic liver abscesses (CA-PLA) and a propensity for metastatic spread to distant sites.7,9 Although these observations were initially made in the Asian Pacific Rim (e.g., Taiwan, Korea, Vietnam and Japan) an increasing number of cases are being reported from North America,10-17 South America,18 the Caribbean,19 Europe,20-22 the Middle East,23,24 Australia,25 Africa and South Africa.20,25 A combination of clinical and bacterial phenotypic features have defined this new *K. pneumoniae* variant, which distinguishes it from cKP strains. The first is its ability to cause serious infection
Pathogenesis of Infection

How does acquisition/colonization with hvKP occur? Presumably acquisition resulting in colonization is the first step necessary for subsequent endogenous hvKP infection. However, the incidence of infection in individuals colonized with hvKP and the time lag from acquisition to infection, if/when it develops, is unknown. Based on data from cKP and limited data from hvKP strains, the GI tract appears to be the dominant site of colonization, with oro-pharyngeal or skin colonization being less frequent. A recent study from South Korea assessed for intestinal colonization with K. pneumoniae in 1,174 individuals. A total of 248 KP isolates were obtained; 54 (4.6%) of which were ST23, which is strongly associated with, but not necessarily diagnostic of, hvKP strains. Intestinal colonization with ST23 strains was greater in those > 25 y of age and lower in Koreans who had lived abroad. Another study assessed the seroepidemiology of 592 K. pneumoniae strains isolated from stool specimens obtained from 954 healthy Chinese adults who were residents of Taiwan, Hong Kong and China or living abroad in Japan, Thailand, Malaysia, Singapore and Vietnam. Overall, 39 (4%) and 19 (2%) of individuals were colonized with a K1 or K2 serotype of K. pneumoniae respectively. Although the K1 and K2 capsular serotypes are common in hvKP strains, cKP strains may also possess these serotypes, and hvKP strains may have a non-K1/K2 serotype. Despite the stated limitations, these data strongly suggest that a certain percentage of Asians are colonized with hvKP strains. These data also support the concept that colonization is requisite for, but does not necessarily lead to, infection.

Still, the means of hvKP acquisition remains undefined. Data from other Enterobacteriaceae, such as E. coli and cKP, would suggest that the vehicle(s) for acquisition and subsequent colonization are some combination of food, water, person-to-person transmission (e.g., close contacts such as family members or sexual partners) and animal-to-person transmission (e.g., pets and their owners). Data on hvKP is limited. A report demonstrated that a healthy father and his son developed primary liver abscess at different times and the wife/mother had asymptomatic intestinal colonization with the same hvKP strain (ST23, K1 serotype). However, it is impossible to tell whether colonization of each family member was from a common food/water source or person-to-person transmission. It is reasonable to consider travel to the Asian Pacific Rim or exposure to people from that area as a risk factor for hvKP infection. Acquisition leading to colonization and subsequent infection from International travel has been documented for Enterobacteriaceae, including cKP and hvKP. Nevertheless, this risk factor has not been observed in all cases acquired outside of Asia. Although hvKP infection primarily occurs in ambulatory patients, acquisition in a healthcare facility also has been described. Further, given the innate virulence of hvKP, acquisition in patients with co-morbidities (e.g., cancer) may result in severe disease. Therefore, contact with healthcare workers or inanimate objects within the facility are possible mechanisms of acquisition and consideration should be given for appropriate infection control measures.

What is the mechanism for hvKP entry into the extraintestinal site of infection? Entry into an extraintestinal organ or site is the next critical step in pathogenesis. However, the mechanism by which this occurs for hvKP is a mystery. Mechanisms for cKP and other Enterobacteriaceae include ascension into the bladder from the perineum, disruption of the bowel enabling entry of...
GI tract colonizers into the peritoneal cavity, micro- or macro-
aspiration of oro-pharyngeal colonizers into the respiratory tract
or disruption or breakdown of the skin barrier. However, infec-
tion with hvKP usually occurs in persons who do not have overt
disruptions of these host barriers to infection.

Although the mechanism of entry in humans has not been
established, several considerations seem most plausible at this point.
In patients who present with pneumonia, it is certainly conceivable
that oro-pharyngeal colonization followed by micro- or macro-
aspiration leads to pneumonia. Although some patients with hvKP
appear to present with aspiration-mediated pneumonia, the pri-
mary site of infection is most often outside of the lungs.4,42

Given the common presentation of pyogenic liver abscess
(PLA), the ability to invade across an intact intestinal mucosa,
which occurs with Salmonella Typhi or ascension up the biliary
tree are plausible routes. But, the usual lack of biliary tract dis-
ease, a hallmark feature of patients with hvKP-mediated PLA,
makes that route less likely. A recent report did demonstrate con-
current intestinal and/or pharyngeal colonization with hvKP in
35/43 and 17/43 patients respectively with PLA.33 Liver aspiration-
feecal-saliva hvKP isolates from the same patient were identical
or closely related by pulsed field gel electrophoresis in all 17
instances evaluated.35 These data suggest, but do not establish,
in an intestinal route of entry. Mouse models of hvKP infection
support the possibility of invasion across the intestinal mucosa.4
Nevertheless, if intestinal invasion can occur in humans, we are
left with a question as to why there are a number of individuals
with intestinal colonization who do not develop infection. Prior
immunity to hvKP, a lower degree of colonization or variable
efficiency of invasion across the intestinal mucosa are potential
explanations. Alternatively, this observation also suggests that
entry may occur from a non-intestinal focus.

Entry through an overt or occult break in the skin resulting
in bacteremia, similar to what occurs in some cases of invasive
Staphylococcus aureus infection,45 is another possibility, albeit con-
jectural. In many cases, it is difficult to distinguish the primary
site of infection from sites of subsequent spread. In fact, it is likely
that a number of cases with multiple organs/sites are seeded from
the initial bacteremia. Of interest, to date, no cases of laboratory
acquisition have been described. Most likely, a variety of entry
sites can lead to hvKP infection.

hvKP factors that contribute to intestinal colonization/
invansion have been identified. Using mouse infection models a
number of factors important in cKP colonization have been iden-
tified, which include capsular polysaccharide (CP),46 lipopoly-
saccharide (LPS), fatty acid and phospholipid synthesis, outer
membrane protein (OMP) A, OMP and DNA folding proteins, a
protein synthesis elongation factor, an aerobic-anaerobic metabo-
listism regulator, hypothetical proteins,47 a high molecular weight
adhesion, O-sialoglycoprotein endopeptidase, lactose metabolic
enzyme, cyclohexadienyl dehydratase, α-glucan phosphorylase,
amide-urea binding protein, harpin type III secretion system,
DNA primase, adenine-specific methylase, nitrogen and glycine
metabolism regulators and a hypothetical protein.48

A number of hvKP genes have also been implicated as impor-
tant for intestinal colonization and/or possible invasion across
the intestinal barrier in mouse models, but some studies do not
experimentally distinguish between these two possibilities. Using
a signature tagged approach, 28 mutants were identified as hav-
ing decreased growth/survival in liver and spleen samples after
intra-gastric (IG) challenge.49 Eight of these, a putative type III
fimbrial usher protein (mrkC), a uracil permease (kva28), a two-
component regulator system (kgzA-kig5, which has been shown
to contribute to capsule formation),49 a monamine regulon posi-
tive regulator (maoR), a LuxR family transcriptional regulator
(kva15) and two hypothetical proteins (kva7,21), when individu-
ally tested, caused no mortality after IG challenge, compared with
100% for their wild-type parent hvKP strain CG43 (ST86, K2
serotype). Yet they were as lethal as CG43 after intraperitoneal
(IP) challenge, demonstrating that these mutations inactivated
genes important for intestinal colonization and/or invasion.

Kfu, which mediates uptake of ferric iron, is more prevalent
in hvKP compared with cKP strains and was shown to be a fac-
tor for virulence in mice after IG but not after IP challenge.50
Although the possibility that Kfu is a factor for invasion cannot
be excluded, its function supports a role as an intestinal coloniza-
tion factor since free ferric iron is available within the intestinal
tract, but not within the host. Likewise, allantoin metabolism
genes, which enable nitrogen assimilation from purine catabo-
lysis or exogenous allantoin have been shown to be present more
frequently in hvKP strains with a K1 serotype, but not with
hvKP K2 or non-K1/K2 serotypes, when compared with cKP
strains.29,38,52 These genes were also shown to contribute to vir-
ulence in mice after IG challenge but not with IP challenge.52
Although a role in invasion cannot be excluded, a role in coli-
zation is biologically more plausible given their function. Still,
the absence of these genes in non-K1 hvKP strains raises the issue
of their relative importance in hvKP infection.

Lastly, by using an intestinal competition assay in mice, dele-
tion of the trehalose utilization gene treC in the hvKP strain
NTUH-K2044 resulted in decreased capsule production, biofilm
formation, and intestinal colonization.53 Likewise, disruption of
celB, whose product participates in the transport of cellulobiose
across the cytoplasmic membrane, resulted in decreased bio-
film formation, intestinal colonization, and mortality after IG
challenge.54 It remains unclear whether the decreased mortal-
ity was due to a difference in colonization, invasion or extrain-
testinal virulence. Nonetheless, these data established that for
NTUH-K2044 biofilm formation promotes intestinal coloni-
zation, a critical step in the pathogenic process.53,54 Although
NTUH-K2044 was also shown to produce more biofilm than
cKP strains,53 the relative role of this increased biofilm produc-
tion for intestinal colonization in hvKP strains compared with
cKP strains is not yet clear.

The ability for hvKP strains to grow/survive post entry is
greater than for cKP isolates. Entry alone does not necessarily
result in infection. The bacteria must be able to survive and pro-
liferate in the face of the host defenses. This is achieved by some
combination of the infecting inoculum, the inherent virulence
of the bacterial strain and the status of the host. For example,
a higher inoculum or compromised host may enable infection
with a less virulent strain. By contrast, hvKP is a professional
pathogen as defined by its ability to cause serious infection in a normal host. Therefore, one would predict a lower inoculum to cause disease. Although this has not been established in humans, both in vitro and animal model data support this concept. In a rat subcutaneous abscess model, the growth/survival of the hvKP strain hvKP1 is significantly greater than all 4 cKP bacteremic isolates tested.\(^1\) Similarly, an increased mortality was observed after intra-venous challenge in mice with hvKP strains compared with cKP strains.\(^2\)

Further, hvKP appears to be an extracellular bacterial pathogen. A defining virulence feature in these organisms is the ability to resist the bactericidal activity of antimicrobial peptides, and complement and phagocytes in the absence of antibody. hvKP1 was shown to be significantly more resistant to the complement-mediated and neutrophil-mediated bactericidal activity than four of four and three of four bacteremic cKP isolates, respectively.\(^3\) Taken together, this body of data support that hvKP strains are more virulent than cKP strains.

What are the mechanisms by which hvKP is able to grow and survive within the host? Do some of these mechanisms explain the enhanced virulence of hvKP compared with cKP? The ability of microbial pathogens to modify their inherent virulence or pattern of spread is part of the evolutionary process of host-pathogens interactions. Most commonly, this occurs by horizontal (lateral) gene transfer via bacteriophage, plasmids, or transposons. Pathogenicity islands and virulence plasmids are common examples of this mechanism. Virulence can also be enhanced via loss of function or point mutations in critical genes (e.g., regulatory genes). Clearly, there has been a modification of the hvKP phenotype. Yet, an incompletely answered question is what are the mechanisms responsible for this change that has made this variant far more virulent than cKP strains, from which it presumably evolved. Virulence plasmid acquisition may be an important mechanism for the increased virulence of hvKP. Genes that encode a number of virulence factors, including those that iron acquisition was needed for optimal systemic virulence which resulted in decreased virulence as well. These data established that iron acquisition was needed for optimal systemic virulence of hvKP. Still, disruption of multiple iron-acquisition systems was needed before a decrease in hvKP’s virulence was observed. Therefore, the inference from these data is that the acquisition of genes that enable aerobactin or yersiniabactin synthesis and uptake alone do not enhance pathogenicity. Perhaps the acquisition of a combination of these iron-acquisition systems contributes to the increased virulence of hvKP.

Recent data, however, has established that not only is iron-acquisition a critical virulence trait for hvKP, but that it is accomplished more efficiently than cKP.\(^4\) The hvKP strain hvKP1 (ST86, K2 serotype) produced more iron-acquisition factors (likely siderophores) than four cKP bacteremic isolates. Further, it was shown that this property enhanced the resistance of hvKP to complement-mediated bactericidal activity in vitro. Most importantly, this trait enabled a significant increase in growth/survival in human ascites ex vivo and in vivo in a mouse model of metastatic infection for hvKP compared with cKP.\(^5\) Therefore, this study established that the ability of hvKP to produce more iron acquisition factors enhanced its virulence. This observation is a critical observation and is the first clear example of why hvKP is more virulent than cKP. The mechanism responsible for this phenotype is under investigation.

Iron acquisition. The ability to acquire iron is essential for bacterial growth and replication. This trait has been shown to play crucial role in the progression of infection, including cKP.\(^6\) The host has a number of iron-binding proteins (e.g., transferrin) that serve to withhold iron from the invading pathogen. In turn, to acquire iron from the host’s iron-binding proteins, K. pneumoniae, like other Enterobacteriaceae produces siderophores. These small molecules are secreted, “steal” iron from the host due to their higher affinity than host binding proteins and then re-enter the bacterial cell by siderophore-specific receptors.\(^7\) Aerobactin, enteroactin, salmochelin and yersiniabactin are siderophores that have been described in K. pneumoniae.\(^8\)

Non-comprehensive data on which iron acquisition elements are present in cKP vs. hvKP strains exists. Gene clusters for the yersinia high pathogenicity island (encodes for yersiniabactin) and iucABCDiutA (encodes for aerobactin and its cognate receptor) were more prevalent in hvKP (38/42 and 39/42 respectively) than cKP (7/32 and 6/32 respectively).\(^9\) In addition, aerobactin production, as demonstrated by a cross-feeding assay, was more common in hvKP strains than cKP strains.\(^2\)

These bioinformatic-molecular epidemiologic analyses suggested that hvKP strains might have the capability to acquire iron more readily than cKP strains. Hsieh et al. began to address this possibility by assessing the virulence of mutant derivatives of the hvKP strain NTUH-K2044 in which the capability to synthesize yersiniabactin (irp), aerobactin (iuc) and salmochelin (iro) were abrogated either alone or in combination.\(^0\) Mutant derivatives in which irp, iuc or iro were disrupted alone were as virulent as their wild-type parent after IP challenge. A decrease in virulence after IP challenge was only seen when irp, iuc and iro were disrupted together. Likewise, disruption of tonB, which encodes for a protein requisite for uptake of siderophores, hemin and ferric citrate resulted in decreased virulence as well. These data established that iron acquisition was needed for optimal systemic virulence of hvKP. Still, disruption of multiple iron-acquisition systems was needed before a decrease in hvKP’s virulence was observed. Therefore, the inference from these data is that the acquisition of genes that enable aerobactin or yersiniabactin synthesis and uptake alone do not enhance pathogenicity. Perhaps the acquisition of a combination of these iron-acquisition systems contributes to the increased virulence of hvKP.
Surface polysaccharides. GNB in general, including hvKP, possess an extracytoplasmic outer membrane. This outer membrane consists of a lipid bilayer with associated proteins, lipoproteins and polysaccharides. The outer membrane interfaces with the bacteria’s environment, including the human host. Therefore its components are often critical determinants in pathogenesis.

Hypermucoviscous phenotype. A distinguishing factor of hvKP strains is its hypermucoviscous phenotype. The vast majority, but not all of the strains that cause CA-PLA possess this phenotype.38 An initial study that investigated its nature reported that it was distinct from the constitutive K2 capsule and the surface polysaccharide colanic acid.60 However, subsequent investigators have reported that it represented an increased amount of capsular material with the same components as the constitutive capsule. Whether this increased amount of polysaccharide represents an increase in the amount of the constitutive capsule36,61 or whether it is an extracapsular polysaccharide (exopolysaccharide) that is physically distinct but biochemically the same as the constitutive capsule remains contested.62

The factor that mediates the expression of the hypermucoviscous phenotype is RmpA/RmpA2 (regulator of the mucoid phenotype). Three genes that are variably present in hvKP strains have been reported to encode for RmpA/RmpA2: a chromosomally located rmpA, rmpA present on a plasmid and rmpA2, which is also located on a plasmid. In one study, 9/48 hvKP strains possessed all three genes, 35/48 possessed p-rmpA/p-rmpA2, 3/48 possessed only p-rmpA and 1/48 possessed c-rmpA alone.36 However, some cKP strains may also possess rmpA/rmpA2. Based on its GC content and the presence of a 5' located IS3 insertion sequence, rmpA2 appears to have been acquired, at least in some instances by horizontal acquisition.63 In CG43 both p-RmpA and p-RmpA2 increase the expression of capsule genes and the hypermucoviscous phenotype, whereas in NTUH-K2044 only p-RmpA, but not c-RmpA or p-RmpA2, do so. Hopefully, future studies in other backgrounds will clarify the roles of each RmpA in mediating mucoviscosity. For clarity, the gene magA was initially reported as the mediator of the hypermucoviscous phenotype, but has since been clarified as being the K1 specific capsular polymerase gene (wzy_K1).26,63

Although the mechanism by which RmpA/RmpA2 mediates mucoviscosity is still being investigated, details are emerging. RmpA (in CG43 and NTUH-K2044) and RmpA2 (in CG43, but not NTUH-K2044) are positive regulators of capsule synthesis by binding to the regulatory 5’ region of capsule genes.61,64 It appears that RmpA/RmpA2 act in a fashion similar to RcsA. RcsA, along with RcsB-D and Lon protease are part of a regulatory system for the synthesis of the surface polysaccharide colonic acid in E. coli.65 RmpA/RmpA2, similar to RcsA/RcsB are part of the UhpA-LuxR transcriptional regulator family. However, a critical difference is that RmpA/RmpA2 are active at 37°C, whereas RcsA is degraded by Lon at this temperature and is much more active at lower, non-physiologic temperatures.61 Similar to RcsA, RmpA is dependent on and interacts with RcsB. Further, rmpA and rmpA2 expression is negatively regulated by Fur.66 The inference from this observation is that mucoviscosity would increase in an iron-depleted state, such as the human host.

In hvKP strains the rmpA/rmpA2 genes are often present on a large, approximately 180–220 kb virulence plasmid that contains other factors that may contribute to virulence. Therefore, interpretation of molecular epidemiologic, plasmid loss/gain studies, or comparison studies using strains with different genetic backgrounds designed to assess the role of RmpA/RmpA2 and/or the hypermucoviscous phenotype are difficult to interpret.36,60,67 Studies that have assessed the virulence of isogenic mutant in infection models present conflicting results. In the genomic background of the hvKP strain CG43, p-rmpA has been shown to add to the virulence of the hvKP strain in a mouse IP challenge model.61 By contrast, in the background of NTUH-K2044 disruption of c-rmpA and p-rmpA did not affect its virulence in mouse IG or IP challenge models.36 Additional studies in other strains are needed to clarify the roles of each RmpA in mediating virulence.

Capsular polysaccharide (CP). At least 78 CP serotypes exist in K. pneumoniae.68 The capsule, especially serotypes K1 and K2, has long been known to be an important virulence factor in cKP. This effect is mediated in part by conferring an increased resistance to complement, antimicrobial peptides, and professional phagocyte-mediated bactericidal activity.69-73

For hvKP strains, eight capsular serotypes have been described to date; K1, K2, K5, K16, K20, K54, K57 and the new capsular serotype KN1.68,74,75 Further, the co-existence of rmpA1/rmpA2 is extremely uncommon in serotypes other than these (1/117).36 In hvKP strains the prevalence of K1, K2 and non-K1/K2 serotypes has ranged from 47–81%, 20% and 23–33% respectively.26,36-38,76 Because the majority of hvKP strains that caused CA-PLA were either a K1 or K2 serotype, these capsular serotypes were initially believed to be the critical virulence factor in this infectious syndrome.26,37 However, up to 1/3 of hvKP strains possess non-K1/K2 serotypes.26,36-38 Further, since cKP strains that possess K1 and K2 serotypes were significantly less virulent in a mouse infection model,29 the presence of a K1 or K2 serotype alone does not confer Klebsiella with a hypervirulent phenotype. Therefore, although capsule is a pathogenesis factor, it seems likely that the high level of virulence observed in hvKP strains is due to an increased expression of capsular material (hypermucoviscous phenotype) in combination with an increased efficiency of iron-acquisition and other traits that remain undefined.

Lipopolysaccharide (LPS). LPS consists of lipid A, which is essential in most GNB, a core region, and an O-antigen that consists of repeating polysaccharide units that confers serotype-specific antigenicity. Eight to 12 LPS serotypes have been described in K. pneumoniae.77 The bulk of, but not all, data supports LPS being an important virulence factor in cKP.72-78 The O1-antigen LPS moeity has also shown to be an important virulence factor in mouse infection models in the hvKP strain NTUH-K2044,81 which was mediated, at least in part, by conferring resistance to complement mediated bactericidal activity. No data are available on whether LPS contributes in some manner to the increased virulence of hvKP strains.

Adhesins. Both cKP and hvKP possess type 1 (mannose-sensitive) and type 3 (mannose resistant) fimbriae. In cKP strains
these fimbriae have been shown to adhere to host epithelial cells from the respiratory and urinary tracts and add to infection.82,83 Although little work has been done on hvKP, a recent study examined the regulation of type 3 fimbriae in the hvKP strain CG43.84 This study confirmed observations that type 3 fimbriae contribute to biofilm formation as well as demonstrating that expression is positively correlated with iron concentration. Although in vivo virulence was not addressed, these data suggest that type 3 fimbriae are less likely to be important within the human host where free iron is limited. The gene cfp29A, which encodes the adhesin CF29K, has been described in both cKP and hvKP strains. But in one study it was more strongly associated with hvKP strains.29,85 We are unaware of any in vivo data designed to assess CF29K as a virulence factor.

Biofilm formation. A bacterial biofilm consists of an aggregate of cells contained within a matrix of surface polysaccharides, proteins and DNA. The ability to produce a biofilm results in enhanced resistance to host defense factors and antimicrobials and is being increasingly recognized as an important virulence property.86,87 Even in the absence of a foreign body, biofilm formation has been shown to be a factor in closed-space infections.88,90 In vitro studies have established that cKP strains are able to produce biofilm, with type 3 fimbriae,95 CP and LPS,95,96 amino acid synthesis genes,95 1-arabinose metabolism,95 sugar phosphotransferase systems,94 the type 2 quorum sensing regulatory system,94,95 the Lys-R-type regulator oxyR96 and a putative cell surface protein95 identified as contributory factors. The hvKP strains NTUH-K2044 and KpL1 have also been shown to produce biofilm with putative gene products similar to those factors identified in cKP being contributory.95,97 These included CP, LPS, pilin, carbohydrate transport and metabolism and type 2 quorum-sensing genes. Studies on the hvKP strain hvKP1 identified the genes that putatively encoded glutamine synthetase, succinyl-CoA synthase α subunit and a transcriptional antiterminator of glycerol uptake operon as being contributory to biofilm formation.98

An important observation by Wu et al. was that hvKP strains produced more biofilm than cKP isolates, thereby suggesting that biofilm formation may be a contributing factor to its increased virulence.55 Although the mechanism(s) responsible for increased biofilm formation in hvKP strains has not yet been defined, the role of biofilm formation for the hvKP strain NTUH-K2044 in promoting intestinal colonization has been discussed (please see the section “hvKP factors that contribute to intestinal colonization/invasion have been identified”). Although it is logical, it is still unclear whether biofilm formation plays a direct role in extraintestinal hvKP infection. Mutant derivatives of the hvKP strain hvKP1 that produced less biofilm were equally resistant to complement mediated bactericidal activity and their growth and survival in a rat subcutaneous abscess model was similar to their wild-type parent.98 Nonetheless, these studies do not exclude a potential effect of biofilm in the other phases/aspects of systemic infection (e.g., metastatic spread).

Do host factors affect the susceptibility to developing hvKP infection? A predilection for infection in Asians has been seen,98,102 which poses a question of host genetic susceptibility vs. geographically defined pathogen exposure and acquisition. Although infections have been described in a variety of ethnic groups, even those acquired in Western countries commonly occur in Asians.11-18,20-22 The breakdown of ethnic groups from 35 cases of hvKP infection reported from Western countries was: Asians 20 (including Filipinos), Africans 6, Caucasians 6, Hispanics 1 and not reported 2.11-13,15,17,19-22 Of course this does not establish a genetic risk for infection since Asians infected in the West may have traveled to or been exposed to individuals who had recently been in the Asian Pacific Rim, which in turn lead to acquisition of hvKP.55 In fact, a case from Denmark in a Caucasian who traveled to Shanghai, China suggests this very scenario.21

Diabetes mellitus (DM) has long been recognized as a disease predisposing to bacterial infections. Ever since the recognition of hvKP infection, DM has been speculated as a significant risk factor. The majority of studies have determined this to be the case,4,7,9,99-103 although others did not conclude that DM was an independent predictor for hvKP infection.25,42 It is critical to note that hvKP infection is seen in all age groups and despite the fact that some patients have co-morbidities, it is frequently seen in younger, healthy patients. DM or any other co-morbidities are not requisite for the development of this potentially devastating disease.

Clinical Disease

A comprehensive understanding of the prevalence and spectrum of hvKP disease is lacking due to the lack of an objective diagnostic test. The lack of an unequivocal genotypic/phenotypic marker(s) for hvKP has precluded a comprehensive understanding of the prevalence and spectrum of hvKP disease. Although a positive “string test,” which reflects the hypermucoviscous phenotype, is the best laboratory-based surrogate marker presently available, as mentioned above it is unclear whether all hvKP strains possess this trait. Further, this test is not routinely performed in clinical laboratories. In addition, the clinical features that characterize hvKP infection are likewise not broadly appreciated. As a result, the incidence of hvKP infection and the clinical spectrum of disease are almost certainly underappreciated. In a number of reports describing Klebsiella infection, information on the characteristics needed to assist in differentiating between cKP and hvKP are lacking. Therefore in this review, infectious syndromes due to K. pneumoniae isolates with a positive string test and/or community-acquired K. pneumoniae infections with clinical features characteristic of hvKP such as metastatic spread will be attributed to hvKP.

The resultant morbidity and mortality from hvKP infection is significant. Despite the fact that the majority of patients with hvKP infection are younger and do not have co-morbidities, it is still associated with a significant mortality rate, ranging from 3 to 42%.4,9,20,26,99,104,105 Remarkable mortality rates of 55% for community-acquired pneumonia with bacteremia43 and of 47% for necrotizing fasciitis3 have been seen. Further, survivors with infection in critical sites often suffer catastrophic morbidity such as loss of vision, neurologic sequelae, or loss of limb.7,8,26,79,99
Sites of infection. Abdominal disease. CA-PLA. Prior to the 1980s, *E. coli* was the most commonly isolated enteric GNB from PLA in the Asian Pacific Rim; usually in the setting of biliary disease and often co-isolated with other pathogens such as anaerobes. But more recently, hvKP has emerged as the dominant cause of PLA. The rate of PLA has increased steadily in Taiwan from 1996 (11.15/100,000) to 2004 (17.59/100,000). In Korea, from 2004–2005, 78% of cases were caused by hvKP with 99% of the hvKP isolates having a K1 serotype. Likewise in Taiwan, approximately 4,000 cases were reported in 2004 with approximately 80% being due to hvKP having a K1 serotype, and from 2005–2008, > 3,000 cases were reported annually. In Western countries, there seems to be an increase in the number of cases of PLA due to *K. pneumoniae*. Two small series reported that *K. pneumoniae* was the responsible pathogen in 36% and 41% of cases, albeit the exact number of cases due to hvKP is unclear. Nonetheless, it is clear that an increasing number of cases of CA-PLA due to hvKP are present in various Western countries and an awareness of this entity, which may be complicated by severe sepsis or metastatic infection is needed.

Primary PLA in ambulatory patients without biliary disease was the defining syndrome that led to the recognition of hvKP. As described above, although the means of hepatic seeding is unclear, it likely occurs hematogenously via the portal or perhaps systemic circulation. hvKP-mediated PLA is almost always mono-microbial. Except for the potential co-incident presence of metastatic complications and usually a normal biliary tract, the clinical and laboratory presentation of hvKP-mediated PLA is not significantly different from other causes of PLA. However, a somewhat anecdotal but interesting feature that warrants further examination is a number of reports of reinfection/relapse at the same or different site, sometimes with the same strain, months to greater than a year after the end of therapy.

*Splenic abscess*. This can be a primary or metastatic site of infection. *K. pneumoniae* was the first or second most common pathogen responsible for splenic abscess in recent series from Korea and Taiwan. The presence or absence of a hypermucoviscous phenotype was not reported in these series. Nevertheless, a number of patients had concomitant PLA or metastatic spread at another site. Since *K. pneumoniae* is an exceedingly rare cause of splenic abscess in adults, it is likely that hvKP was the responsible pathogen.

*Spontaneous bacterial peritonitis*. Although hvKP infection has not been explicitly described to occur in the setting of hepatic cirrhosis with attendant portal hypertension and ascites, this must be the case since it has been described as a cause of spontaneous bacterial peritonitis.

*Thoracic disease. Pneumonia*. Although cKP is a relatively common cause of healthcare-associated pneumonia in the West, over the last several decades, *K. pneumoniae* has been an exceedingly rare cause of community-acquired pneumonia (CAP) in North America, Europe and Australia. By contrast, it is an important cause of severe CAP associated with bacteremia in South Africa and Taiwan. Sixty-seven percent (33/49) of patients with CAP were due to hvKP strains and 94% of these affected individuals were younger patients with no underlying disease. A more recent study that assessed all cases from 2001 to 2008 reported that bacteremic hvKP CAP accounted for 31% (46/148), just slightly more than *S. pneumoniae*. Importantly, when compared with *S. pneumoniae*, hvKP infected patients experienced a higher mortality (55.1% vs. 27.3%) with, not surprisingly, septic shock and respiratory failure being independent predictors of death. In primary CAP due to hvKP, airspace disease, which is frequently bilateral or lobar disease is the usual radiographic pattern. This contrasts with pulmonary infection due to hematogenously mediated metastatic spread (e.g., liver abscess via the hepatic vein) where nodular, usually bilateral densities are seen that are more common in the lower lobes. In both pathophysiologic patterns cavitation (necrosis) can occur.

*Empyema/complicated parapneumonic effusion*. As would be expected in geographic regions with a high incidence of hvKP CAP, *Klebsiella pneumoniae* (characteristics to differentiate cKP from hvKP not always determined) is a leading or the most common cause of empyema. Although the majority of pleural space infections are due to a pneumonia, spread from a contiguous abdominal source (e.g., PLA) or hematogenous seeding from a distant site may occur.

*Endophthalmitis*. This devastating complication of hvKP infection, when first described in 1986, was one of the first hints that something was different with the *K. pneumoniae* isolates responsible (Fig. 2). Endogenous endophthalmitis (EE), which occurs via hematogenous dissemination, is much less common than exogenous endophthalmitis, which results from trauma or surgery. EE due to enteric GNB was an uncommon infection in ambulatory, healthy hosts until the advent of hvKP and may occur as a primary or metastatic infection. Patients with PLA have 0.83–11% risk of developing EE. Painful ocular
swelling, redness and the sudden onset of blurred vision are most common symptoms. On examination, hypopyon and increased intraocular pressure may be seen. Bilateral involvement occurs in 13–25% of patients.\textsuperscript{119,121-123} EE may be the presenting manifestation of hvKP infection, occurring as such in 45% of cases in one report.\textsuperscript{115} Prognosis even with aggressive treatment is dismal, with poor vision and blindness being the rule. Still, early recognition and treatment for one eye may prevent a worse outcome from occult infection in the other.\textsuperscript{8,119,121,124} This is attributable to the virulence of hvKP and delayed recognition.

Central nervous system disease. Meningitis. The face of community-acquired meningitis has changed in Southeast Asia over the past 30 y\textsuperscript{125} and is at risk of changing beyond the Asian Pacific Rim as hvKP spreads across the globe. Alarmingly, \textit{K. pneumoniae} has become a major cause of community-acquired meningitis in Asia in the absence of neurosurgery or head trauma;\textsuperscript{125-128} a remarkable infection in healthy, ambulatory adults and almost unheard of in the West\textsuperscript{129} until recently.\textsuperscript{13} Although not all of the responsible strains were characterized and established to be hvKP in the cited reports, a number have been.\textsuperscript{14,20,25,42} These cases, combined with the coincidental spread of hvKP through the Asian Pacific Rim, strongly implicate hvKP as being responsible. Meningitis may be the presenting primary infection or secondary to metastatic spread.\textsuperscript{130}

Other CNS infections. In addition to meningitis, alone or in combination, brain abscess, subdural empyema, and epidural abscess have been described.\textsuperscript{131-133}

Musculoskeletal and soft tissue infection. hvKP has become a common cause of necrotizing fasciitis in Taiwan, causing a similar number of cases as group A streptococcus and having a higher mortality (47% vs. 19%).\textsuperscript{75} It also has been described outside of the Asian Pacific Rim.\textsuperscript{21,209} Psoas abscess,\textsuperscript{7,109,134} deep neck infection,\textsuperscript{11,16,17} osteomyelitis\textsuperscript{7,13,109} and septic arthritis\textsuperscript{7,109} have all been described and may be the presenting site of infection. Recurrent soft-tissue infection at different sites has also been described.\textsuperscript{109} Discitis, vertebral osteomyelitis, and paraspinal abscess may occur in conjunction with an epidural abscess as described above.\textsuperscript{132,133}

Urinary tract. Although the ascending route is the most common mechanism for the development of urinary tract infection (UTI) in general as well as for cKP, this may not be the case for hvKP. Although the urinary tract is cited as a source of hvKP bacteremia,\textsuperscript{42} we have been unable to identify any reports on ascending UTI, despite the plausibility of this route with hvKP being an intestinal colonizer. Bacteremic spread to the kidneys, perinephric region, and prostate resulting in abscess formation are well described.\textsuperscript{7,8} Although additional data are needed, perhaps we should consider the presence of hvKP in the urine as a potential marker for bacteremia, similar to \textit{S. aureus}.\textsuperscript{135}

Miscellaneous. Nearly every site in the body has been infected with hvKP. A few less common sites include orbital cellulitis,\textsuperscript{136} mediastinitis\textsuperscript{61} and a Bartholin abscess.\textsuperscript{137}

Bacteremia/endovascular. Bacteremia is an extremely common complication of hvKP site-specific infection. In one report in which bacteremic isolates were established to be hvKP strains by a positive “string test,” infected foci included PLA (32.5%), pneumonia (20.5%), urinary tract (10.8%), biliary tract (8.4%), soft-tissue (6%), meningitis (4.8%), empyema (4.8%), spontaneous bacterial peritonitis (2.4%) and endophthalmitis (1.2%).\textsuperscript{42} Primary bacteremia was observed in 22.9% of cases. Interestingly, 14.8% of hospital-acquired \textit{K. pneumoniae} bacteremias were due to hvKP strains.

A case of native valve endocarditis\textsuperscript{38} due to hvKP as well as a case of Lemierre syndrome (septic internal jugular venous thrombophlebitis),\textsuperscript{139} likely due to hvKP, have also been reported.

Treatment of hvKP Infection

Compounding an already challenging clinical situation is the recent propensity for cKP to become multi-, extreme or pan-drug-resistant, including the acquisition of extended-spectrum β-lactamases and carbapenemases, such as the recently described NDM-1.\textsuperscript{5,140} To date, most strains of hvKP have been very susceptible to antimicrobials except ampicillin.\textsuperscript{26,43} Nonetheless, some cases of infection due to MDR-hvKP have already been described,\textsuperscript{75,142} and as expected, outcome is worse with inappropriate treatment.\textsuperscript{100} As a result, management of infections due to hvKP will become extremely challenging, and morbidity and mortality rates will further increase. The confluence of hypervirulence and extreme or pan-drug resistance in hvKP has the potential to create a "post-antibiotic" scenario; similar to what was feared with methicillin-resistant \textit{S. aureus}, which was never realized. hvKP strains may be the next “superbugs” in waiting.

A basic tenet of infectious diseases is the need to drain abscesses/closed space infections for optimal outcome. Since hvKP strains often cause abscesses, source control is a major aspect of the overall management plan. In the present era of interventional radiology and percutaneous drainage of accessible abscesses, open surgical drainage occurs uncommonly. However, the physical property of hypermucoviscosity possessed by hvKP may make catheter drainage challenging. Although we are unaware of any studies that have addressed this issue, open drainage may need to be considered in select cases.

A Large Number of Knowledge Gaps on hvKP Exist

Enhancing our understanding of this highly virulent pathogen is critical, but a large number of knowledge gaps remain. Perhaps first and foremost is a lack of awareness of hvKP and its clinical manifestations, particularly among physicians in Western countries. The epidemiology of hvKP strains has had some recent advances, yet overall it remains poorly understood. An increased understanding of reservoirs, acquisition, and the route(s) of entry may enable prevention of disease. Are all hvKP strains “string-test” positive? The development of a more objective diagnostic test that can be employed by the clinical microbiology laboratory to reliably identify hvKP strains is requisite. This will enhance our ability to perform more comprehensive epidemiologic studies. It will also enable the full spectrum of infectious syndromes and the incidence of infection, especially outside of the Asian Pacific Rim to be defined. It will also assist the clinicians in disease management. The knowledge that an hvKP strain is causing infection should prompt a search for concomitant or subsequent
metastatic sites of infection, which may require drainage or a site-driven modification of the antimicrobial regimen. It is critical to be particularly vigilant for endophthalmitis and CNS infection. Anecdotal data suggests that hvKP infection or relapse may develop months to years after treatment has been completed; thereby long-term follow-up will be necessary. Lastly, a more objective diagnostic test will enable studies on whether the nature and duration of therapy for hvKP infection should be different from cKP and other enteric GNB. It will be important to identify traits, other than the ability of hvKP strains to more efficiently acquire iron, that are responsible for their enhanced virulence compared with cKP strains. The hypermucoviscous phenotype may also qualify, but additional studies are needed. A critical and fascinating question is why do hvKP strains have the propensity for metastatic spread. This is a highly unusual phenotype may also qualify, but additional studies are needed.

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