Hypervirulent *Klebsiella pneumoniae*

Thomas A. Russo,[a,b,c,d] **Candace M. Marr**[a,e]

[a]Department of Medicine, University at Buffalo-State University of New York, Buffalo, New York, USA
[b]Department of Microbiology and Immunology, University at Buffalo-State University of New York, Buffalo, New York, USA
[c]The Witebsky Center for Microbial Pathogenesis, University at Buffalo-State University of New York, Buffalo, New York, USA
[d]The Veterans Administration Western New York Healthcare System, Buffalo, New York, USA
[e]Erie County Medical Center, Buffalo, New York, USA

(continued)

SUMMARY Hypervirulent *K. pneumoniae* (hvKp) is an evolving pathotype that is more virulent than classical *K. pneumoniae* (cKp). hvKp usually infects individuals from the community, who are often healthy. Infections are more common in the Asian Pacific Rim but are occurring globally. hvKp infection frequently presents at multiple sites or subsequently metastatically spreads, often requiring source control. hvKp has an increased ability to cause central nervous system infection and endophthalmitis, which require rapid recognition and site-specific treatment. The genetic factors that confer hvKp's hypervirulent phenotype are present on a large virulence plasmid and perhaps integrative conjugal elements. Increased capsule production and aerobactin production are established hvKp-specific virulence factors. Similar to cKp, hvKp strains are becoming increasingly resistant to antimicrobials via acquisition of mobile elements carrying resistance determinants, and new hvKp strains emerge when extensively drug-resistant cKp strains acquire hvKp-specific virulence determinants, resulting in nosocomial infection. Presently, clinical laboratories are unable to differentiate cKp from hvKp, but recently, several biomarkers and quantitative siderophore production have been shown to accurately predict hvKp strains, which could lead to the development of a diagnostic test for use by clinical laboratories for optimal patient care and for use in epidemiologic surveillance and research studies.

KEYWORDS Friedlander's bacillus, *Klebsiella pneumoniae*, abscess, aerobactin, colonization, hypervirulent, infection control, metastatic spread, virulence determinants, virulence plasmid

INTRODUCTION

Klebsiella pneumoniae is an increasingly important bacterial pathogen that is capable of causing severe organ and life-threatening disease. A critical trait of *K. pneumoniae* that has enabled its ongoing evolution is the ability to acquire new genetic material. As a result, two pathotypes termed classical *K. pneumoniae* (cKp) and hypervirulent *K. pneumoniae* (hvKp) are presently circulating, each of which presents unique challenges for the clinician (1, 2). Both pathotypes are global pathogens, but the

TABLE 1 Demographic and clinical features that can assist in differentiating infection due to hypervirulent and classical *K. pneumoniae* strains[a]

Parameter	Finding for pathotype	
	hvKp	cKp
Location for the development of infection	More commonly the community[b]	More commonly a health care setting
Host	All ages; often otherwise healthy	Older, with some form of compromise
Ethnic background	Often Asian, Pacific Islander, Hispanic	No ethnic predilection
Hepatic abscess	Usually occurs in the absence of biliary disease	Usually occurs in the presence of biliary disease
Number of sites of infection	Often multiple	Usually single
Unusual infectious syndromes for *K. pneumoniae*	Endophthalmitis, meningitis,[c] brain abscess, necrotizing fasciitis, splenic abscess, epidural abscess	None
Copathogens at the site of infection	Rare, usually monomicrobial	Not uncommon, especially with abdominal, soft tissue, or urinary catheter infection

[a]These are general features; exceptions occur. Definitive diagnosis requires identification of specific biomarkers, but assays for these markers are not presently FDA approved or routinely performed by clinical microbiology laboratories.
[b]With the advent of XDR cKp strains acquiring the hvKp virulence plasmid and thereby the hypervirulent phenotype, an increasing number of hvKp infections are developing in the health care setting; to date, this has been primarily reported from China.
[c]hvKp meningitis occurs in patients with a competent meningeal barrier (as opposed to those with an incompetent meningeal barrier, e.g., neonates or those who have undergone neurosurgery or trauma).

incidence of infections due to hvKp has been steadily increasing over the last 3 decades in countries that comprise the Asian Pacific Rim (3–7). By contrast, to date, cKp has been the dominant offending agent in Western countries, but infections due to hvKp are being increasingly recognized outside Asia (8, 9).

Clinicians are all too familiar with cKp, which most commonly is an opportunistic pathogen causing infections primarily in the health care setting in hosts with comorbidities, who are immunocompromised, or who have existing barrier breakdown (e.g., intravascular devices, endotracheal tube, or surgical wound). This pathotype has demonstrated the ability to acquire an increasing number of elements that confer antimicrobial resistance, which has earned it a place among the ESKAPE (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* species) pathogens (10). The most problematic are genes that encode extended-spectrum β-lactamases (ESBLs) (e.g., CTX-M, SHV, and TEM) that hydrolyze third-generation cephalosporins, aztreonam, and (in some instances) fourth-generation cephalosporins, and genes that encode carbapenemases (11). It is logical that extensively drug-resistant (XDR) cKp strains are able to thrive in the health care setting where significant antimicrobial use gives them a selective advantage. A major challenge with infections due to XDR cKp involves difficulties with treatment. XDR cKp has been responsible for lethal hospital outbreaks (12), and a woman infected with a pan-drug-resistant (PDR) cKp strain died from a lack of treatment options (13), a harbinger of the feared postantibiotic era.

The characteristics of hvKp and its differences from cKp are less well appreciated (Table 1). hvKp is best described as a virulent pathogen (14). The majority of reported infections due to hvKp have been acquired in the community. Features that are highly suggestive of hvKp infection are its ability to infect healthy individuals of any age and the propensity of infected patients to present with multiple sites of infection and/or develop subsequent metastatic spread, an unusual occurrence for other members of the family *Enterobacteriaceae*. The hallmark clinical syndrome is a hepatic abscess in the absence of biliary tract disease. However, hvKp can infect nearly every site of the body. A few examples of these infectious syndromes include nonhepatic abscesses, pneumonia, necrotizing fasciitis, endophthalmitis, and meningitis. A trait that was initially believed to be sensitive and specific for hvKp strains was a hypermucoviscous phenotype, which is defined by a positive string test (15). This has since been shown not be the case; not all hvKp strains are hypermucoviscous, and some cKp strains possess this characteristic (16, 17). This misperception has created some confusion in the literature

TABLE 2 Major knowledge gaps that exist for hypervirulent *K. pneumoniae*

Area of interest	Knowledge gap
Epidemiology	Incidence of infection in various countries
	Prevalence of antimicrobial resistance
	Incidence of health care-associated infections
	Mechanism of acquisition
Pathogenesis	Mechanism of entry
	Delineation of hvKp-specific virulence genes and mechanism of action
	Mechanism of metastatic spread
	Factors responsible for tissue damage
	Carcinogenic potential
Host susceptibility	Ethnic/genetic predisposition
Treatment	Optimal approach for source control
	Treatment duration
	Management of endophthamitis, especially for XDR strains
	Role of adjunct therapy
Infection control	Is there a benefit for implementing infection control measures when a hospitalized patient is infected with an hvKp antimicrobial-sensitive strain on a ward or an ICU?
	Is there a benefit for implementing infection control measures when a hospitalized patient is infected with an hvKp antimicrobial-sensitive strain to protect selected patient groups (e.g., those of certain ethnic backgrounds, such as Asian, or immunocompromised hosts)?
	Is there a benefit of prophylaxis for close contacts?

when this phenotype was used alone to define an hvKp strain. Likewise, chromosomal genes that encode the aerobactin (*iutA*) receptor or *iroE* is present in a number of cKp strains and alone cannot be used to define an isolate as being hvKp, nor can the presence of the K1 or K2 capsule type. However, hvKp has acquired a number of virulence genes present on large virulence plasmids (e.g., pK2044 and pLVPK) and within integrated chromosomal elements (ICE) that confer its hypervirulent phenotype. Biomarkers present on the virulence plasmid have been shown to most accurately differentiate hvKp from cKp strains (17).

Although initial isolates of hvKp were antimicrobial sensitive, management challenges included rapid initiation of therapy to prevent subsequent spread, detection of occult abscess to enable source control, and appropriate site-specific therapy (e.g., meningitis, endophthalmitis, and prostatic abscess). Most recently, clinicians have been faced with an even greater challenge, the confluence of antimicrobial resistance determinants possessed by cKp and the virulence factors possessed by hvKp on the same or coexisting plasmids. The result is the evolution of multidrug-resistant (MDR) and XDR hvKp. This has occurred by two mechanisms. The first was via hvKp strains gaining antimicrobial resistance genes by acquisition of resistance plasmids (18, 19) or by the insertion of resistance elements into hvKp's virulence plasmid (20, 21). The converse has also occurred; XDR cKp has acquired a modified hvKp virulence plasmid (22). This scenario caused a lethal intensive care unit (ICU) outbreak. A hypervirulent XDR strain is approaching the worst-case scenario. To date, such strains have been described only in China; however, the prospect of XDR hvKp undergoing wider dissemination is concerning.

The need to increase awareness of hvKp and its evolutionary trajectory is paramount. Significant knowledge gaps exist on its epidemiology, pathogenesis, host susceptibility, optimal treatment, and appropriate infection control measures (Table 2). Further, the existence of hvKp strains that evolved when XDR cKp strains acquired the hvKp virulence plasmid has blurred the traditional epidemiologic differences between these pathotypes, namely, hvKp infection being community acquired and antimicrobial sensitive and cKp infection being health care associated and commonly more antimicrobial resistant. This recently recognized development will create new challenges for

the clinician until the time when the clinical microbiology laboratories have the capability to routinely identify hvKp isolates. The goal of this report is to summarize our present understanding of this dangerous and evolving pathogen. For the purposes of this review, we focus on the literature in which hvKp strains were defined by the presence of more predictive biomarkers (e.g., *rmpA* and *iucA* to *-D*) (17), the presence of an hvKp virulence plasmid, the demonstration of *in vivo* virulence in an appropriate model, or a highly suggestive clinical scenario (e.g., invasive infection in an otherwise healthly host from the community, especially with multiple sites of infection or metastatic spread).

HISTORY AND EVOLUTION

A genomic analysis of 328 *K. pneumoniae* isolates supports the division of *K. pneumoniae* into three distinct species, *K. pneumoniae*, *K. quasipneumoniae*, and *K. variicola* (23, 24). Human infection has been reported for all of these species, and *K. quasipneumoniae* and *K. variicola* are frequently misidentified as *K. pneumoniae* by clinical microbiology laboratories (25, 26). *K. pneumoniae* is responsible for the majority of human infections (24, 25, 27), and hvKp strains belong to *K. pneumoniae* (28). Although hypermucoviscous strains of *K. quasipneumoniae* and *K. variicola* have been described (29, 30), these isolates do not have the genomic content that predicts a hypervirulent phenotype; however, it seems likely that this event will occur at some point or has already occurred and is unrecognized due to the difficulties for clinical microbiology laboratories to identify *K. quasipneumoniae* and *K. variicola*. Nonetheless, the focus of this review is on hvKp; therefore, *K. quasipneumoniae* and *K. variicola* will not be further discussed.

The Emergence of Present-Day hvKp

The first clinical report that brought hvKp to the forefront was a 1986 publication by Liu et al., who reported 7 cases of invasive *K. pneumoniae* infection in individuals from the community who presented with hepatic abscess in the absence of biliary tract disease and septic endophthalmitis (31). Some individuals had additional infectious syndromes, such as meningitis, pneumonia, and prostatic abscess. Several features of these patients were distinctive and characteristic for hvKp. First, those infected were healthy members of the community, although 4/7 were diabetic. Second at presentation, patients either had multiple sites of infection or had experienced subsequent metastatic spread. At that time most infections due to *K. pneumoniae* were occurring the health care environment, and unlike the case for selected Gram-positive pathogens (e.g., *Staphylococcus aureus*), it was unusual for infections due to *Enterobacteriaceae* to involve multiple sites or undergo metastatic spread. However, the moniker of hvKp was not yet assigned to these strains.

Interestingly, a 1986 nonclinical report by Nassif and Sansonetti described seven strains of *K. pneumoniae* (K1 and K2 serotypes) that were highly virulent in mice as demonstrated by a 50% lethal dose (LD_{50}) of $<10^3$ CFU (32). A more detailed analysis of 4 of these strains demonstrated the presence of a large (180-kb) plasmid that contained genes for the production of aerobactin and its cognate receptor. This plasmid was absent in avirulent strains as defined by an LD_{50} of $>10^6$ CFU. Subsequent studies demonstrated that this plasmid also contained genes that conferred a hypermucoid phenotype, which proved to be mediated by the capsular polysaccharide regulator RmpA (33, 34). Details on the clinical syndromes caused by these strains were not reported. However, based on our present understanding of genes and phenotypes that define hvKp (17), these isolates would be predicted to be hvKp.

In 2004, Fang et al. reported that *K. pneumoniae* strains that caused hepatic abscesses in patients from Taiwan were more likely to possess a hypermucoviscous phenotype than noninvasive strains (15). Hypermucoviscosity was defined by the formation of viscous strings >5 mm in length when a loop was used to stretch the colony on agar plate, also known as a positive string test (15). A subsequent report further supported this association (35). As a result, for a period hvKp strains were

sometimes designated in the literature as hypermucoviscous. However, eventually the designation hypervirulent *K. pneumoniae* was more commonly utilized (36–39). The report by Pomakova et al. also designated the pathotype responsible for the majority of health care associated infections as classical *K. pneumoniae* (39). This distinction between cKp and hvKp frames the genotypic and phenotypic differences between these pathotypes. As discussed, the use of the term hypermucoviscous has proven to be problematic, since this phenotype is not optimally sensitive or specific for hvKp strains: not all hvKp strains are hypermucoviscous, and some cKp demonstrate this phenotype (16, 17). Some studies used solely a positive string test to define hvKp strains, which has resulted in some strains of *K. pneumoniae* being misclassified as hvKp and consequently created some confusion in the literature.

Friedlander's Bacillus: Likely an hvKp Pathotype or Variant

The clinical syndrome Friedlander's pneumonia was eventually recognized to be due to *K. pneumoniae* (40–42). This entity and the offending agent were first described in 1882 by Friedlander (43), hence the initial designation as Friedlander's bacillus (*Bacillus friedlanderi*). A subsequent and now antiquated designation was *Bacillus mucosus capsulatus* (44). The acute syndrome has a number of distinctive clinical features which are consistent with some, if not all, of the offending strains being either hvKp or at least *K. pneumoniae* isolates that had acquired a portion of the hvKp virulence factor repertoire.

In the preantibiotic era, Friedlander's pneumonia had a mortality rate of approximately 80%, which was 3- to 4-fold greater than pneumonia caused by *Streptococcus pneumoniae* (45, 46). Presentations were usually acute, and death could ensue within 24 to 48 h and on average occurred 5.5 days after presentation, compared to 9 days for pneumonia due to *S. pneumoniae* (46, 47). Bacteremia was noted, on average, in 60% of cases (45, 46). Radiographically, findings were indistinguishable from pneumococcal pneumonia, with bronchopneumonic, lobular, and lobar manifestations observed, which were often multifocal. However, in contrast to pneumococcal pneumonia, tissue destruction leading to overt cavitation and/or necrosis observed on histology was far more likely to develop (48). Although not diagnostic, a bulging fissure and/or cavitation increased the likelihood that the pneumonia was due to Friedlander's bacillus (40). After cavitation, empyema was the next most common pulmonary complication; purulent pericarditis also could develop (48, 49). If the patient survived the acute episode, progression to chronic cavitary disease that mimicked tuberculosis and persisted for months could develop (50). Nearly all cases of Friedlander's pneumonia occurred in ambulatory patients. Although chronic alcoholism was touted as a critical risk factor, many patients were healthy hosts (45, 48, 49, 51). Perhaps the increased risk of infection in alcoholics was due not solely to compromised host defense factors but also to the increased likelihood of macroaspiration. Males were more commonly infected, and although infections were reported in all age groups, the fifth and sixth decades of life were most common (47–49, 52). Likewise, in most contemporaneous studies of hvKp, men are more commonly infected than women (9, 53, 54). Mercifully, Friedlander's pneumonia accounted for only 0.5 to 5% of community-acquired pneumonias (42, 48, 49, 52).

Friedlander's bacillus has also been implicated in a variety of extrapulmonary infections in the presence or absence of pneumonia. These include renal abscess, hepatic abscess, osteomyelitis, cavernous sinus thrombosis, abscess of the jugular bulb, meningitis, brain abscess, splenic infection, spontaneous bacterial peritonitis, and soft tissue abscesses in the neck and arm (47–49, 55–61). Similar to the case with individuals infected with hvKp, multiple sites of infection were noted in a number of patients. Extrapulmonary sites of infection were undoubtedly underestimated in an era in which advanced imaging modalities were nonexistent. Interestingly, septic endophthalmitis was not noted, which could be easily diagnosed clinically.

Additional features suggested that Friedlander's bacillus was most consistent with hvKp isolates. A phenotypic feature of many hvKp strains is hypermucoviscosity, i.e., an

inoculation loop can generate a viscous string >5 mm in length from the bacterial colony; this trait is due to increased capsular polysaccharide production mediated by RmpA and/or RmpA2 (62). Although hypermucoviscosity is not pathognomonic for hvKp since this phenotype also can be observed in cKp strains (17), it is suggestive. Numerous reports remark on Friedlander's bacillus possessing this characteristic. In cases of meningitis the spinal fluid is often referred to being "gelatinous" and "the drawing out of a filament from the stylet of the spinal needle" (56). Likewise, "[o]n agar plates the colonies appear...as round, raised, slimy, gray colonies, which string out when drawn up with a wire loop" (48). Sputum was commonly described as "tenacious" or gelatinous (41, 49), and cut lung sections were described as "covered by a characteristic viscid, abundant, mucinous exudate which sticks to the knife" (48). Another paper states that "[t]he name *Bacillus mucosus capsulatus* (Friedlander's bacillus) draws attention to the two most prominent and distinctive features of the organism, namely, the marked degree of capsular development and its power of producing large amounts of mucoid material in its growth both on artificial media and in the human body" (44). A serotyping schema was developed for Friedlander's bacillus with types A (equates to K1), B (equates to K2), and C (equates to *K. pneumoniae* rhinoscleroma), and group X (other) (63, 64). The majority of strains were types A and B (45, 46, 48, 49, 57), with type A being most common, similar to the observation for hvKp strains (2, 17, 65), although cKp strains also can produce K1 and K2 capsules (66).

In one series that reviewed cases of meningitis due to *K. pneumoniae*, patients were more likely to have diabetes mellitus (56), also similar to what has been observed in most studies on hvKp-infected individuals (67–75). Additionally, in a recent study authored by Lam et al., hvKp sequence type 23 (ST23) was calculated to have evolved around 1878, lending further credibility to Friedlander's bacillus being the first description of an hvKp strain (76).

Lastly, in experimental reports studying Friedlander's bacillus, "[s]ubcutaneous or intraperitoneal injections of 1:1 million or 1: 1 billion dilutions of young cultures often kill mice in 1–3 days" (49); likewise, another report presented data that 10^{-5}, 10^{-6}, and 10^{-7} dilutions of a culture grown "4-6 h" resulted in 100% mortality of mice challenged intraperitoneally with 0.5 ml of diluted bacteria over 15 to 48 h (63). Although some guesswork is required, if one assumes a "young culture" and a "4-6 h" culture maximally consist of 1×10^9 CFU/ml, then lethal doses would be in the range of 1.0 to 5,000 CFU. Another study reported that 9.0×10^4 CFU killed mice within 18 h, "a result not obtainable with coliform organisms or *A. aerogenes*" (59). A lethal effect from these low challenge inocula would clearly identify such strains as hvKp and not cKp (17).

Clinical challenges with Friedlander's pneumonia included early recognition and appropriate treatment. *S. pneumoniae* was responsible for the overwhelming majority of cases of pneumonia, and at that time treatment with penicillin was efficacious but was ineffective for Friedlander's bacillus, for which tetracyclines and/or streptomycin were the preferred antimicrobials. Given the fulminant course and high mortality seen with untreated Friedlander's pneumonia, a lack of recognition was problematic. A similar scenario occurred with meningitis due to *Neisseria meningitidis* versus Friedlander's bacillus (58). This scenario echoes a different form of diagnostic issues that occur with hvKp today: *K. pneumoniae* can be readily identified, but differentiating cKp from kvKp is more challenging. As discussed below, hvKp presents different management challenges and if this pathotype is unrecognized, the consequences could be significant, especially for XDR hvKp strains (22).

Taken together, the described features of infection due to Friedlander's bacillus, namely, the ability to cause life-threatening disease in healthy patients from the community, multiple sites of infection or subsequent metastatic spread (including meningitis and brain abscess), hypermucoviscosity, and capsule type, as well as experimental mouse data are consistent with at least some of these strains being hvKp. Of course, it would be interesting and informative if properly stored isolates of Friedlander's bacillus were available for sequencing and *in vivo* assessment in appropriate infection models. These data would also generate insights into the evolution of
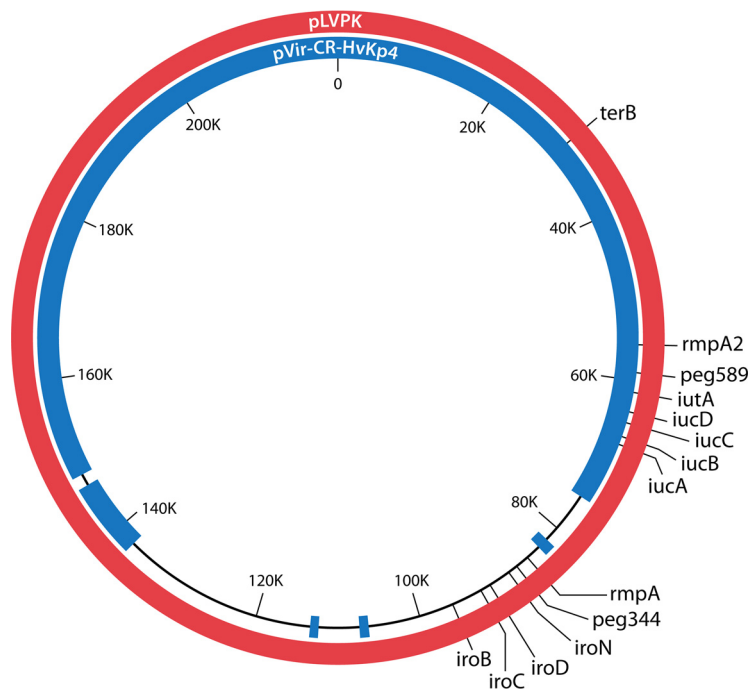
FIG 1 Schematic representation of the hvKp virulence plasmid pLVPK (red circle, 219,385 bp) (83) and pVir-CR-HvKp4 (blue circle, 178,154 bp) (22). The locations of various virulence genes and/or biomarkers are marked.

present-day hvKp strains. For example, was a virulence factor(s) which enables present-day hvKp to cause endophthalmitis absent from the Friedlander's bacillus? Did Friedlander's bacillus have a greater tropism for the lung than hvKp, or were nonpulmonary sites underrecognized due to the lack of modern-day imaging technologies? Further, it is intriguing to speculate that cKp evolved from hvKp by loss of the virulence plasmid and perhaps other genetic material once introduced into the health care environment.

hvKp Viewed through the Genomic Lens

Origins of hvKp. Recent molecular epidemiologic studies have shed additional light on the origins of hvKp. Lam et al. performed a comparative analysis of 97 genomes from clonal group 23 (CG23) strains of both human and equine origin (76). CG23 is strongly associated with the K1 capsule and severe, invasive clinical disease that occurs with hvKp infection (38, 66, 77, 78). Ninety-four of the 97 genomes contained virulence plasmid sequence and the plasmid-associated gene loci *iro* (salmochelin biosynthesis), *iuc* (aerobactin synthesis), *rmpA* (regulator of mucoid phenotype), and *rmpA2*, all of which are highly predictive of an hvKp strain (17, 76). These data identified several sublineages, with CG23-I being dominant, accounting for 81 of 97 isolates. Equine isolates were nested within CG23-I. Estimates of the dates for the most recent common ancestors for the entire CG23 population, the CG23-I sublineage, and the equine strains were 1878, 1928, and 1972, respectively. Therefore, these data, which are representative of 37 to 64% of hvKP isolates (17, 79–82), support the concept that hvKp strains have been circulating as long as the 1800s. They also support the notion that Friedlander's bacillus could have been an hvKp strain or perhaps an evolutionary variant.

hvKp virulence plasmid. Initial sequencing of hvKp strains identified the presence of the large, highly similar virulence plasmids pK2044 (224,152 bp) and pLVPK (219,385 bp) (83, 84) (Fig. 1). The loss of this plasmid significantly decreased virulence (32, 34, 85). Further, the best-characterized virulence factors with experimental support for conferring the hypervirulent phenotype are encoded by genes present on these plasmids, which include *iuc* (biosynthetic genes for the siderophore aerobactin), *peg-344* (a metabolic transporter of unknown function), and *rmpA* and *rmpA2* (regulators

that increase capsule production) (32, 34, 62, 85–88) (Fig. 1). Lery et al. described the presence of two virulence plasmids in the hvKp strain Kp52.145 (also known as B5055) (89). A 121-kb plasmid contained *iuc*, *iro*, and *rmpA*, whereas the second, 90-kb plasmid contained *rmpA2*. Ye et al. studied 40 hvKp strains isolated from patients with community-acquired hepatic abscess, all of which possessed *iuc*, *iro*, *rmpA*, and *rmpA2* (78). Plasmid profiles of these 40 strains demonstrated that 35 of 40 strains possessed at least one plasmid. Nineteen strains contained a single plasmid similar in size to pK2044 (approximately 220 kb). Twelve strains possessed a single plasmid with sizes ranging from 140 to 250 kb, and four strains retained 2 or 3 plasmids. Interestingly, five strains had no detectable plasmid, but *iuc*, *iro*, *rmpA*, and *rmpA2* were detectable by PCR, suggesting chromosomal integration. Struve et al. determined that all 30 hvKp strains isolated from cases of liver abscess or community-acquired pneumonia harbored pLVPK-like plasmids that contained *iuc*, *iro*, *rmpA*, and *rmpA2*, but some plasmids had undergone deletions in other regions (90). Likewise, in the CG23 genomes analyzed by Lam et al., pK2044-like virulence plasmids were detected in 94 strains (which included 27 CG23 strains sequenced and analyzed by Struve (76, 90). *iro* was present in all 94 plasmids, and *iuc*, *rmpA*, and *rmpA2* were variably present in 92 plasmids.

More recently, cKp strains have been described that have acquired hvKp virulence plasmids and thus have a hypervirulent phenotype. The pLVPK-like virulence plasmid pVir-CR-hvKP4 (178,154 bp) was acquired by the ST11 cKp strain *K. pneumoniae* 4, which showed an enhanced virulence phenotype (22). However, pVir-CR-hvKP4 had a 41,231-bp deletion compared to pLVPK (Fig. 1), which included the virulence genes *rmpA* and *iro*; the *iuc* genes and *rmpA*2 were retained, and the presence of *rmpA2* appeared to confer a hypermucoviscous phenotype. Presently, the effect, if any, of this deletion on the hypervirulent phenotype is unclear. Unrecognized virulence genes may have been lost. But, the loss of *iro*, which encodes salmochelin, may be inconsequential for systemic infection based on data from a mouse subcutaneous-challenge model that demonstrated that salmochelin did not contribute to virulence (87). Further, a redundancy may exist for RmpA and RmpA2 since each can enhance capsule production (22, 62, 87). Aerobactin production appears to be less dispensable (86, 87). Therefore, minimally the ability to produce aerobactin and either RmpA or RmpA2 is likely needed to confer some degree of hypervirulence. Another report from Taiwan described the ST11 cKp strain TVGHCRE225, which harbored pVir (297,984 bp), a hybrid hvKp virulence plasmid (91). Approximately 38% of pVir possessed 49% and 47% coverage with pK2044 and pLVPK at 99% identity; the remaining portion of pVir possessed 61% coverage with pPMK-NDM, a resistance plasmid present in an NDM-producing *K. pneumoniae* strain, at 99% identity. Interestingly, although *iroBCDN*, *iucABCDiutA*, *rmpA*, and *rmpA2* were present in pVir, TVGHCRE225 pVir was not maximally virulent in a mouse systemic infection model, suggesting that the absent portions of pK2044 and pLVPK contained important and unrecognized virulence determinants.

Integrative and conjugative elements. Not surprisingly given *K. pneumoniae*'s receptivity to horizontal gene transfer and recombination, ICE (also known as genomic or pathogenicity islands or mobile genetic elements) are commonly observed in both cKp and hvKp strains. Integration usually occurs at tRNA sites. In one study, 73% of the *K. pneumoniae* strains had an ICE inserted into one or more of the four asparagine tRNA genes (92). The best-characterized and -studied ICE family, first described by Lin et al., was defined by the presence of biosynthetic genes for the siderophore yersiniabactin (93). This 76-kb ICE (ICE*Kp1*) in the hvKp strain NTUH-K2044 was more prevalent in hvKp strains (38/42) than cKp strains (5/32), suggesting a role in hvKp pathogenesis. In addition to a region homologous to the high-pathogenicity island of *Yersinia* that contained yersiniabactin biosynthetic genes, another region was homologous to the virulence plasmid pK2044 and contained homologues to genes that encoded the synthesis of the siderophore salmochelin (*iro*) and the capsular polysaccharide regulator RmpA. However, subsequent studies demonstrated that ICE*Kp1* was not representative of ICE*Kp* homologues present in the majority of other hvKp strains. Lai et al. described a more widely conserved ICE*Kp* (KPHPI208-GM1 also designated ICE*Kp10*)

that consisted of 8 genomic modules (94). The yersiniabactin encoding genes were retained, but the *rmpA* homologue and the *iro* genes were absent (94). In addition, a 50-kb region that encoded the genotoxin colibactin and the bacteriocin microcin E492 was present (94). Struve et al. reported that ICE*Kp10* homologues were present in all 27 hvKp CG23 strains studied, although deletions of genes that encoded colibactin and E492 were present in 4 strains and genes that encoded yersiniabactin were deleted in 3 of those 4 strains (90). In the 3 non-CG23 hvKp strains studied, ICE*Kp10* was poorly conserved, with 2 of 3 strains possessing only genes that encoded yersiniabactin (90). This body of work has been extended by Lam et al. (76, 95). Their comparative analysis of 97 CG23 genomes demonstrated that the 81 members of sublineage CG23-I had acquired ICE*Kp10*, which contained genes that encode yersiniabactin and colibactin. This event was estimated to occur in 1928, which was followed by global population expansion of CG23-I.

With the availability and analysis of an increasing body of sequence data, it is clear that ICE*Kp* acquisition within the general *K. pneumoniae* population of both cKp and hvKp strains is robust and that many variants exist; 14 have been reported to date (95). Further, the acquisition of other ICE or genomic islands is the rule (89, 92). However, the acquisition and/or maintenance of these elements may not always be beneficial, depending on the strain and environment, as evidenced by the presence of various gene disruptions or module deletions in ICE*Kp* variants (95). Selective pressures are likely site and strain specific. A pathogenic role for yersiniabactin in cKp has experimental support (96). But presently, a role for yersiniabactin in hvKp infection is less clear (87). It is proposed that acquisition of colibactin was the critical event for the increase in hvKp strains within the CG23-I clade (76). Potential mechanisms include some combination of colibactin mediating enhanced colonization, mucosal invasion, and/or dissemination (97). Further, additional factors present on ICE*Kp* or other genomic islands may prove to be important in various settings. ICE*Kp* does appear to be *K. pneumoniae* specific, which suggests an important species-specific evolutionary role (95). Further, the acquisition of ICE*Kp10* and subsequent expansion of CG23-I support an important role for factors encoded by this element in the biology of hvKp CG23-I. Future studies will hopefully further clarify the relative importance of specific ICE-encoded factors for hvKp compared to cKp and their role for survival in environmental niches, mucosal colonization, and infection.

Molecular definition of hvKp. Analyses of CG and ST, which is based on core genes (98), and capsule types have been used to define hvKp (99). However, the utilization of these typing modalities to differentiate hvKp from cKp strains is imperfect. The genes used to identify ST and capsule type are present in both hvKp and cKp strains (66). Although selected STs (e.g., ST23, ST65, and ST86) and capsule types (e.g., K1 and K2) are commonly associated with hvKp strains, genes that enable hypervirulence are more broadly distributed across a number of STs and capsule types (24, 65, 66, 79, 80, 100). Further, ST and capsule types commonly associated with hvKp strains may not possess the requisite virulence genes that confer hypervirulence. For example, K1, K2, and K54 capsule types are also expressed by cKp strains (65, 66, 100, 101). In addition, CG23 strains may not possess virulence plasmid sequences or the associated virulence genes (e.g., *iuc*, *rmpA*, and *rmpA2*) (76). Lastly, as described above (hvKp virulence plasmid), an extensively drug-resistant ST11 cKp strain that was endemic in China acquired a 170-kb pLVPK-like virulence plasmid. The hypervirulent phenotype conferred by this genetic event resulted in a lethal outbreak (22). These variations are likely due to the ability of *K. pneumoniae* to undergo a significant degree of horizontal gene transfer and recombination, including genes that encode capsule types (24, 66, 76, 90, 100–102). Taken together, these data support the concept that hvKp is best defined by its virulence gene repertoire (24, 35, 66, 101).

The delineation of hvKp virulence genes remains incomplete, and it remains unknown which combination of genes are needed for maximal virulence. Genes present on the virulence plasmids (e.g., pK2044 and pLVPK) (83, 84, 90) and within ICE (76, 92, 94, 103) have been implicated by molecular epidemiologic associations (24, 35, 65, 66,

76, 90). To date, virulence genes present in hvKp strains, but not in cKp strains, that have been shown to contribute to virulence *in vitro*, *ex vivo*, and *in vivo* are present on the virulence plasmids (62, 86–88). Factors encoded on ICE are less accurate for defining hvKP since these genomic elements can be present in cKp strains as well (e.g., yersiniabactin) (17) or are present in only a subset of hvKp strains (e.g., colibactin) (94, 103). A recent study demonstrated that *iroB*, *iucA*, *peg-344*, *rmpA*, and *rmpA2* were the most accurate molecular markers for defining hvKp (17), all of which have been shown to present on virulence plasmids. *K. pneumoniae*'s proven propensity for undergoing recombination or deletion of genes under selective pressure supports the concept that the best markers should be critical factors in conferring the hypervirulent phenotype. If such markers are lost, then the phenotype will no longer be hypervirulent. To date, based on experimental data, *iuc*, *rmpA*, and *rmpA2* best fit this role. It appears that the functions of *rmpA* and *rmpA2* may be redundant. If so, *iuc* and/or either *rmpA* or *rmpA2* would be predicted to be the best markers. The study by Gu et al. in which an XDR cKp strain became hypervirulent supports this concept since *iro*, *peg-344*, and *rmpA* were deleted in the relevant plasmid (22). Of course, as more hvKp-specific genes are identified, additional markers may join this list or prove to be even more accurate.

K. pneumoniae and zoonotic infection. *K. pneumoniae* is capable of causing infection in a variety of nonhuman hosts. Lethal outbreaks have been described to occur in sea lion pups from New Zealand (104), in which meningitis was a prominent clinical manifestation, and in juvenile sea lions from California, in which pneumonia, lung abscess, and empyema were the predominant manifestations (105). In the pups, the responsible isolates were hypermucoviscous, ST86, and possessed the K2 capsule type and *rmpA* (104); subsequent sequence data supported 7/9 of these strains as being hvKp based on the presence of *rmpA* and *iucD* (106). In the juveniles, 21/21 strains were hypermucoviscous and possessed the K2 capsule type and *rmpA*. A lethal outbreak was reported in which 7 African green monkeys from a research facility developed multiple abscesses (107). The one strain studied possessed the K2 capsule type and *rmpA*. Nine strains were studied from buffalo and cows that developed mastitis (108). All strains were lethal when BALB/cByl mice were intraperitoneally challenged with 10^2 to 10^6 CFU and 6/9 strains had *rmpA* identified by PCR, again consistent with at least some of these strains being hvKp. Two of 33 *K. pneumoniae* strains isolated from nasal swabs of sick cattle suffering from respiratory disease in China were *rmpA* positive (109). Lam et al. performed a genomic analysis of 15 *K. pneumoniae* K1 strains isolated from horses (76). Compared to human isolates, these strains appeared to be hvKp by virtue of possessing the pK2044 virulence plasmid. Entry of this type of strain into the horse population was inferred to occur via a single event, and the type of strain since has circulated within equine hosts via sexual transmission. There was no evidence of human-to-horse transmission in this study. Other than the equine isolates studied by Lam (76), the evolutionary relationship between zoonotic isolates that appear to be hvKp strains and human hvKp strains awaits further study. Since humans have the potential to interact with these animals directly or indirectly via waste products deposited into the environment, it would not be surprising if at least some of the genetic elements that define hvKp originated from an animal host.

EPIDEMIOLOGY

Acquisition and Colonization May Lead to Infection

K. pneumoniae organisms can be members of normal animal and human microbiotas and/or the microbiotas of various environmental habitats (110, 111). Acquisition of and colonization with *K. pneumoniae* appear to be requisite for, but do not necessarily lead to, infection (112–117). Otherwise healthy individuals from the community are at risk for developing hvKp infection, whereas it is uncommon for cKp infection to develop in this population. Healthy people can be colonized with cKp, but in the absence of some form of host compromise, infection rarely occurs. By contrast, healthy individuals colonized with hvKp are at much greater risk for developing infection. However, the frequency with which infection develops after colonization with hvKp and

the factors that modulate this risk are not well understood. The relative importance of colonization versus that of the quantity of the colonizing hvKp strain, host factors, and degrees of hvKp virulence is an important issue that requires active investigation.

Colonization with Undefined Pathotypes of *K. pneumoniae*

In healthy humans from the community in Western countries, the prevalences of *K. pneumoniae* colonic colonization ranged from 5 to 35% (112, 117, 118). In Asian countries, *K. pneumoniae* colonization rates in stool from health adults were 87.7%, 61.1%, 75%, 58.8%, 57.9%, 18.8%, 52.9%, and 41.3% for Malaysia, Singapore, Taiwan, Hong Kong, China, Japan, Thailand, and Vietnam, respectively (115). Another study from Korea reported a *K. pneumoniae* colonization rate in stool of 21.1% (248/1,175) (113).

In Western countries, 1 to 5% of healthy humans from the community are nasopharyngeally colonized with *K. pneumoniae*. In children <10 years of age from Brazil and Vietnam, 1.4% (17/1,192) and 1.6% had nasopharyngeal colonization with *K. pneumoniae,* respectively (119, 120). By contrast, 7% of Indonesian children (16/243) were colonized with *K. pneumoniae* (121). Nasopharyngeal colonization rates increase with age; in Indonesia 15% of adults (38/253) were found to be colonized with *K. pneumoniae* in the nasopharynx (121) and in Vietnam the overall colonization rate was 14.7% but exceeded 20% in those >40 years of age (120). Increased nasopharyngeal colonization rates were associated with poorer states of sanitation and increased contamination of food and water (121), age, smoking, alcohol use, and living in a rural community (120). In Malaysia, 32% of samples from street food were contaminated with *K. pneumoniae* (122). Interestingly, in a study of community-acquired pneumonia from Indonesia, *K. pneumoniae* was the most common bacterial agent identified, causing 14% of 148 cases; by contrast, *S. pneumoniae* caused 13% of cases (123). Data such as these support the concept that increased colonization has the potential for increasing the incidence of infection.

The dogma is that skin colonization with *K. pneumoniae* is uncommon and transient. However, in one study from the United States, axillary colonization was relatively common, occurring in up to 50% of individuals, and colonization of other dermal sites, albeit uncommon, increases in warmer months (124).

Colonization with hvKp

Obtaining accurate data on hvKp colonization rates of individuals from the community is more challenging since hvKp-specific markers have not always been used to determine their relative proportions compared to cKp. A colonic colonization study of healthy Koreans demonstrated a colonization rate of 4.6% for hvKp (based on less sensitive K1 capsule and ST23 sequence typing) (113). Another report demonstrated colonization rates of 14.1%, 14.9%, 11.3%, 12%, 11.7%, 16.7%, 2.7%, and 0% for healthy individuals from Malaysia, Singapore, Taiwan, Hong Kong, China, Japan, Thailand, and Vietnam, respectively, for putative hvKp strains (based on K1 and K2 capsule types, phenotypes not optimally sensitive or specific) (115). For Australia, 1.3% (1/80) of *K. pneumoniae* isolates from rectal swabs were hvKp strains (28). In a study that performed nasopharygeal cultures on adults seen at an outpatient otorhinolaryngology clinic for sinusitis and rhinitis in Taiwan, 11.5% (39/340) of isolates were *K. pneumoniae* and 77.5% of *K. pneumoniae* isolates tested were predicted to be hvKp based on being *rmpA* positive (125). We were unable to identify data on dermal colonization with hvKp. Despite the lack of optimal data, it is clear that a significant minority of Asians are colonized with hvKp. More data on hvKp colonization rates from Western countries, in which there is a lower incidence of hvKp infection, would be welcomed. These data may generate insights into the relative risk of acquisition versus genetic factors (e.g., ethnic background) for subsequent infection. Likewise, data on skin colonization could be insightful, since this represents a potential source of entry.

A point of concern is that a variety of Gram-negative bacilli, including cKp, emerge as the dominant colonizers of both mucosal and skin surfaces in the health care setting,

particularly in association with antimicrobial use, indwelling devices, severe illness, and extended length of stay (117, 126, 127). Hospitals and long-term-care facilities have been identified as important reservoirs for XDR cKp (128, 129). In these settings, transmission from health care workers to patients, especially with lax hand hygiene, and transmission via instrumentation are important mechanisms that could be minimized via appropriate infection control measures (130, 131). Although this venue was once the realm of cKp, that reality is changing as of late. In part, this is due to XDR cKp strains that acquired the hvKp virulence plasmid, thereby evolving into XDR hvKp strains (22). Additional cases of health care acquisition of hvKp also have been described (132, 133). If hvKp even partially replaces cKp as a colonizer in the health care setting, which will undoubtedly lead to infection in a proportion of these patients (134), then the incidence of hvKp infections, morbidity, mortality, and costs are predicted to increase, given the vulnerability of this patient cohort and the virulence of hvKp, particularly if XDR hvKp is the offending pathogen (135, 136).

Settings for Acquisition and Subsequent Development of Infection

One of the initial defining features of hvKp infection is acquisition in the community (31, 35, 70, 75, 137). The mechanism for acquisition of hvKp within the community is presently undefined, but based on data from cKp and other *Enterobacteriaceae*, some combination of contaminated food or water, person-to-person transmission (e.g., close contacts such as family members or sexual partners), and perhaps zoonotic transmission is possible. Support for food as a possible source comes from a report that identified two probable hvKp strains (ST23, K1, positive string test) that harbored bla_{KPC-2} from cucumber (138).

Although the majority of hvKp infections are community acquired, there are increasing numbers of reports that describe infections developing in health care settings (22, 132, 133). This is due to a combination of increasing recognition of antimicrobial-sensitive hvKp strains causing nosocomial infection, an increasing prevalence of hvKp strains that have acquired antimicrobial resistance determinants and therefore are more likely to survive and be transmitted in this setting, and lastly, the fact that XDR cKp strains that were entrenched in the health care environment have evolved into hvKp strains by virtue of acquiring the hvKp virulence plasmid (22).

Geographic Distribution of hvKp Infection

The predominance of infections to date has been reported from the Asian Pacific Rim. However, infections are increasingly being reported worldwide (8, 9, 139). With an increasing awareness and the identification of validated biomarkers (140), hopefully an accurate assessment of the incidence of hvKp infection across the globe will be achieved. Table 3 summarizes some of the data presently available.

STRUCTURE AND FUNCTION

hvKp, similar to other *Enterobacteriaceae*, possesses an extracytoplasmic outer membrane, which consists of a lipid bilayer with associated proteins, lipoproteins, and lipopolysaccharide (LPS). The capsular polysaccharide is situated outside the outer membrane. Although also produced by cKp strains, the most common hvKp capsule types are K1, K2, K5, K20, K54, and K57, with K1 and K2 accounting for approximately 70% of hvKp isolates (2, 17, 65, 99). However, if the recently recognized trend of cKp isolates acquiring the hvKp virulence plasmid, which confers the hypervirulent phenotype, continues, then an expanding number of capsule types (e.g., K47 and K64) is predicted to be observed for hvKp strains (141, 142). hvKp strains also possess the O-antigen moiety of LPS. The K1 and K2 capsule types are usually associated with the O1 O-antigen type; therefore, this is the most common O-antigen type observed for hvKp strains (143). The capsule and outer membrane interface with the external environment, including the human host. These components are critical determinants in pathogenesis (e.g., capsule) and antimicrobial resistance (e.g., permeability barrier and efflux pumps). Additionally, secreted products play an important role for both host

TABLE 3 Estimated proportion of hvKp[a] organisms among *K. pneumoniae* infections in various geographic locales

Site	Time frame	Isolate source/characteristic	No./total (%) of *K. pneumoniae* infections due to hvKp[b]	Reference
Australia	2001–2014	Urine	3/193 (1.6)	28
Australia	2001–2014	Mixed clinical (minus urine)	19/141 (13.5)	28
Canada (Alberta)	2001–2007	Community-acquired blood isolates	9/134 (6.7)	354
Canada (Quebec)	2009–2013	Blood isolates	1/110 (0.9)	17
China	2015	ST11, carbapenem resistant	11/387 (3)	22
China	2008–2012	Blood isolates	32/70 (46)	355
China	2014–2016	Carbapenem-resistant isolates	32/66 (48.5)	311
China	2014–2016	Carbapenem-sensitive isolates	31/45 (68.9)	311
India	2014–2015	Urine, respiratory, and blood isolates	3/370 (0.8)	356
India	2014–2015	Carbapenem-resistant blood isolates	6/86 (7)	357
Japan	2011–2012	Sputum and urine isolates	22/130 (16.9)	133
Nepal	2008–2012	Mixed clinical	1/131 (0.76)	
Spain (Barcelona)	2007–2013	Blood isolates	37/878 (4.2)	139
UK (Oxford)	2008–2011	Blood isolates	4/69 (5.8)	17
USA (Texas)	2009–2010	Clinical isolates	4/64 (6.3)	358
USA	2013	Carbapenem-resistant blood isolates	0/97 (0)	311
USA	2007–2013	Urine isolates	1/191 (0.5)	28
USA	1937–2014	Mixed clinical isolates (minus urine)	26/490 (5.3)	28
Vietnam	2003–2009	Mixed clinical isolates	16/41 (39)	28

[a]Defined by the presence of *iuc* or *rmpA* or *rmpA2*.
[b]Collection bias cannot be excluded.

infection (e.g., iron acquisition molecules [siderophores]) and environmental niche survival and colonization (type VI secretion systems) (144).

A relatively unique structural feature of hvKp strains compared to cKp and other *Enterobcteriaceae* is the RmpA- and/or RmpA2-mediated overproduction of capsular polysaccharide, which is capsule type independent. This phenotype (15) is not necessarily synonymous with a mucoid colonial morphology and has been shown to contribute to systemic virulence (62). Its roles in other aspects of the infectious process, such as colonization, metastatic spread, and transmission, have been less well studied.

PATHOGENESIS

The hypervirulent phenotype of hvKp strains is built on the foundation of virulence factors possessed by cKp strains. These factors have been reported and reviewed elsewhere (1, 145–151). In this section, we focus on factors that are primarily hvKp specific.

Colonization

The epidemiology of acquisition and colonization by hvKp has been discussed. A number of bacterial factors are required to overcome the combination of host factors and competing microbes, which may be site specific. It is important to delineate the factors and define the mechanisms that enable hvKp to successfully colonize various epidermal and mucosal surfaces since this represents a potential point of intervention for decreasing the incidence of infection. To date, the bulk of studies have focused on gastrointestinal colonization, and the majority of genes identified are also variably present in cKp strains.

Colibactin is a peptide-polyketide that is produced by nonribosomal synthesis. Its biosynthetic genes (*pks*) are located within a mobile genetic element (ICE*Kp10*) in hvKp strains which also usually contains genes for yersiniabactin and microcin E492 synthesis (76, 90). This element is present in most CG23 (K1 capsule type) hvKp strains, but less commonly in other hvKp strains (76, 94, 103). The acquisition of ICE*Kp10* by the sublineage CG23-I was calculated to have occurred in 1928, with subsequent global dissemination (76). This suggests that colibactin may have been an evolutionary asset. The *pks* gene cluster also can be present in cKp strains (90), and these genes are highly homologous to those reported for *Escherichia coli* (152) and other *Enterobacteriaecae* (153). Colibactin has been shown to promote colonization in *E. coli* (154) and in hvKp

strain 1084 (97). Microcin E492 is an 8-kDa bacteriocin that is active against *Enterobacteriaceae* (155). Activity requires attachment of salmochelin, which enables the uptake of microcin by the target bacteria (156). Therefore, hvKp strains that produce the combination of colibactin, microcin E492, and salmochelin would be predicted to have a significant colonization advantage in the competitive colonic environment.

Several genes have been identified by signature-tagged mutagenesis that appear to play a role in some combination of intestinal colonization and/or invasion across the mucosal barrier after intragastric (i.g.) challenge in mice (157). hvKp strain CG43 (ST86, K2 serotype) was used in this study. After i.g. instillation, the recovery of 28 mutant derivatives was less from liver and spleen homogenates than that of their wild-type parent. Gastric challenge with mutant derivatives with single disruptions of genes that encoded a LuxR family transcriptional regulator (*kva15*), a putative type III fimbrial usher protein (*mrkC*), a monamine regulon positive regulator (*moaR*), a two-component regulator system (*kvgA-kvgS*, which has been shown to contribute to capsule production) (158), a uracil permease (*kva28*), or 2 hypothetical proteins (*kva7* and *kva21*) resulted in 0% mortality, compared to 100% mortality observed for their parent, CG43. However, after intraperitoneal (i.p.) challenge, these mutants were as lethal as CG43. These data are consistent with a role for these factors in intestinal colonization and/or invasion across the mucosa. However, all of these genes are also present in cKp strains and therefore are not hvKp specific.

A mediator of ferric iron uptake, Kfu, is more prevalent in hvKp stains than in cKp strains. Kfu was shown to contribute to virulence after i.g., but not i.p., challenge in mice (159, 160). These data support a role for intestinal colonization and/or invasion. However, given its known role in free iron acquisition, which is available in the gastrointestinal tract, a contribution to colonization seems more likely. Likewise, genes that metabolize allantoin are more prevalent in hvKp strains with a K1 capsule type than in cKp strains, but not in hvKp strains with non-K1 capsule type serotypes (65, 66, 161). Similarly, these genes were requisite for maximal virulence after i.g., but not i.p., challenge in mice, thereby supporting a role for intestinal colonization and/or invasion (161). The products of these genes enable nitrogen assimilation from either exogenous allantoin or the catabolism of purines, substrates present in the gastrointestinal tract. Therefore, although a role in mucosal invasion cannot be excluded, it is biologically more plausible that the products of these genes play a role in colonization. It should be noted that the absence of these genes in non-K1 hvKp strains suggests that the ability to metabolize allantoin is not requisite for the hvKp hypervirulent phenotype but may increase the pathogenic potential of K1 strains by increasing their ability to colonize the gastrointestinal tract.

The sensitivity to antimicrobial peptides (SAP) transporter was shown to increase colonic colonization of the undefined *K. pneumoniae* strain Ca0437 in a mouse i.g. challenge model (162). The SAP transporter also enhanced adherence to intestinal epithelial cells *in vitro*. Interestingly, and unpredictably, the SAP transporter affected transcriptional levels of other genes, including those that encoded type I fimbriae. Therefore, it is unclear whether the effect was direct or indirect.

Lastly, in the hvKp strain NTUH-K2044, the disruption of *treC*, whose product enables trehalose utilization, resulted in decreased intestinal colonization in mice when the strain was in competition with its wild-type parent. Additional effects observed were decreased capsule production and biofilm formation, suggesting potential mechanisms (163). Similarly, the result of the loss of *celB*, whose product is needed for the transport of cellobiose into the cytoplasm, led to decreased biofilm formation, intestinal colonization, and lethality in mice challenged i.g. (164). Although the experimental design is not discriminatory for which step(s) in the pathogenic process was affected, these data are consistent with capsule and/or biofilm formation as important factors in mediating intestinal colonization, a first and requisite step in *Klebsiella* pathogenesis (163, 164). However, it has also been shown that capsule promotes colonic colonization for cKp strains as well (165). It is unclear whether the ability of NTUH-K2044 and other hvKp strains to produce more capsule and biofilm than cKp strains (163) enhances their

ability to colonize compared to that of cKp and perhaps other *Enterobacteriaceae* strains.

Entry

For some hvKp infections, the route of entry seems straightforward. Oropharyngeal colonization could lead to pneumonia via micro- or macroaspiration. Colonic/perineal colonization could lead to urinary tract infection via the ascending route, although this appears to be uncommon for hvKp (2). For some patients, cryptogenic liver abscesses due to *K. pneumoniae* have been associated with colonic carcinoma (166); although the *K. pneumoniae* strains were undefined, it is likely that a number of them were hvKp. In the health care setting, disruptions of mucosal or epithelial barriers (e.g., endotracheal tubes, surgical incisions, and catheters) may enable entry (22).

However, for most patients that develop hvKp infection, the initial site of entry is unclear. To date, most hvKp infections are community acquired, and they often occur in otherwise healthy hosts for whom there is no overt mucosal or epithelial barrier disruption. Since hepatic abscess is the most commonly reported infectious syndrome, it seems logical that hvKp is able to cross the intestinal mucosa and seed the liver through a portal bacteremia. A gut-vascular barrier exists which protects the host from indiscriminate entry of pathogens from the intestinal microbiota (167). Certain pathogens, such as *Salmonella enterica* serovar Typhi, have developed the ability to translocate across the normal intestinal mucosa, mediated in part by type III secretion systems (168). But for hvKp strains in humans, this does not routinely appear to be the case, since colonization does not necessarily result in infection. The mechanism by which hvKp is able to cross mucosal and/or epithelial barriers in humans is unclear. Considerations include entry through occult disruptions in the skin, with resultant bacteremia and subsequent spread to distant sites, a mechanism employed by *Staphylococcus aureus*. Another possibility is that the quantity of hvKp organisms colonizing the intestinal tract is a critical factor for entry. In support of this hypothesis, oral ampicillin or amoxicillin treatment, agents inactive against *Klebsiella*, was associated with an increased risk of subsequent hvKp infection (169). If the magnitude of the intestinal colonizing hvKp titer proves to be an important factor for facilitating entry, then as hvKp becomes increasingly antimicrobial resistant, it is predicted that the risk of infection will increase with antimicrobial use, especially in the health care setting. Of course, yet-to-be-defined host genetic differences that enable increased intestinal binding and/or translocation may be contributory. Needless to say, an improved understanding of the mechanism that enables hvKp to enter the host would facilitate preventative strategies.

Experimentally, hvKp strains have been shown to be capable of translocating across human intestinal epithelial cell lines and mouse colonic epithelial cells (170). A number of bacterial factors have been identified that could facilitate entry through the intestinal barrier. Based on experimental design, the factors identified by Tu et al. could contribute to entry and/or colonization (please see above for details) (157). The SAP transporter was shown to increase translocation of Ca0437 across intestinal epithelial cell monolayers *in vitro* in a mouse i.g. challenge model (162). But, the models used to identify these factors may not optimally translate. The identified factors are not hvKp specific and are present also in cKp and, in some instances, other *Enterobacteriaceae*. In contrast to hvKp, these pathogens can colonize the intestinal tract but require an overt mucosal disruption for entry. Therefore, it would appear that these factors alone cannot be responsible for hvKp entry leading to infection.

Paradoxically, studies using hvKp strain 52145 demonstrated that capsule impeded entry into A549 epithelial cells (171), and those using undefined *K. pneumoniae* strains demonstrated that capsule impeded invasion of an ileocecal epithelial cell line, at least in part by decreasing adherence (172). Further studies on the effect of increased capsule production that occurs with hvKp strains on adherence and cellular invasion would be of interest.

Growth and Survival

hvKp strains have been shown to be more resistant to phagocytosis, neutrophil- and complement-mediated activity, and neutrophil extracellular traps (NETs) than cKp strains (15, 39, 99, 173). hvKp strains also demonstrate enhanced growth in human body fluids *ex vivo* and increased virulence in a variety of infection models compared to cKp strains (39, 174). The hvKp-specific factors identified to date that mediate these phenotypes and clinical manifestations are discussed in the following sections. However, undoubtedly additional factors will be defined in the future.

RmpA, RmpA2, and capsule production. Capsule is an established virulence factor for cKp (175–177). However, a critical feature that contributes to the hvKp phenotype is the ability to produce increased amounts of capsular polysaccharide. This is mediated at least in part by RmpA and/or RmpA2, which are hvKp-specific factors located on the hvKp virulence plasmid (17, 83, 178). The loss of RmpA and/or RmpA2 decreases capsule production and virulence (33, 62, 178, 179). Glucose is an environmental signal that has been shown to increase capsule production (178, 180). As a result, it has been speculated that the association of diabetes mellitus and hvKp infection may be due in part to increased serum glucose levels in this patient group. A number of other regulators have been shown to modulate capsule production and/or the transcription of capsular polysaccharide biosynthetic genes (149, 158, 180–182). However, these factors also are present in cKp strains. This implies that RmpA and RmpA2 are critical factors for contributing to the increased virulence of hvKp strains relative to that of cKp strains. The regulator Fur (ferric uptake regulator) has been shown to repress capsule production in hvKp strain CG43 via repressing the expression of *rmpA* and *rmpA2* (62, 181). Therefore, hvKp capsule production is predicted to be increased in iron-limiting environments, such as within the human host.

In studies using hvKp strains, the capsular polysaccharide has been shown to protect against phagocytosis (149, 183, 184) and human defensin-mediated bactericidal activity (185), and it attenuated the production of human defensins *in vitro* (185). It also enhanced infection in mouse pneumonia models (171, 183, 184). It is logical to assume that increased capsule production may increase these biologic functions relative to smaller amounts of capsule produced by cKp strains, but experimental data are limited (62).

Capsule type. Several investigations have examined whether the K1 and/or K2 capsule types enhanced virulence compared to non-K1/K2 types (99, 186). These studies have variously reported that metastatic spread was more common in the K1/K2 groups and that diabetes mellitus was less common. However, it is clear that non-K1/K2 hvKp strains are capable of causing multisite infection, metastatic spread, and lethal disease (17, 187). Further, in the absence of some combination of increased capsule production and/or the presence of additional hvKp virulence factors, K1/K2 capsule type cKp strains do not possess the hypervirulent phenotype. Therefore, although it is possible that capsule type could modulate the overall virulence capability of hvKp, hypervirulence is by no means unique to these capsule types.

Iron acquisition and aerobactin. The primary mechanism of iron acquisition in *K. pneumoniae* is through the production of small molecules called siderophores that are secreted, bind iron, and reenter the bacterial cell through specific receptors (188, 189). hvKP strains variably have the capability to produce 4 different siderophores: enterobactin, salmochelin, yersiniabactin, and aerobactin. Molecular epidemiologic studies have shown that salmochelin, yersiniabactin, and aerobactin are more commonly present in hvKp strains than cKp strains (95, 159, 174). Yersiniabactin is also present in cKp strains, whereas salmochelin and aerobactin are hvKp specific (17). Enterobactin is ubiquitous in *K. pneumoniae* strains but is inactivated by the host protein lipocalin 2 (190); therefore, enterobactin is unlikely to play a role in systemic infection.

Surprisingly, quantitative siderophore assays with hvKP strains have demonstrated that hvKp strains produce quantitatively more siderophores than cKp strains (17, 86, 191). A total siderophore concentration of $>30 \mu g/ml$ was strongly predictive of an isolate being hvKp and increased lethality in a mouse systemic infection model (17).

Further, despite the ability to produce 4 different siderophores, aerobactin accounts for >80 to 90% of total production (86). *Ex vivo* and *in vivo* studies using isogenic constructs that variably express enterobactin, salmochelin, yersiniabactin, and aerobactin demonstrated that only aerobactin significantly enhances survival in human ascites, serum, and outbred mouse systemic and pulmonary infection models (86). These data are consistent with aerobactin being the primary virulence determinant among hvKp's siderophores that enables systemic infection. It remains unclear whether the total amount of siderophores produced by hvKp or specific characteristics of aerobactin are the critical feature responsible for mediating increased virulence. Yersiniabactin has been shown to be an important factor for cKp in mouse infection models (96). It is unclear why this is not the case for hvKp strains. Perhaps the quantitatively dominant amount of aerobactin produced by hvKp strains obscures a potential contribution by yersiniabactin. Interestingly to date, data do not support a role for salmochelin in systemic infection (86). However, genes that produce salmochelin are hvKp specific (17), suggesting that salmochelin plays a yet-to-be-defined role in the pathogenesis of hvKp infection. One possibility is that salmochelin, in conjunction with the microcin E492, is a critical mediator of hvKp colonization as discussed above (see "Colonization"). It is interesting that in the XDR cKp strains *K. pneumoniae* 1 to 5 that acquired a 178-kb pLVPK-like virulence plasmid and were subsequently responsible for a lethal ICU outbreak, the salmochelin biosynthetic genes were deleted from this plasmid (22). Perhaps, the XDR phenotype combined with barrier disruption in these patients made salmochelin production dispensable.

PEG344. *peg-344* is hvKp specific and is located on the hvKp virulence plasmid (17). The function of PEG344 is unknown, but homology modeling suggests a possible role as a transporter located in the inner membrane. When hvKp was grown in human ascites, the RNA abundance of *peg-344* was increased (88). A potential role in virulence was assessed in outbred CD1 mice. PEG344 was required for full virulence in a pneumonia model, as measured by survival and competition experiments, but did not appear contribute to the pathogenesis of systemic infection that developed after subcutaneous challenge (88). The mechanism by which PEG344 contributes to survival in pulmonary infection is unknown.

Colibactin. Besides a potential role in colonization, colibactin also has been shown to contribute to survival in the bloodstream of mice infected intranasally or intravenously and, to a lesser extent, after orogastric challenge (97). The responsible mechanism is unclear.

LPS. Both cKp and hvKp strains possess a complete LPS. The role of LPS has been studied in hvKp strains. In one study LPS did not appear to play a role in pneumonia in a mouse infection model (183). However, in others, it has been shown to protect against phagocytosis, complement-mediated bactericidal activity, antimicrobial peptides, and enhanced virulence in mouse pneumonia, systemic infection, and orogastric challenge models (148, 149, 184, 192–194). Presently, however, studies have not identified unique structural features in LPS produced by hvKp strains (e.g., lipid A substitutions) that would suggest these findings are specific for hvKp. Similar results have been obtained when cKp strains were studied (195).

Tellurite and silver resistance. Genes for tellurite (*terZA* to -*E* and *terWXY*) and silver resistance (*silS*) are often present on the hvKp virulence plasmid and therefore have been hypothesized to be important for systemic infection (85, 196). But these genes are not hvKp specific (17, 150), and the loss of tellurite resistance did not affect virulence in a mouse pneumonia model (150).

cAMP receptor protein. cAMP receptor protein (CRP) is a transcriptional regulator with pleiotropic effects. An hvKp strain (NTUH-K2044) with in which *crp* was disrupted was less virulent than its wild-type parent when mice were challenged via the IP route (197). CRP was also shown to positively regulate *allS* (allantoin metabolism) (197), but allantoin metabolism genes do not appear to be important for systemic infection (161). Therefore, these data support a role for an unrecognized gene(s) regulated by CRP in systemic infection, which may or may not be hvKp specific (198).

Metastatic Spread

In humans, multiple sites of infection and/or metastatic spread are more common with hvKp than cKp strains (17, 174). cKp and other members of the *Enterobacteriaceae* family rarely establish infection in secondary sites as a result of bacteremia, except in the setting of an immunocompromised host (e.g., neutropenia). The primary means by which hvKp strains infect multiple sites is via the bloodstream; whether this occurs at the time of entry and/or when a primary site of infection (e.g., hepatic abscess) is established (which, in turn, serves as the source for subsequent bacteremias and distant spread) is unclear. Likely both mechanisms are operational. Regardless, the ability to invade the bloodstream and survive the resident host defense factors is the first requisite step. Resistance of hvKp strains to the bactericidal activity of complement, which is mediated in part by capsule, is needed to accomplish this and contributes to this step in the process (99). However, most pathogenic members of the *Enterobacteriaceae* family are also capable of causing bacteremia and are resistant to the bactericidal activity of complement as well as the other host defense factors within the bloodstream. This suggests that hvKp is more efficient in invading tissue from the bloodstream. The mechanism by which this occurs is incompletely defined. Although the animal models used presently to study hvKp can measure bacteremia and subsequent spread to various organs or sites, models that directly measure hvKp tissue invasion from the bloodstream at the cellular level could assist in identifying potential factors that enable systemic tissue invasion.

Thrombophlebitis of the hepatic and portal veins has been described in association with hepatic abscess (199–201), but this complication could only account for spread to the lungs unless a patent ductus arteriosus also was present. Further, thrombophlebitis of the hepatic and portal veins and metastatic spread has been described in association with hepatic abscess due to other bacterial pathogens, albeit less frequently (201).

A "Trojan horse" mechanism has been postulated with neutrophils implicated as a possible vehicle (202). hvKp strains were shown to be able to survive within neutrophils (202, 203) and delay apoptosis up to 24 h (203), and i.p. injection of infected neutrophils resulted in disseminated infection; however, it was unclear if the integrity of the injected neutrophils was maintained postinjection (202). However, a cKp strain was also shown to be able to survive within macrophages and trigger apoptosis (176). Further, this concept, at least for professional phagocytes such as neutrophils or macrophages, seems counterintuitive, since these cells are attracted to the site of infection and would not be expected depart this inflammatory environment after acquiring bacterial cargo.

In most infections complicated by bacteremia, titers of 1 to 10^2 CFU/ml commonly are seen (204). Titers of $>10^2$ CFU/ml for *S. aureus*, *H. influenzae*, *S. pneumoniae*, and *N. meningitidis* have been associated with more severe disease and metastatic spread (204–207). Therefore, a quantitatively high titer of hvKp during bacteremia could be responsible or contributory. There is some limited support for this hypothesis. Albeit in subcutaneously infected outbred CD1 mice, 10^4 to 10^5 CFU/ml were measured in blood 48 h after bacterial challenge (191) and titers of 10^5 CFU/ml were measured after intranasal or intravenous challenge (97). Another possibility is that spread could be driven hvKp's increased capsule production. Although speculative, perhaps this phenotype results in greater *in vivo* clumping of bacterial cells, which, in turn, enhances survival with hematogenous dissemination.

Colibactin has been suggested to contribute to meningeal spread (97). Whether this is directly mediated by colibactin or due to the magnitude of bacteremia is unclear. It should be noted that the hvKp strain NTUH-K2044 was isolated from a patient with meningitis, but this isolate does not produce colibactin (93).

Tissue Damage

hvKp infection often results in abscess formation. However, to date there is limited insight into the responsible bacterial or host factors. The best-defined factor is colibactin, which has been shown to be genotoxic, causing DNA damage and cell death (94, 97). However, non-colibactin-producing hvKp strains (e.g., non-CG23-K1 capsule type)

also have caused abscesses in multiple sites. This suggests the possibility that unrecognized hvKp factors also may be contributory. Undoubtedly an unregulated host response resulting in collateral damage is contributory to some degree as well.

Association with Malignancy

The incidence of colonic cancer increased over the first decade in the new millennium in Taiwan. Several studies have identified an increased risk of colonic cancer in patients with hepatic abscess due to *K. pneumoniae* compared to patients without a hepatic abscess or with hepatic abscesses due to non-*K. pneumoniae* strains (208, 209). Since some *K. pneumoniae* strains, including hvKp, can produce the genotoxin colibactin, it has been hypothesized that such strains are the causative agent. An alternative hypothesis would be that hvKp-mediated hepatic abscess is a marker for cryptogenic colonic carcinoma, similar to *Streptococcus bovis* bacteremia/endocarditis (210) or infection due to *Clostridium septicum* (211). Further, in another epidemiologic study from Taiwan, an increased risk of hepatocellular carcinoma was observed in patients with a history of liver abscess (212). Given the well-established risk of hepatocellular carcinoma due to hepatitis B and C virus infection, although those infections are more chronic, there is a biologic plausibility for this association. More data are clearly needed to define cause and effect and the relative risks. However, presently it is reasonable to consider a screening colonoscopy for patients diagnosed with a hepatic abscess due to hvKp, especially for those not recently studied or with risk factors (e.g., age or family history). Whether long-term follow-up should be performed for the possible development of hepatocellular carcinoma in patients who have suffered a hepatic abscess due to hvKp is less clear.

HOST SUSCEPTIBILITY RISK FACTORS

Ethnic Background

Although hvKp infections occur in all ethnic groups, even those acquired in Western countries commonly involve Asians (37, 39, 213–221) and (to a lesser degree) Pacific Islanders and Hispanics (9, 215, 216). One explanation could be that hvKp infection occurs more frequently in Asians from geographically defined pathogen exposure, acquisition, and increased colonization (113), a requisite step for subsequent infection. In some cases, there is a history of Asians infected in the West that travelled to or were exposed to individuals who had recently been in the Asian Pacific Rim (39). In fact, a case in a Caucasian from Denmark who traveled to Shanghai, China, suggests this very scenario (220). Alternatively, an underlying genetic abnormality that is more commonly, but not exclusively, present in Asians, Pacific Islanders, and Hispanics could also be contributory. This concept of genetic susceptibility is consistent with a case report involving a Japanese father and son who developed infection due to hvKp, but the mother was only colonized (114). Further, another report from Singapore suggests that genetic background may contribute to the development of hvKp infection. In 70 patients with liver abscess, among whom 67 cases were probably caused by hvKp, only 1.4% of these infections were in Indians, despite Indians comprising 7.4% of the population and being more likely to be diabetic. However, differences in diet and colonization were potential factors that were not accounted for (81). Conversely, in a study from France, of 14 patients with hepatic abscess due to hvKp, 5 were Caucasian, 6 were African, and only 3 were Asian (8).

Data are needed to address whether a genetic variation is contributory to hvKp infection. These data would have important implications for the development of preventative strategies and/or infection control processes (see "Infection Control and Prevention" below). Potential mechanisms remain speculative. However, considerations include genetic variants that enhance of binding of hvKp within the gastrointestinal tract or enable increased survival within the host. A nongenetic mechanism that negatively modulates host defenses is the development of autoantibodies directed against a host factor; although this has not been described for hvKp, it has been implicated in infections mediated by other pathogens (222, 223).

Diabetes Mellitus

Diabetes has been implicated as a risk factor for a variety of infections, including those due to hvKp. The majority of studies support this contention (67–75), although some reports concluded that diabetes mellitus (DM) was not predictive for developing hvKp infection (99, 132, 174). Poor glycemic control has been associated with an increase in metastatic complications (224). For the syndromes of endophthalmitis and necrotizing fasciitis due to hvKp the association is stronger in most (54, 225–229) but not all (230) studies. An unsubstantiated but biologically plausible mechanism for this observation is metastatic seeding by hvKp during bacteremia as a result of DM-related loss of vascular patency or integrity. Equally important as the association of hvKp infection with DM is the fact the hvKp infection is frequently seen in younger, otherwise healthy individuals. The clinician needs to be cognizant of the fact that this potentially devastating disease can develop in the absence of DM or any other comorbidities (99).

Sex

Males might be slightly more likely to be infected than females. Siu et al. reviewed several studies of hepatic abscess due to hvKp (53). Overall, males were more likely to be infected than females (55% [483/871]); however, geographic differences were noted. Males were infected in 68% (26/38), 42% (136/321), and 63% (321/512) of cases in the United States, South Korea, and Taiwan, respectively. Among 61 patients with hvKp infection complicated by endophthalmitis, 80.3% (49/61) were male (231). By contrast, in another study, men and women were similarly infected by hvKp strains causing liver abscesses: 52.5% (21/40) were male and 47.5% (19/40) were female (78).

Immunoglobulin Deficiencies

Recurrent hvKp bacteremia and low levels of IgG2 have been reported (232). Additional studies that examined immunoglobulin levels and hvKp infection would be of interest.

Treatment with Selected Medications

A retrospective population study reported that individuals who used ampicillin or amoxicillin in the prior 30 days had an increased risk (odds ratio [OR], 3.5) of developing a cryptogenic hepatic abscess due to *K. pneumoniae* (it is predicted that most of these cases would be due to hvKp) (169). Mice challenged orally with hvKp and then treated orally with ampicillin for 5 days starting 2 days after bacterial challenge had increased mortality compared to mice treated with water alone (169). Similarly, individuals that used proton pump inhibitors had an increased risk (OR, 4.7) of developing a cryptogenic hepatic abscess due to *K. pneumoniae* compared to controls (233). Although these are single reports, both are biologically plausible. Proton pump inhibitors could lead to increased acquisition as has been described for enteric pathogens (234). Treatment with ampicillin or amoxicillin could increase the titer of colonizing hvKp (given the intrinsic resistance of *K. pneumoniae* to these agents) by killing bacteria that mediate colonization resistance, which, in turn, could lead to increased entry. But, this remains speculative since the mechanism for entry by hvKp is presently unknown.

Treatment of Esophageal Varices

There have been several reports from Taiwan in which various treatments for esophageal varices were complicated by central nervous system (CNS) infection or endophthalmitis due to *K. pneumoniae* (235–237). Although no studies were performed to confirm that these infections were due to hvKp, the clinical sites of infection and geographic location are highly suggestive.

INFECTIOUS SYNDROMES

Sites of Infection

Abdominal disease. The defining clinical syndrome of hvKp infection that first led to its recognition in the 1980s is cryptogenic pyogenic liver abscess (PLA) (31, 67, 69) (Fig. 2). Prior to the 1980s, *Escherichia coli* was the most commonly isolated enteric

FIG 2 An image from an abdominal CT scan of a previously healthy 24-year-old Vietnamese man shows a primary liver abscess (red arrow) with metastatic spread to the spleen (black arrow). (Courtesy of Chiu-Bin Hsaio and Diana Pomakova; reprinted with permission from McGraw-Hill Education [353].)

Gram-negative bacillus isolated from PLA in the Asian Pacific Rim (238). Since then, the predominant pathogen of PLA in this region has been steadily shifting to *K. pneumoniae*, mirroring the increasing prevalence of hvKp over the same period. By 2004, approximately 80% of all cases of PLA in Taiwan were caused by *K. pneumoniae* (239–242).

Beyond triggering epidemiologic shifts in the etiologies of PLA, hvKp is driving an increasing overall incidence of PLA in regions where it is endemic. In Taiwan, PLA cases increased from 11.15 to 17.59 per 100,000 between 1996 and 2004 (5). In comparison, incidence of PLA in North America over the same time frame was 3.6 per 100,000, with pathotype-undefined *K. pneumoniae* isolated from only 9.2% of cultured liver abscesses (243). More recent data seem to suggest that the epidemiologic trends observed in the Asian Pacific Rim have begun diffusing across the West. Some regions of Europe and North America still report low but increasing rates of this infection (214, 219). For example, a review of 158 pyogenic liver abscesses in Paris, France, revealed that the majority were due to mixed enteric flora and associated with biliary disease or instrumentation (8). However, within the subset of cryptogenic PLA cases, *K. pneumoniae* is now the most commonly isolated pathogen, with 8.7% of all PLA cases due to hvKp (8). Regions of the United States with substantial Asian populations have reported even higher rates than these. Two small series out of New York City reported that *K. pneumoniae* was the responsible pathogen in 41% and 36% of cases, respectively (216, 244), and a tertiary hospital in California has reported that *K. pneumoniae* has superseded all other causes of PLA regionally (215). The *K. pneumoniae* in these series was not specifically identified as hvKp. Nonetheless, an increasing number of cases of PLA due to hvKp are being reported in various Western countries (39, 213–215, 219, 221, 245, 246), supporting the inference that the epidemiologic trends observed in East Asia are likewise occurring to various degrees worldwide.

The clinical and laboratory presentation of hvKp-mediated PLA is superficially like that of other PLA; presenting signs and symptoms typically include abdominal pain, fever, chills, and leukocytosis regardless of causative pathogen (247). However, several specific features of hvKp PLA set it apart as a unique syndrome. hvKp-mediated PLA is almost always monomicrobial, while non-hvKp PLA is almost always polymicrobial (67, 248). hvKp PLA is also associated with significantly more metastatic complications, which are detailed below (53, 67, 249). Unlike other liver abscesses, which are often consequences of biliary pathology or preceding interventional procedures, hvKp PLA typically occurs in individuals with normal biliary and hepatic function (249). Though

not established definitively as a distinguishing feature of hvKp, a number of reports describe late reinfection or relapses of hvKp infection at the same or different sites months after initial therapy had been completed (69, 114, 245, 250). Further investigations will be required to substantiate if this is a characteristic of hvKp, to understand the mechanism by which it may occur, and, if so, optimal treatment. Hypothesized mechanisms include the survival of the hvKp infecting strain at the site of initial infection with subsequent relapse due to inadequate therapy or persistent colonization with subsequent reinfection, perhaps facilitated by the host having an increased susceptibility to hvKp infection.

Regional thrombophlebitis has been reported in up to one-third of cases of PLA due to *K. pneumoniae*, compared to approximately 5% with other causes of PLA (251). Affected vasculature may be the hepatic vein or, less commonly, the portal vein (199, 200). Although this complication may be responsible for septic emboli to the lungs, resolution occurs with the management of the infection. There are no controlled data, but anticoagulation does not appear to be beneficial or necessary for recannulation (199, 252).

Multiple other foci of intra-abdominal infection are possible in invasive hvKp syndromes, including splenic abscess. Specific data regarding the incidence of splenic abscess due to hvKp are lacking. However, regions where hvKp is endemic, such as Taiwan and Korea, have reported *K. pneumoniae* as a leading cause of splenic abscess (253–255). High rates of concurrent PLA were noted in *K. pneumoniae* splenic abscesses (44%) but not with splenic abscesses of other etiologies (0%) (256). Historically, *K. pneumoniae* has been a relatively rare cause of splenic abscess, isolated alone or in polymicrobial growth in only 5% of cases (257). It is reasonable to infer that hvKp produces these epidemiologic changes.

In contrast to splenic abscess, preliminary data would suggest that the microbiology of spontaneous bacterial peritonitis is not changing substantially with the emergence of hvKp. *E. coli* remains the most common cause of monomicrobial SBP in Taiwan, with monomicrobial *K. pneumoniae* comprising only 3 to 7% of all cases (70, 258). Though phenotypically hypermucoviscous strains of *K. pneumoniae* have been reported to cause SBP (70), the invasive syndrome characteristic of hvKp is significantly less likely to occur in cirrhotic patients than noncirrhotic (132).

Thoracic disease. Data from the 1990s suggest that *K. pneumoniae* accounted for less than 1% of cases of community-acquired pneumonia (CAP) requiring hospitalization in North America, Argentina, Europe, and Australia (70, 259–261). Pneumonia due to cKp does occur but almost always in health care settings in patients with comorbid conditions. By contrast, *Klebsiella* has been reported as an important cause of severe, bacteremic CAP in South Africa and Taiwan over the same time frame (70). A more recent study from Taiwan assessing cases of bacteremic CAP from 2001 to 2008 reported that hvKp now has superseded *S. pneumoniae* as the most common etiology regionally (6). Importantly, patients with bacteremic CAP due to hvKp had significantly higher rates of respiratory failure, bilateral lobar involvement, septic shock, and mortality than patients with bacteremic *S. pneumoniae* CAP. Mortality in the above-referenced study was 55.1% for those infected with hvKp (6). Cases of hvKp CAP outside the Asian Pacific Rim are still relatively rare but are being reported in increasing frequency. A recent French study found that 24% of patients admitted from the community to the ICU with *K. pneumoniae* infection had community-acquired hvKp pneumonia (262). These patients had significantly higher rates of multiorgan failure than other patients admitted to the ICU with other causes of CAP, as has been observed in countries where hvKp is endemic (262).

Though the characteristic features of hvKp are community onset infections, hospital-acquired ventilator-associated pneumonia due to hvKp has been reported from China (263, 264). Disturbingly, multiple nosocomial outbreaks of ventilator-associated pneumonia due to carbapenemase-producing hvKp have now been reported across Asia, with uniformly negative outcomes. An outbreak of 5 cases of VIM-2-positive hvKp, harbored on an IncN plasmid, caused 80% mortality in an Iranian ICU (265), and

FIG 3 A previously healthy 33-year-old Chinese male presented with endophthalmitis. (Courtesy of Chiu-Bin Hsaio; reprinted with permission from McGraw-Hill Education [353].)

similarly, five XDR ST11 cKp *K. pneumoniae* strains, harboring bla_{KPC-2}, $bla_{CTX-M-65}$, and bla_{TEM-1}, that acquired an hvKp virulence plasmid caused a uniformly fatal outbreak of ventilator-associated pneumonia in China (22).

In additional to lobar pneumonia, hvKp may cause a variety of other pulmonary infections, including empyema, lung abscess, and septic pulmonary emboli. hvKp has become the most common cause of community-acquired empyema in Taiwan and is associated with high mortality rates (32.4%) (266), significantly higher than those of non-*Klebsiella* empyema (267). Although most pleural space infections are due to an adjoining pneumonia, spread may also occur via transdiaphragmatic rupture of pyogenic liver abscess (267). *K. pneumoniae* has now also become the most common single cause of lung abscesses in Taiwan, though it has not become more common than mixed anaerobic lung abscesses considered collectively (3). More patients with *K. pneumoniae* lung abscess have concomitant bacteremia and multiple cavities observed radiographically than those with anaerobic bacterial lung abscess (3).

Septic pulmonary emboli often occur as a complication of hvKp-mediated PLA (268) and nonhepatic sites infected by hvKp (67, 269–272). Characteristic radiographic findings of septic pulmonary emboli due to hvKp are similar to those for pulmonary emboli due to infection by other pathogens and include pulmonary nodules with or without cavitation, adjacent pleural effusions, peripheral wedge-shaped opacities, and ground-glass opacities (268).

Endophthalmitis. Endophthalmitis, a devastating complication of hvKp infection, was first described in 1986 and was one of the first clinical manifestations recognized that distinguished hvKp from cKP infection (31) (Fig. 3). Endogenous endophthalmitis (EE) due to enteric Gram-negative bacilli was extraordinarily uncommon in ambulatory, healthy hosts until the advent of hvKp. Now it has become a frequent complication: approximately 5% of individuals with hvKp bacteremia ultimately develop EE (132). By contrast, exogenous endophthalmitis, which is associated with trauma or surgery rather than hematogenous spread, has rarely or never been attributed to hvKp.

The most typical presentation of hvKp EE is painful ocular swelling, redness, and sudden onset of blurred vision (229). Bilateral involvement occurs in 13% to 25% of patients (226, 229, 231, 273). Due to its rapid onset, some patients may sustain irreversible blindness even before a systemic infectious process is recognized (226). Onset also may occur as late as 30 days after hvKp's initial presentation (231). Even with intravenous and intravitreal antibiotic treatment, outcomes of EE are poor; posttreatment visual acuity is light perception or worse in 89% of cases (229). Forty-one percent of affected eyes eventually required evisceration or enucleation (229). An instructive case report that underscores the aggressive nature of this infection describes a patient

undergoing treatment for hvKp bacteremia and PLA who reported a vague "veil-like" visual disturbance while in hospital. Because the patient retained perfect visual acuity and was without hypopyon or vitritis on exam, treatment was deferred. The patient's vision declined to 20/400 (6/120) overnight, with interval development of vitritis on exam. Recovery of visual acuity, despite aggressive treatment, was suboptimal. Diagnosis of a small peripheral retinal abscess was made in retrospect (274). Though most cases of hvKp EE are reported in Southeast Asia, cases are now being documented worldwide in increasing incidence (275–278). Prompt recognition and treatment of hvKp EE may improve outcomes and may—in cases of unilateral initial symptoms— prevent a worse outcome from occult infection in the contralateral eye (31, 227, 229, 231).

Central nervous system disease. As with other hvKp-mediated infectious syndromes, the face of community-acquired meningitis has changed in Southeast Asia because of the emergence of hvKp (279). Alarmingly, *K. pneumoniae* has become a major cause of community-acquired meningitis in Asia in the absence of neurosurgery or head trauma (7, 279–281). Shifts also are being observed beyond the Asian Pacific Rim as hvKp spreads across the globe. Gram-negative meningitis in community-dwelling, healthy adults was almost unheard of in the West up until recently (282), but this has begun to change (283).

In Taiwan, 50% of cases of community-acquired meningitis requiring ICU admission are due to *K. pneumoniae* (284). Outcomes of *K. pneumoniae* community-acquired meningitis are uniformly worse than for *S. pneumoniae* community-acquired meningitis, with higher rates of septic shock, extrameningeal infectious foci, in-hospital mortality, and 28-day mortality (285). Although not all the strains in the above-referenced studies have been genetically characterized as hvKp, several studies have confirmed that the syndrome of community-acquired *K. pneumoniae* meningitis was attributed to the hvKp pathotype (132, 174, 219). Hypervirulent *K. pneumoniae* meningitis may be the presenting primary infection or secondary to metastatic spread (286, 287).

Characteristic imaging findings are not yet well characterized for hvKp meningitis. One case report described the presence of multiple, irregular cord-like structures that bridged the dura and pia mater in the subarachnoid space and were hyperintense relative to cerebrospinal fluid on fluid-attenuated inversion-recovery magnetic resonance imaging (288). Another report described initial MRI findings of patchy leptomeningeal enhancement, followed by a focal nodular lesion in the subacute phase that subsequently resolved with treatment (289).

Some cases of hvKp meningitis have been diagnosed concurrently with brain abscesses, which tend to be diffuse and multiple (290, 291). Ventriculitis may also occur simultaneously (291). Other CNS manifestations of invasive hvKp disease reported to date include subdural empyema and epidural abscess (290, 292–295).

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 but having a higher mortality (47% versus 19%) (296). Though most common in Southeast Asia, cases have been reported worldwide (220, 297). Intramuscular abscesses may occur, with or without concurrent necrotizing fasciitis (67, 298). Of note is hvKp's propensity to cause psoas abscess. In Taiwan, where hvKp is endemic, *K. pneumoniae* is second only to *S. aureus* as causative agent of nontuberculous psoas abscess (250). Pyomyositis, especially of the lower extremities, has also been reported, both alone and in association with contiguous septic arthritis (299). Osteomyelitis may occur and may involve multiple distant sites. In fact, the multifocal, lytic nature of hvKp osteomyelitis has been mistaken for malignancy, with the correct diagnosis made only after progression to contiguous necrotizing fasciitis (300). Bone pain due to osteomyelitis may be the primary presenting complaint in a patient later discovered to have disseminated hvKp infection (301).

Deep neck infections have been described as the primary presenting complaint of systemic hvKp infections, often in the setting of other systemic metastatic complications (37, 217). Neck abscesses may be complicated by septic thrombophlebitis (i.e.,

Lemierre syndrome) and descending mediastinitis (213). In addition to the above deep foci of infection, superficial skin and soft tissue infection has been reported, with cultures of cutaneous septic emboli eventually providing the underlying diagnosis of disseminated hvKp infection (302).

Genitourinary tract. Most urinary tract infections occur via the ascending route, as fecal flora ascends through the urethra to infect the bladder, occasionally reaching the kidneys and the systemic circulation. cKp causes infections in this manner. This pathogenesis mechanism is not as clearly established for hvKp, though biologically plausible. The urinary tract is cited as a source of hvKp bacteremia (132), but the primary mechanism by which hvKp establishes bacteremic infection appears to be independent of the urinary tract. To the contrary, most genitourinary infections reported due to hvKp result from hematogenous seeding from preceding bacteremia. Bacteremic spread to the kidneys, perinephric region, and prostate resulting in local abscess formation are well described (31, 67, 303). Although additional data are needed, hvKp isolated from the urine may serve more reliably as a marker for hvKp bacteremia than a source for it, similar to *S. aureus* bacteriuria (304).

Bacteremia/endovascular infection. Bacteremia is an extremely common complication of hvKp site-specific infection. The most common underlying infection in cases of hvKp bacteremia is pyogenic liver abscess, though many other primary sources are possible (132). A unique feature of hvKp bacteremia is the high proportion of cases that occur with no infectious source immediately apparent. Individuals with hvKp bacteremia are more likely to have blood cultures turn positive before the primary site of infection is identified or cultured, compared with those infected with cKp (305). Despite the range of aggressive clinical manifestations hvKp is capable of, endocarditis is an extremely rare presentation of hvKp disease. A case of native valve endocarditis due to hvKp has been reported (306), but purulent pericarditis has been reported more frequently, either as a direct extension from PLA (307) or via hematogenous spread (290). Septic thromboembolism associated with hvKp infection occurs commonly, both regionally in the areas of primary infection and as distant embolic sequela. Details regarding hepatic, pulmonary, and internal jugular septic thromboemboli due to hvKp are discussed in their respective clinical syndrome discussions above.

Miscellaneous. Infections of nearly every body site have been reported with hvKp. A few less common manifestations of hvKp infection include orbital cellulitis (308), epididymitis (270), and Bartholin's abscess (309). It is likely, given the tissue invasive nature of hvKp, that more unusual manifestations of invasive hvKp infection will continue to be reported.

DIAGNOSIS

Microbiologic Identification

A significant issue that is presently impeding optimal care of hvKp-infected patients is the inability of clinical microbiology laboratories to distinguish cKp from hvKp. To resolve this shortcoming, the availability of a commercial test that has been approved by appropriate regulatory bodies is needed. Identification of hvKp as the infecting agent would be important. Specifically, if infection due to hvKp was not previously considered, this would suggest to the treating physician the need to obtain additional imaging (computed tomography [CT] or magnetic resonance imaging [MRI]) in search of additional sites of infection, which may be unrecognized and could require source control (e.g., drainage) (295). Further, the identification of certain occult sites of infection, such as in cases of meningitis (which may be mistaken for sepsis-related changes in mental status), brain or prostatic abscesses, or endophthalmitis, would be important since site-specific antimicrobial regimens that achieve adequate drug concentrations are needed for an optimal outcome (31). Of particular note is endophthalmitis, a devastating complication of hvKp infection. Ocular infection may not be present or apparent at presentation. Due to the rapidity of tissue damage at this site, immediate treatment is required to maximize the odds of maintaining visual acuity. Therefore, established or suspected hvKp infection dictates involvement of an ophthalmologist,

who has the capability of performing an appropriate evaluation and immediately initiating treatment specific for endophthalmitis, such as vitrectomy and intravitreal antibiotics if needed (229, 231). The hypermucoviscous phenotype of hvKp can be problematic in the management of abscesses. Its increased viscosity can impede percutaneous drainage (PD) and increase the likelihood of the catheter becoming clogged (39, 310). If it is known at the time of catheter placement that hvKp is the infecting strain, then the clinician can consider the use of the largest bore practical. Once the drainage catheter is placed, it would be equally important to perform more frequent irrigations than usual to try to maintain drainage, which, in turn, will decrease the need for subsequent open surgical drainage (SD) if percutaneous drainage fails. Anecdotally, hvKp infection has been associated with relapse (69, 114, 245, 250). In the absence of controlled data, when hvKp is identified as the infecting agent, a more prolonged treatment course may be needed to maximize cure rates and minimize relapse.

Presently, the suspicion of an astute clinician is the only means by which hvKp would be considered (Table 1). However, clinical criteria are becoming increasingly problematic. The clinical definition that requires the occurrence of a tissue-invasive, community-acquired infection in a healthy host precludes recognition of hvKp infection in patients who have comorbidities, are immunocompromised, or are in a health care setting; the last scenario is becoming increasingly common.

Fortunately, *peg-344*, *iroB*, *iucA*, $_p$*rmpA*, $_p$*rmpA2*, and siderophore production greater than 30 μg/ml have been shown to accurately differentiate hvKp from cKp strains (17). These biomarkers could enable the development of a diagnostic test which, if FDA approved, could be used by clinical laboratories for the identification of hvKp strains. A sensitive and specific test is needed not only for patient care but also for use in surveillance and research studies (140). This study and others have demonstrated that the accuracy of the string test for defining hvKp was not optimal, especially in low-prevalence regions, and that this diagnostic modality should no longer be used as the sole means for identifying hvKp (16, 17). However, it is important to note that genetic variation is commonplace with *K. pneumoniae*. Therefore, it would therefore seem logical that the best marker for hvKp strains would be one that clearly contributes to the hypervirulence phenotype. Total siderophore production has been shown to strongly correlate with *in vivo* virulence (17, 86, 87), and aerobactin has been shown to be the dominant siderophore produced by hvKp strains and the critical siderophore that enhances virulence *ex vivo* and *in vivo* (87). Further, increased production of capsule, which is mediated by *rmpA* or *rmpA2*, also has been shown to contribute to the hypervirulent phenotype (33, 62, 178, 179). Therefore, total siderophore production, or *iuc* and/or either *rmpA* or *rmpA2*, would be predicted to be the most accurate and durable marker. This concept is supported by the report by Gu et al. in which an XDR cKp strain became hypervirulent despite *iro*, *peg-344*, and *rmpA*, but not *iuc* and *rmpA2*, being deleted in the acquired hvKp plasmid (22). Of course, as more hvKp-specific genes are identified, additional markers may prove to be viable alternatives or even more accurate.

A facile assay to measure quantitative siderophore production would require development for routine use in clinical laboratories. However, identification of genetic biomarkers could be easily achieved via a PCR assay (311). Identification of hvKp via matrix-assisted laser desorption ionization–time of flight (MALDI-TOF) mass spectrometry (MS) has been explored but requires further refinement (312–314).

Radiographic Considerations

hvKp infection is characterized by often having multisite involvement upon presentation or subsequent metastatic spread. Infected sites may declare themselves by some combination of signs or symptoms or may be occult (292, 295). Defining the full extent of hvKp infection is critical since selected sites may require a modification of the antimicrobial regimen (e.g., CNS, prostate) and/or dictate the need for source control.

Therefore, the clinician should have a low threshold for performing appropriate radiographic studies with the goal of defining the full extent of infection.

TREATMENT

Source Control

hvKp infection is often manifested by abscess development. The liver is the most common location, but nonhepatic abscesses have been described for virtually every organ and anatomic location. There is a limited body of data that addresses the management of hvKp mediated abscess. Further, extrapolation of data from non-hvKp strains may not be applicable due to important differences between hvKp and other pathogens, namely, its hypermucoviscous phenotype, which can result in an extremely viscous fluid content within the abscess. Lastly, management may be driven by the location of the abscess and acuity of illness.

A retrospective study from Singapore compared percutaneous drainiage with open surgical drainage (SD) for the management of hepatic abscess larger than 5 cm; 80% were multiloculated (310). *K. pneumoniae* was the offending pathogen in 67% (24/36) and 61% (27/44) of the PD and SD groups, respectively. Although the pathotypes were undefined, it is likely that a high proportion of these *K. pneumoniae* strains were hvKp given the location of the study and that the majority of abscesses were cryptogenic (8). Overall, there was no difference in mortality between the groups, but the SD group had a shorter length of stay, were less likely to fail therapy, and required fewer subsequent procedures; no subgroup analysis for the *K. pneumoniae* infections was performed. A retrospective study from Taiwan compared PD alone ($n = 46$), PD followed by hepatic resection (PD-HR) for patients that failed PD ($n = 19$), and HR as the initial treatment for patients ($n = 16$) with liver abscess and an APACHE II score of $\geq$15 (315). The mortality rate was lower in the HR group than in the PD group, but the rates were similar between the HR and PD-HR groups. The HR group was reported to consist of patients with peritonitis, biliary tract infection, or suspected malignancy. No microbiologic data were reported, and the majority of abscesses were described as cryptogenic. Another study from Singapore reported that hepatic abscesses due to *K. pneumoniae* (unclear what proportion of organisms were hvKp) that were >5 cm (71/109) were more likely to have a delayed response to therapy but not an increased risk of death or readmission; the presence of loculations was not predictive of a delayed response. Of these 109 patients, 7 were treated with open or laparoscopic surgical drainage, 65 with percutaneous drainage, and 37 with antimicrobials alone (26 of which had abscess <5 cm) (316).

Given the limited published data set, which primarily addresses hepatic abscesses, a reasonable approach for hvKp-mediated abscesses in any location should be an individualized assessment of risk and benefit. Abscesses in critical sites (e.g., brain and epidural space) or ruptured abscesses would warrant consideration for more immediate surgical intervention. Large abscesses in noncritical sites may be best managed by percutaneous drainage pending accessibility, with a surgical intervention reserved for failures. Since abscess fluid with hvKp infection is commonly viscous, the largest-bore drainage catheter feasible should be used, with frequent flushing to try to prevent catheter blockage, a reported complication (310). Smaller abscesses (<5 cm) have the potential to be cured with antimicrobial therapy alone. Imaging can be used to assess the response to therapy and define duration of therapy. With the availability of biomarkers to accurately identify hvKp (17), controlled trials that address various issues related to source control would be welcomed.

hvKp infection also can result in necrotizing fasciitis (296). Although there are no controlled data that addresses the management of this manifestation of hvKp infection, the standard of care for this potentially lethal entity is rapid surgical intervention (fasciotomy, debridement, and amputation) in addition to medical treatment (228, 296).

Antimicrobial Resistance

Antimicrobial resistance can be mediated by several mechanisms (317), all of which

are variably occurring. The first is acquisition by an hvKp strain of a conjugal plasmid(s) that contains antimicrobial resistance determinants (19). Since hvKp strains have not acquired antimicrobial resistance determinants as rapidly as cKp strains, there has been speculation that plasmid incompatibilities, a physical barrier due to overexpression of capsule, and CRISPR systems could be contributory (76). The second mechanism consists of acquisition and integration of an ICE containing antimicrobial resistance determinants into either the chromosome or virulence plasmid of an hvKp strain (20, 318). The third mechanism is disruption or mutations in chromosomal genes (e.g., genes for outer membrane proteins [OMPs]) (319). The fourth is acquisition of the hvKp virulence plasmid by MDR or XDR cKp strains (22, 319). The hvKp virulence plasmid appears to be nonconjugal. However, a potential mechanism for mediating transfer has been postulated. Dong et al. demonstrated that there is a common 11.2-kb region between at least some hvKp virulence plasmids and a conjugal plasmid that encodes the KPC carbapenemase. This suggests the possibility of initial integration of these extrachromosomal elements, subsequent transfer, and resolution. However, this hypothesis requires experimental confirmation (319).

Broad-spectrum β-lactamases. All *K. pneumoniae* strains, including hvKp, are intrinsically resistant to ampicillin and ticarcillin and are inconsistently susceptible to nitrofurantoin.

Aminoglycoside, trimethoprim-sulfamethoxazole, tetracycline, and fluoroquinolone resistance genes. The determinants for resistance to aminoglycosides, trimethoprim-sulfamethoxazole, tetracycline, and fluoroquinolones are frequently linked on conjugal or transferable plasmids containing genes for extended-spectrum β-lactamases (ESBLs) and carbapenemase.

ESBLs. ESBLs (e.g., CTX-M, SHV, and TEM) are modified broad-spectrum β-lactamases that hydrolyze third-generation cephalosporins, aztreonam, and (in some instances) fourth-generation cephalosporins, in addition to the drugs hydrolyzed by broad-spectrum β-lactamases. Gram-negative bacteria that express ESBLs may also possess porin mutations that result in decreased uptake of cephalosporins, β-lactam–β-lactamase inhibitor combinations, and carbapenems, thereby further reducing susceptibility to these agents. hvKp strains possessing ESBLs have been described in a number of studies (320–322). In one investigation from China in which 230 clinical *K. pneumoniae* isolates from 2013 were studied, 85/230 (37%) were predicted to be hvKp based on the presence of *rmpA*, and of these, 11 (13%) produced an ESBL (249).

AmpC β-lactamases. High levels of expression confer resistance to the same substrates as do ESBLs, plus to the cephamycins (e.g., cefoxitin and cefotetan). Some strains of *K. pneumoniae*, including hvKp isolates, have acquired plasmids containing AmpC β-lactamase genes (322, 323).

Carbapenemases. Carbapenemases (e.g., KPC [class A], NDM, VIM, and IMP [class B], and OXA [class D]) confer resistance to the same drugs as do ESBLs, plus to cephamycins and carbapenems. Transposon-mediated spread (e.g., Tn*4401* for KPC) is also important. An increasing number of reports, primarily but not exclusively from Asia (324–327), have described hvKp strains that have acquired carbapenemases. Acquisition of a KPC is most common (18–20, 22, 91, 324, 328–331), but NDM-1- and OXA-producing isolates also have been described (326, 327, 332–336). It is not uncommon for carbapenemase-producing strains to possess ESBLs as well as multiple additional linked antimicrobial resistance determinants. In addition, carbapenem resistance may be conferred by the combination of an ESBL and porin mutations (e.g., OMPK35/ 36) (142, 328, 336).

Polymyxin resistance. Several mechanisms have been identified that confer resistance to polymyins. The recent emergence of the polymyxin resistance gene *mcr-1* on a stable, transferable plasmid is extremely concerning since polymyxins (polymyxins B and E [colistin]) currently are a last line of defense against strains that produce metallocarbapenemases (e.g., NDM-1). Unfortunately, this resistance mechanism has been described for hvKp (337). Another mechanism that mediates polymyxin resistance is increased expression of the PhoP-PhoQ-Arn pathway. Activation of PhoP-PhoQ

results in overexpression of the *arn* operon, which results in the addition of cationic groups to the phosphate moieties of lipid A. This, in turn, leads to a decrease in negative charge and decreased activity in polymyxins. Insertion into *mgrB*, which encodes the PhoP-PhoQ regulatory pathway suppressor MgrB, results in polymyxin resistance (338). This mechanism also has been described for hvKp strains (91, 319).

Tigecycline resistance. Tigecycline resistance has been reported for an cKp strain that evolved into an hvKP strain via acquisition of a portion of an hvKp virulence plasmid (91). Overexpression of the efflux pump gene *acrR* and its regulatory gene *ramA*, which has been associated with tigecycline resistance, was demonstrated.

Effect of Antimicrobial Resistance Genes on hvKp Biofitness

The literature is conflicting on the effect of antimicrobial resistance genes on hvKp biofitness. This may due to the mechanism (autonomous resistance plasmid versus integrated resistance determinants) and the nature (e.g., ESBL versus carbapenemase) of resistance. Reports in the clinical literature of lethal outbreaks due to XDR hvKp strains are highly concerning but uncontrolled (22). Some studies in which hvKp strains were unable to maintain antimicrobial resistance plasmids interpreted this finding as a potential negative effect on biofitness (336). By contrast, an hvKp strain that contained a conjugal plasmid that produced an AmpC β-lactamase demonstrated plasmid stability in the absence of selection and high lethality, similar to the case with the prototypical strain NTUH-K2044 in a mouse infection model (323). A 2014 report described the introduction of a KPC-containing plasmid into an hvKp strain without a loss in resistance to complement-mediated bactericidal activity or lethality in mice (339). A clinical hvKp isolate (strain 3) that was carbapenem resistant due to the combination of ESBL production and decreased OMPK35/36 expression was highly virulent in a mouse lethality assay, but two other hvKp strains that expressed KPC were not (328).

Treatment Options

Antimicrobials. There are no controlled trials that have assessed the efficacy of various antimicrobials against hvKp infection. This is due, in part, to the inability of clinical microbiology laboratories to differentiate cKp from hvKp strains. The recent identification of biomarkers that can accurately identify hvKp strains should enable future clinical trials (140). This issue has become increasingly important with the ever-increasing incidence of XDR hvKp infections.

Given the potential severity of hvKp infection and its propensity for metastatic spread, the empirical regimen chosen should be predicted to be active pending susceptibility results. This would be predicated to minimize subsequent spread (e.g., endophthalmitis). hvKp strains that are carbapenem resistant are most problematic. Ceftazidime-avibactam, colistin, and tigecycline were active against all 65 carbapenem-resistant hvKp strains tested *in vitro*, but none possessed a metallocarbapenemase (e.g., NDM) (142). Although colistin and tigecycline have been active *in vitro*, these agents were not curative in a lethal ICU outbreak due to a KPC2-producing XDR hvKp strain (22), although these patients were immunocompromised and active therapy was not optimally timely in all cases. Once susceptibility results are available, antimicrobial therapy should be deescalated appropriately.

It is important to be cognizant that a number of sites infected by hvKp present increased therapeutic challenges due to the poor penetration of selected antimicrobials. If active based on susceptibility data, for CNS infection, ceftriaxone and meropenem are reliable agents; for prostatic infection fluoroquinolones, trimethoprim-sulfamethoxazole or fosfomycin achieves therapeutic concentrations in this site; for ocular infection, a combination of systemic and intravitreal therapies (e.g., cefazolin, ceftazidime, aminoglycosides, and imipenem) is appropriate. Intraocular steroid treatment has been used (322), but its role, if any, is unclear. Given the rapidly of ocular damage and subsequent loss of vision with hvKp infection, clinical trials are sorely needed to assess various agents and therapeutic approaches, especially with the advent of XDR hvKp strains that severely limit treatment options.

Passive immunization. The confluence of the expanding development and use of monoclonal antibodies (MAbs) for a variety of medical conditions and the increasing prevalence of XDR and PDR strains have increased interest in antibody-based therapy. Surface exposure and conservation are desirable target characteristics. OMPs are tempting targets due to many having a high degree of conservation. But OMPs may be problematic targets due to shielding by surface polysaccharides (340, 341). Surface polysaccharides are ideally situated and form the basis for the pneumococcal, meningococcal, and *Haemophilus influenzae* type b vaccines. Experimentally, this approach has been successfully used to treat and prevent hvKp infection with MAbs directed against the K1 capsule (342) and the O-antigen moiety of LPS (192). The challenge for using passive immunization for the treatment of hvKp infection will be overcoming antigenic diversity of the surface polysaccharides (143). Capsule types are more diverse than O-antigen types (143). Successful passive immunization for the treatment of hvKp infection likely will require the availability of multiple capsule or perhaps O-antigen MAbs and a point-of-care test that can rapidly identify the capsule or O-antigen type from the infecting strain.

Phage therapy. Treatment of bacterial infections with bacteriophage has been used in certain countries in Eastern Europe and the former Soviet Union (343). Although this approach has potential, a variety of scientific and regulatory concerns exist (344). Nonetheless, the increasing incidence of infections due to XDR and PDR bacteria has led to a resurgence of research in this arena. Lin et al. identified a bacteriophage that recognized the K1 capsule (but not other capsule types), was bactericidal against the hvKp strain NTUH-K2044, and was efficacious in a mouse infection model (345). Similar results were obtained for a bacteriophage that recognized the K5 capsule (346). It is unknown whether a bacteriophage can be identified that would recognize all hvKp strains. If not, similar to passive immunization, bacteriophage therapy of hvKp infection will require point-of-care testing for the presence of the bacteriophage receptor in the infecting strain. This area is intriguing but is still in development.

INFECTION CONTROL AND PREVENTION
Reservoirs and Mechanism of Spread

There is a lack of data to guide hvKp infection prevention and control practices beyond standard precautions. The reservoirs and mechanism of spread for hvKp strains have not been established. Pending the generation of hvKp-specific data, utilizing cKp-based data seems reasonable. Potential reservoirs include both the environment and colonized patients. Neonatal ICU incubator water (347) and waste disposal hoppers (348) were recently identified as a potential environmental sources for NDM-1- and KPC-producing *K. pneumoniae*, respectively. However, it is not known whether these findings are applicable to hvKp. Further, it remains unclear which of these reservoirs, if either, is the most important source for transmission. Data for cKp from a multicenter ICU study demonstrated that cephalosporin-resistant *K. pneumoniae* appeared to be more easily transmissible than *E. coli*; this finding heightens concern for spread regardless of the source (349).

Regardless of the mechanism, it is clear that hvKp strains can undergo nosocomial spread. Gu et al. described a lethal outbreak in an ICU due to an XDR hvKP strain (22). Likewise, additional studies are suggestive of nosocomial dissemination (331, 332). In addition, data published by Harada et al. (114) and unpublished data from our group have demonstrated that healthy, close contacts of hvKp-infected patients may be colonized and/or infected with the index hvKp strain. However, presently the relative roles of environmental and person-to-person acquisition are unclear.

Is Enhanced Infection Control Beneficial for Antimicrobial-Sensitive hvKp?

Whether enhanced infection control is beneficial for antimicrobial-resistant hvKp is a critical question that is presently unanswered. It is further complicated by the fact that many hvKp infections may not be recognized, which would preclude institution of appropriate infection control measures if deemed appropriate. Until clinical microbiol-

ogy laboratories implement testing to identify hvKp, a presumptive or potential diagnosis of hvKp infection relies on an astute physician (Table 1). This task is feasible when a patient from the community presents with typical epidemiologic and clinical features, but it presently is difficult to impossible with health care-associated hvKp infection.

Nonetheless, if a presumptive diagnosis of hvKp infection is made, it seems reasonable to assume that hospitalized patients would be at a greater risk for developing infection once colonized. The frequency remains undefined. Data on which patient groups (e.g., those of particular ethnic backgrounds) or settings (e.g., ICUs), if any, are at greater risk for developing or fostering infection also would be informative, and perhaps these data could be used for targeted interventions. Regardless, when considered from a risk-benefit perspective, the consequences of hvKp infection due to antimicrobial-sensitive strains can be severe even in an otherwise healthy host. It is predicted that consequences would be more significant in patients with comorbidities or various degrees of immunocompromise. Therefore, contact precautions are worthy of consideration. At this time, there is a lack of data to determine if healthy contacts or hospitalized patients exposed to hvKp-infected persons should be empirically treated to decrease the chances of subsequent infection or whether these individuals should be screened for hvKp colonization and, if colonized, preemptively treated.

Infection Control Measures for MDR (ESBL-Producing) and XDR (Carbapenemase-Producing) hvKp

The need for point-of-care testing to diagnose infection due to XDR hvKp would appear to be less pressing since infection control measures for patients infected with antimicrobial-resistant hvKp strains should be equivalent to those employed for other highly drug-resistant pathogens independent of virulence potential. For patients infected with carbapenemase-producing hvKp strains, contact precautions, informing receiving facilities that the patient being transferred is colonized or infected with a carbapenem-resistant isolate, and cleaning of areas that the patient is in contact with on a daily basis are recommended (350). Consideration should also be given to active surveillance for extensively drug-resistant strains and contact screening.

There is an ongoing debate as to whether ESBL-producing *Enterobacteriaceae* warrant contact precautions, at least in the nonoutbreak setting (351, 352). Similar to considerations for antimicrobial sensitive hvKP, the consequences of infection with MDR-hvKp is increased relative to other *Enterobacteriaceae* and likely antimicrobial-sensitive hvKp due to decreased treatment options. Therefore, until data become available, it seems reasonable to strongly consider contact precautions and, if feasible, screening of contacts and active surveillance for MDR hvKp, particularly in an outbreak setting.

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Thomas A. Russo (M.D., C.M.) is a Professor of Medicine, Chief of the Division of Infectious Diseases, and a Vice Chair in the Department of Medicine in the Jacobs School of Medicine & Biomedical Sciences at the University at Buffalo. Dr. Russo received his medical degree from McGill University, completed his internship and residency at Harvard-New England Deaconess Hospital, and completed a clinical and research fellowship in infectious diseases at Harvard Medical School and Tufts-New England Medical Center. Following his fellowship, Dr. Russo was a senior staff fellow at the National Institute of Allergy and Infectious Disease's Laboratory of Clinical Investigation for 5 years before being appointed at the University at Buffalo in 1994. Dr. Russo's research focus has been on pathogenesis and vaccine and drug development against extraintestinal pathogenic Escherichia coli, Acinetobacter baumannii, and hypervirulent Klebsiella pneumoniae.

Candace M. Marr (D.O.) is a Clinical Associate Professor in the Department of Medicine and the Division of Infectious Diseases in the Jacobs School of Medicine & Biomedical Sciences. She received her medical degree from Lake Erie College of Osteopathic Medicine, summa cum laude. She completed internal medicine residency and infectious disease fellowship at the University at Buffalo, where she was inducted into Alpha Omega Alpha. She is a 2014 recipient of the IDSA Kass grant and a 2013 recipient of the John Latorolla and Marie Mazzio Memorial Award for academic excellence. Her current research efforts pertain to clinical management of biofilm-associated infections, especially of orthopedic hardware. She has presented original research both regionally and nationally and has published multiple articles on Clostridium difficile and hypervirulent Klebsiella pneumoniae.