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Hypervirulent *Klebsiella pneumoniae*: Characterization, Pathogenesis, and Infectivity

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ABSTRACT

Hypervirulent *Klebsiella pneumoniae* (HvKp) is an emerging pathogen associated with severe and invasive infections, including pyogenic liver abscesses, septicemia, and pneumonia. Its hypervirulence is linked to enhanced capsular polysaccharide production resulting in hypermucoviscosity, efficient siderophore-mediated iron acquisition, and increased tissue invasiveness. HvKp strains are predominantly associated with capsular serotypes K1 and K2. HvKp poses an increasing public health threat due to its rising antimicrobial resistance, which complicates treatment strategies. This review aims to summarize the clinical impact, resistance patterns, and virulence mechanisms of HvKp infections, thereby highlighting their growing significance in clinical microbiology and infectious disease research. HvKp infections are increasingly prevalent, with studies demonstrating that 15–30% of *Klebsiella* isolates in endemic regions such as China and Taiwan are hypervirulent. These infections are associated with higher mortality rates, ranging from 8.1–16.7% for severe outcomes, including liver abscesses and sepsis. Furthermore, HvKp strains are frequently resistant to multiple antibiotics, with resistance rates to carbapenems ranging from 12–20% and frequent production of extended-spectrum β-lactamases (ESBLs). The hypermucoviscosity phenotype of HvKp contributes to its increased invasiveness, particularly in immunocompromised individuals, although HvKp notably also causes severe disease in immunocompetent hosts, resulting in infections that are particularly severe and difficult to treat. HvKp infections pose a growing global health threat due to their high prevalence, severe clinical outcomes, and increasing antimicrobial resistance. These strains require heightened clinical awareness and surveillance to better manage and prevent transmission, underscoring the need for continued research into their pathogenesis and resistance mechanisms. Ultimately, preventing HvKp infections in both community and hospital settings requires a multifaceted approach, encompassing improved public health practices, management of predisposing conditions such as diabetes mellitus, and stringent infection control measures within healthcare facilities.

INTRODUCTION

Klebsiella pneumoniae is a Gram-negative bacterium belonging to the family *Enterobacteriaceae*, characterized by distinct O and K antigens on its cell surface [1]. The O antigen protects *K. pneumoniae* against the bactericidal effects of cationic antimicrobial peptides (CAMPs) [2]. The capsular polysaccharide K antigen is a key virulence determinant that facilitates bacterial evasion of the host immune system [3]. In addition to these surface antigens, *K. pneumoniae* harbors a diverse array of virulence factors that directly contribute to its pathogenicity. For instance, hypermucoviscosity, a phenotype characterized by the overproduction of capsular polysaccharide, enhances immune evasion and contributes to virulence, particularly in invasive infections such as pneumonia. Iron acquisition via siderophores is crucial in systemic infections such as septicemia, as this mechanism is essential for bacterial survival and proliferation within the host, host immune

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defenses sequester iron through a process known as nutritional immunity. Additionally, adhesins play a critical role in urinary tract infections (UTIs) by enabling bacterial adherence to the uroepithelium [4]. Furthermore, *K. pneumoniae* is a significant causative agent in healthcare-associated infections such as central line-associated bloodstream infections (CLABSIs) and ventilator-associated pneumonia (VAP).

Classical *K. pneumoniae* (cKP) strains are of significant clinical importance due to their capacity to develop multidrug resistance (MDR) through chromosomal mutations and horizontal acquisition of resistance genes, often via plasmids [5]. While community-acquired infections can occur, persistent cKP infections are more frequently observed in healthcare settings, particularly in intensive care units (ICUs) and long-term care facilities. In these settings, cKP strains typically infect individuals with compromised immune systems, including those with alcohol use disorder, diabetes mellitus, immunosuppression due to underlying conditions or immunosuppressive therapy, or multiorgan dysfunction [6].

cKP is commonly responsible for hospital-acquired infections, such as pneumonia and UTIs, in immunocompromised or hospitalized individuals and is often characterized by MDR [7]. In contrast, HvKp is associated with more severe, community-acquired infections, liver abscesses, septic shock, and other invasive conditions [8]. For example, in a study among invasive strains (n=53) causing primary liver abscess and metastatic complications, the overwhelming majority—98.1% (52 of 53)—exhibited the hypermucoviscous phenotype and were positive for the *magA* gene. In contrast, among the non-invasive strains (n=52), the hypermucoviscous phenotype was found in only 17.3% (9 of 52) of the isolates, and the *magA* gene was present in just 26.9% (14 of 52), demonstrating a statistically significant difference between the two groups [9]. These findings illustrate that HvKp is distinguished by enhanced virulence factors, particularly hypermucoviscosity, which facilitates immune evasion and increases the pathogen's ability to disseminate to normally sterile body sites. Although both pathotypes can exhibit antibiotic resistance, the defining threat of HvKp is its propensity to cause invasive infections with atypical clinical presentations, such as pyogenic liver abscess and endophthalmitis [10].

From the mid-1980s through the 1990s, a distinct pathotype of *K. pneumoniae*, termed HvKp, was first identified in Taiwan, where it was initially associated with community-acquired pyogenic liver abscess syndrome [10, 11], leading to the current categorization of *K. pneumoniae* into two pathotypes: cKP and HvKp. Although some HvKp strains may harbor both virulence genes and antimicrobial resistance genes, they are primarily defined by their enhanced virulence potential, including hypermucoviscosity and increased invasiveness [12].

Typically, cKP infections are encountered in hospital settings, particularly within ICUs or long-term care facilities, which accommodate immunocompromised patients [13]. cKP generally causes non-invasive, localized infections such as UTIs and pneumonia, generally without metastatic spread, in contrast to HvKp. Furthermore, cKP infection can induce alterations in hematological parameters, similar to other severe bacterial infections; for instance, leukopenia, neutropenia, and thrombocytopenia have been reported [14]. Additionally, the growing ability of cKP strains to acquire plasmids carrying various antimicrobial resistance genes, such as those encoding ESBLs and carbapenemases, and virulence genes increase their clinical significance [15].

HvKp strains are distinguished from cKP by exhibiting a prominent hypermucoviscosity phenotype, which can be assessed by the string test, characterized by the formation of viscous strings (>5 mm) when colonies grown on blood agar are touched with an inoculation loop. This phenotype is frequently associated with enhanced biofilm formation and the presence of the *rmpA* (regulator of mucoid phenotype) and *magA* (*magA*, now identified as the K1-specific polymerase *wzy_K1*) genes. Additionally, HvKp strains often carry the *iuc* (aerobactin) and *iro* (salmochelin) gene clusters, which are crucial for iron acquisition, enhancing bacterial virulence by facilitating survival and proliferation in iron-limited host environments [16]. Furthermore, a significant proportion of HvKp isolates belong to capsular serotypes K1 and K2 [17]. Clinically, HvKp is frequently associated with abscess formation, particularly hepatic abscesses, and exhibits a propensity for metastatic spread, even in immunocompetent individuals. This contrasts with cKP, which typically manifests as opportunistic infections primarily affecting individuals with underlying comorbidities and/or compromised immunity [18]. Phenotypically, HvKp exhibits enhanced resistance to complement- and neutrophil-mediated killing *in vitro* and demonstrates greater virulence *in vivo* compared to cKP strains [19]. Importantly, the emergence of HvKp strains that have acquired MDR has been documented, posing a significant clinical threat [20].

This review focuses on elucidating the pathogenesis and mechanisms of infection of HvKp by examining the mechanisms underlying its capacity to cause severe invasive infections in both community-acquired and healthcare-associated settings. It provides a comprehensive overview of the phenotypic and molecular characteristics that distinguish HvKp from cKP, including virulence determinants and antimicrobial resistance patterns. By analyzing the virulence factors and immune evasion strategies employed by HvKp, this review synthesizes current literature to inform the development of targeted therapeutic and preventive interventions. Ultimately, this review aims to deepen the

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understanding of HvKp pathogenesis and thus guide strategies to improve clinical outcomes in infected patients.

Phenotypic and molecular characterization of HvKp virulence

Phenotypic characterization. HvKp can be differentiated from cKP based on several key phenotypic characteristics, which are essential for laboratory identification and clinical diagnosis. The hallmark phenotype of HvKp is hypermucoviscosity [21]. This characteristic can be reliably identified using the string test (formation of a viscous string > 5 mm) and sedimentation test. In addition to hypermucoviscosity, other major phenotypic markers include siderophore production and capsular antigen expression. Siderophores are high-affinity iron-chelating molecules produced by *K. pneumoniae* to sequester iron from the host environment, an essential nutrient for bacterial growth and virulence; however, HvKp strains typically produce a broader repertoire and higher quantities of siderophores. Additionally, capsular antigens contribute significantly to HvKp's ability to evade the host immune system by inhibiting phagocytic uptake and complement deposition, while also facilitating biofilm formation. While cKP strains exhibit some degree of immune evasion, with their capsule providing limited protection against complement-mediated killing and phagocytosis, HvKp strains demonstrate stronger complement resistance and enhanced antiphagocytic properties. This is largely due to a thicker, more protective capsule and additional virulence factors. These characteristics make HvKp more effective at evading the immune system, thereby causing more severe infections compared to cKP strains [20–22]. In summary, these phenotypic traits contribute synergistically to the enhanced virulence of HvKp and its resultant capacity to cause severe invasive infections [23].

Hypermucoviscosity. Hypermucoviscosity in HvKp is primarily attributed to the overproduction of capsular polysaccharide and extracellular polysaccharide, a process frequently linked to the acquisition of the *rmpA* and *rmpA2* genes [24]. This manifests phenotypically as increased colony viscosity and has been associated with enhanced surface spreading on agar media [25]. The phenotype can be assessed *in vitro* through established methods, including the qualitative string test and the quantitative sedimentation test, as detailed in Table 1 [26]. Importantly, this phenotype confers several advantages to HvKp, including impairment of phagocytic clearance through physical hindrance of phagocyte-bacterium interactions, promotion of enhanced biofilm formation, and enhanced resistance to environmental stressors, such as desiccation and antimicrobial agents [27]. Collectively, these properties enable HvKp to effectively evade host innate immune defenses, facilitating dissemination within the host and resulting in severe systemic infections [28]. Historically, the clinical significance of this phenotype was first highlighted by the emergence of HvKp in Taiwan, where it was isolated from patients presenting with PLA, septicemia, and endophthalmitis [29].

The string test is a rapid phenotypic method for assessing hypermucoviscosity. A positive string test, an indicator of the hypermucoviscous phenotype in *K. pneumoniae*, is characterized by the formation of a viscous mucoid string ≥5 mm in length when a colony grown on blood agar is stretched using an inoculation loop [30]. Clinically, this finding is significant because it correlates with the enhanced virulence potential of the isolate and serves as a valuable screening tool in clinical microbiology laboratories for identifying isolates capable of causing severe infections in both immunocompetent and immunocompromised patients [31]. The string test for HvKp demonstrates high sensitivity (typically 80–100%) and moderate specificity (typically 80–90%) for identifying HvKp strains when compared to molecular detection of virulence genes, making it an effective, though not definitive, presumptive diagnostic tool due to potential variability in interpretation and culture conditions [32].

Siderophore. Iron (Fe) is an essential micronutrient for microorganisms, playing a critical role in numerous essential metabolic processes. Iron primarily exists in two oxidation states: the less soluble ferric (Fe^{3+}) and the more bioavailable ferrous (Fe^{2+}) form [33]. For optimal growth and metabolism, bacteria require iron concentrations in the range of 10^{-7} to 10^{-5} M (0.1–10 µmol/L) [34]. However, despite total iron concentrations within the human host of typically 10 to 50 µmol/L, free iron availability is extremely limited [35]. Furthermore, iron bioavailability can be marginally lower in infected individuals [36]. This is because bacteria often encounter iron-restricted environments, a host defense mechanism known as nutritional immunity, wherein the host sequesters iron using proteins such as transferrin, lactoferrin, and ferritin. Furthermore, iron bioavailability is typically reduced in infected individuals due to host-mediated iron sequestration [36]. To overcome iron restriction, bacteria synthesize siderophores that effectively sequester host iron, a process crucial for their survival, proliferation, and pathogenesis [37]. Microorganisms, particularly Gram-negative bacteria, synthesize four principal classes of siderophores: hydroxamates, catecholates (*e.g.*, enterobactin), carboxylates (*e.g.*, citrate-based siderophores), and mixed-ligand types (*e.g.*, yersiniabactin) [38]. HvKp strains characteristically produce multiple siderophores, including enterobactin, yersiniabactin, salmochelin, and aerobactin, with the latter two being particularly associated with hypervirulence. These siderophores are encoded by specific gene clusters, including *iuc* (aerobactin), *iro* (salmochelin), *irp/ybt* (yer siniabactin), and *ent* (enterobactin). Regarding HvKp specifically, siderophore production is a key virulence determinant, as it enables the pathogen to thrive in iron-restricted host

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environments. This superior iron acquisition enhances bacterial survival, growth, and persistence, thereby enabling the pathogen to overcome host nutritional immunity and directly contributing to the hypervirulent phenotype of HvKp [39].

The effectiveness of siderophores depends on the bacterium's ability to produce and utilize specific types, such as enterobactin, aerobactin, yersiniabactin, and salmochelin [40]. Of these siderophores, enterobactin, encoded by the *ent* gene cluster, exhibits the highest affinity for iron among known bacterial siderophores; however, its effectiveness is limited by host lipocalin-2, which can sequester enterobactin. Aerobactin is highly prevalent in HvKp strains (reported in up to 90–100% of strains), and studies in murine models demonstrate its significant contribution to virulence, likely due to its stability under host physiological conditions, contrasting with its comparatively lower prevalence (~6%) in cKP [41]. Yersiniabactin biosynthesis is encoded within the high-pathogenicity island (HPI), a genomic region indispensable for the virulence of *Yersinia* spp. and other pathogens, including *K. pneumonia* [42]. Additionally, yersiniabactin is also particularly effective in facilitating biofilm formation. Furthermore, HvKp strains frequently harbor the gene clusters encoding salmochelin production (the *iro* gene cluster), in addition to other virulence genes such as *rmpA* [43]. Therefore, variations in siderophore profiles serve as valuable markers for differentiating HvKp from cKP.

Phenotypic detection of siderophore production is essential for characterizing iron acquisition capabilities. Siderophore production can be detected using the colorimetric Chrome Azurol Sulfonate (CAS) assay, which can be used for both qualitative and semi-quantitative detection. This assay relies on a color change from blue to orange or pink when siderophores remove ferric iron (Fe^{3+}) from the CAS-Fe dye complex, thereby releasing the free dye which changes color [44]. The CAS assay can be performed on agar plates (CAS agar), where siderophore production is indicated by an orange halo surrounding the bacterial colony, or in liquid culture. Additionally, the CAS assay can be adapted to a 96-well microplate format for efficient high-throughput screening of multiple bacterial isolates under various growth conditions, including different iron concentrations and media compositions, which is particularly valuable for epidemiological studies and surveillance [45]. However, the CAS assay does not distinguish between different siderophore types, and molecular detection of siderophore biosynthesis genes (*e.g.*, *iuc*, *iro*, *irp*) is required for specific identification.

Capsular antigen. The capsule, which constitutes the K antigen, is a dense polysaccharide layer that encases the bacterial cell surface. In *K. pneumoniae*, this structure is composed of repeating sugar units that vary antigenically among strains [46]. This capsule serves several critical virulence functions, including protecting the bacterium from the host immune system by inhibiting phagocytosis and complement activation, and in some contexts, facilitating adherence to host tissues and biofilm formation, thereby facilitating the establishment of infection [47].

The capsular phenotype also confers additional bacterial functions, including resistance to desiccation, prevention of entrapment within host mucus during colonization, thus facilitating respiratory tract colonization, and evasion of the host immune system via inhibition of phagocytosis [48]. Notably, the degree of capsular expression, manifesting as hypermucoviscosity (characterized by the overproduction of capsular polysaccharide and extracellular polysaccharide), and elevated siderophore production serve as key phenotypic markers differentiating cKP from HvKp [49]. Specific capsular serotypes, particularly K1 and K2, are strongly associated with the HvKp phenotype. As a result of these differences, cKP strains, lacking these pronounced virulence-associated phenotypes, typically cause opportunistic infections such as UTIs, pneumonia, bacteremia, and sepsis, primarily in immunocompromised individuals rather than healthy hosts [50]. Notably, HvKp is increasingly detected in hospitalized settings and is also responsible for these clinical infections [51]. The overproduction and increased thickness of the capsule in HvKp are largely attributed to the presence of the *rmpA* and *rmpA2* genes, while the absence of these genes correlates with a thinner capsule [52]. A summary of these phenotypic characteristics is provided in Table 1.

Table 1. Key phenotypic differences between classical and hypervirulent *K. pneumoniae*

Phenotypic characteristic	Test/assay	cKP phenotype	HvKp phenotype	References
Hypermucoviscosity	String test	Negative (≤ 5 mm string)	Positive (> 5 mm string)	[53]
	Sedimentation assay	High sedimentation (rapid pelleting)	Low sedimentation (slow pelleting)	
Siderophore profile	Siderophore gene detection (PCR)	Enterobactin, Yersiniabactin	Enterobactin, yersiniabactin, salmochelin, aerobactin (typically all four)	[54]
	Siderophore production (CAS assay)	Lower production (*e.g.*, ≤ 9 mm halo)	Higher production (*e.g.*, > 9 mm halo)	[55]
Capsular Antigens	Predominant serotypes (molecular serotyping)	K2, K3, K20, K23, K47	K1, K5, K54, K57	[56]

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Molecular markers are essential for distinguishing between the two pathotypes. cKP and HvKp can be differentiated in part by the presence of the *rmpA* and *rmpA2* genes, among other virulence markers [57]. Furthermore, distinct capsular serotypes are associated with each pathotype, with *rmpA* being particularly prevalent in K1 and K2 strains; cKP strains frequently exhibit serotypes K3, K20, K23, and K47, whereas HvKp is commonly associated with K1, K2, K5, K54, and K57. In addition to specific serotypes, which have been linked to distinct infection types (*e.g.*, K1 with liver abscesses, K2 with pneumonia) [58], other capsule-associated genes such as *wabG* (LPS core biosynthesis), *uge* (UDP-galacturonate epimerase), and *ycfM* (outer membrane protein) also contribute to bacterial pathogenesis, making them valuable markers for differentiating cKP from HvKp [59]. Together, these genetic markers provide a comprehensive approach for identifying HvKp strains.

Molecular characterization of HvKp

The role of the *uge* gene in capsule biosynthesis. Among the genes involved in capsule biosynthesis, the *uge* gene plays a particularly important role. The *uge* gene in *K. pneumoniae* encodes UDP-galacturonate 4-epimerase, an enzyme critical for the biosynthesis of nucleotide sugars required for the production of both the O-antigen of LPS and the K-antigen capsular polysaccharide, which contain galacturonic acid residues [60]. Mutations within the *uge* gene disrupt this pathway, leading to defective capsule formation and attenuated virulence. Consequently, mutant strains exhibit increased susceptibility to phagocytosis and to β-lactam and polymyxin antibiotics [61]. Because a functional *uge* gene is present in nearly all strains of *K. pneumoniae*, particularly in virulent isolates (with a prevalence of 80–100% reported in hypervirulent isolates) [62], the integrity of this gene can serve as a molecular marker for differentiating cKP from HvKp strains. The presence of a mutated, non-functional *uge* gene is indicative of reduced virulence potential and is more commonly observed in cKP strains, as outlined in Table 2.

The *magA* gene and K1 serotype association. The *magA* (mucus-associated gene A) gene, subsequently identified as the K1-serotype-specific capsular polysaccharide polymerase (*wzy*_K1), and thus exclusive to K1 strains, is a key component of the *K. pneumoniae* capsule gene cluster, located within a 35-kbp locus that contains 24 open reading frames (ORFs) with homology to genes involved in lipopolysaccharide biosynthesis and glycosylation [63]. Functionally, the protein encoded by *magA* is a significant virulence factor that contributes to severe *Klebsiella* infections, including septicemia, pneumonia, liver abscesses, and occasionally lung abscesses [64]. These infections are frequently observed in individuals with compromised immune systems but notably can also occur in immunocompetent individuals, a hallmark feature distinguishing HvKp from cKP. Reflecting its role in hypervirulence, the prevalence of the *magA* gene is significantly higher in HvKp strains. For example, a study by Yu *et al.* [65] reported its presence in 70–90% of hypervirulent K1 strains, confirming the strong association between this gene and the K1 serotype. This serotype is strongly associated with invasive infections such as PLA and bloodstream infections. Therefore, detection of *magA* effectively serves as a molecular marker for the K1 capsular serotype. While *magA* remains commonly used in the literature, *wzy*_K1 is the current standard nomenclature.

Capsular polymerase (*wzy*) gene and serotype specificity. The *K. pneumoniae* capsule synthesis (*cps*) locus, also referred to as the K locus, is a highly variable genetic region responsible for capsule biosynthesis. Within this locus, a key gene is *wzy*, which encodes the capsular polysaccharide polymerase (Wzy) [66]. This enzyme functions to link the repeating polysaccharide subunits together, and its sequence variation is the primary determinant of the approximately 80 distinct capsular (K) serotypes, enabling molecular serotyping through *wzy* sequencing. Notably, specific *wzy* alleles, particularly those encoding K1 and K2 capsular types, are strongly associated with the HvKp phenotype and enhanced capsule production [67]. Certain *wzy* variants, particularly those defining the K1 and K2 serotypes, which are strongly associated with invasive infections such as liver abscesses, are highly prevalent in clinical isolates, making this gene a critical target for the molecular characterization and surveillance of HvKp. *Wzy* alleles can be identified through PCR-based methods or whole-genome sequencing, enabling rapid capsular serotype determination.

Regulator of mucoid phenotype A (*rmpA*) gene. The *rmpA* gene is a transcriptional activator that regulates the characteristic mucoid phenotype of *K. pneumoniae* by upregulating exopolysaccharide (EPS) and capsular polysaccharide synthesis [68]. cKP strains can acquire the virulence-associated *p-rmpA* gene through horizontal gene transfer via plasmids. The *p-rmpA* gene is typically located on large virulence plasmids, often alongside other virulence genes such as *iuc* and *iro*. This plasmid-borne gene, along with its homolog *p-rmpA2*, both contribute to hypermucoviscosity and are distinct from the chromosomally encoded *c-rmpA*. While both genes can influence capsule expression, the plasmid-borne *p-rmpA* is most consistently associated with the hyperproduction of capsular polysaccharide that characterizes the hypermucoviscous phenotype [69]. As a result, the detection of *rmpA* (particularly *p-rmpA*) is strongly correlated with virulence and is frequently observed in severe infections such as PLA, septicemia, and pneumonia. *rmpA* is present in the majority of HvKp strains (typically > 90%) but is rarely detected in cKP strains. Furthermore, serum resistance, which is a crucial factor in the pathogenesis of PLA, is associated with the combined presence of *rmpA* and *ompA* (encoding outer

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membrane protein A) [70]. Therefore, the presence of *rmpA*, often in conjunction with *ompA*, serves as key molecular markers for differentiating cKP from HvKp.

Tellurite resistance as a virulence-associated marker. Tellurite, a rarely encountered oxyanion in natural environments, exhibits significant toxicity towards bacteria; a concentration of 1 µg/mL is considered toxic to both *E. coli* and *K. pneumonia* [71]. Resistance to tellurite in *K. pneumoniae* is conferred by proteins encoded by the *ter* operon, which mediate tellurite reduction and detoxification. This operon includes the *terA*, *terB*, *terC*, and *terD* genes, among others [72]. In *K. pneumoniae*, tellurite resistance not only indicates an ability to withstand environmental stress but is also frequently co-located with other virulence genes on the same plasmid [73]. Consequently, this phenotype may be associated with resistance to certain antibiotics and host defense mechanisms, due to co-carriage of resistance genes on the same plasmid, thereby enhancing the bacterium's survival within the host. Tellurite resistance can be assessed phenotypically by growth on medium containing potassium tellurite, or genetically by PCR detection of *ter* genes. Crucially, the *ter* operon is often located on the large virulence plasmids (typically >100 kb) characteristic of HvKp, making tellurite resistance, a valuable surrogate marker for identifying HvKp strains [72].

Other plasmid-encoded markers associated with HvKp. Beyond well-characterized virulence genes, the large virulence plasmids typical of HvKp often carry hypothetical or putative genes whose functions remain incompletely characterized, they can still serve as useful molecular markers. These peg (protein-encoding gene) designations originate from automated genome annotation and represent open reading frames of unknown or predicted function. For instance, the hypothetical protein peg-1631 has been detected during PLA infections caused by HvKp and was used as a positive control marker for HvKp identification [74]. Additionally, several other putative genes located on HvKp virulence plasmids, such as the transporter peg-344 and the carboxymuconolactone decarboxylase family protein peg-589, are frequently co-detected with established virulence genes like *rmpA*, *magA*, *iucA*, and *iroB* in HvKp isolates [75]. While the precise contributions of these Peg loci to pathogenesis are still under investigation, their consistent co-localization with core virulence determinants makes them useful surrogate markers for detecting HvKp strains and characterizing the virulence plasmids they carry.

Table 2. Key genetic markers for differentiating cKP and HvKp strains

Virulence Factor Category	Gene	cKP	HvKp	References
Capsule/LPS biosynthesis	*uge*	+ (functional)	+ (functional)	[76]
Capsule serotype-specific genes	*magA* (*wzy*_K1)	−	+	[63,77]
	*wzy*_K1	−	+	[78]
	*wzy*_K2	+/−	+	
	*wzy*_K3	+	−	
	*wzy*_K5	−	+	
	*wzy*_K20	+	−	
	*wzy*_K23	+	−	
	*wzy*_K47	+	−	
	*wzy*_K54	−	+	
	*wzy*_K57	−	+	
Hypermucoviscosity	*rmpA* (*p-rmpA*, *p-rmpA2*) (Plasmid-borne)	−	+	[77]
	c-rmpA (Chromosomal)	+	−	
Siderophore production	*ent* (enterobactin)	+	+	[79]
	irp2 (yersiniabactin)	+/−	+	
	iroB (salmochelin)	−	+	
	iucA (aerobactin)	−	+	
Tellurite resistance	*ter* operon (*terA*, *terB*, *terC*, *terD*)	−	+	[72,80]
Other plasmid-associated markers	peg-1631 (hypothetical protein)	−	+	[74]
	peg-589 (carboxymuconolactone decarboxylase)	−	+	[81]
	peg-344 (putative transporter)	−	+	[75]

Abbreviations: cKP, classical *Klebsiella pneumoniae*; HvKp, hypervirulent *K. pneumoniae*; LPS, lipopolysaccharide. +, gene typically present; −, gene typically absent; +/−, variable presence

Pathogenesis of HvKp. The enhanced virulence of HvKp compared to cKP is attributed to a complex interplay of bacterial virulence factors, host immune responses, and resulting tissue damage [82]. Understanding these mechanisms is crucial for developing effective treatments and preventing severe complications [83]. The key pathogenic determinants of HvKp are described below:

- Capsule and Hypermucoviscosity: thick polysaccharide capsule, particularly associated with K1 and K2 serotypes and regulated by genes such as *rmpA*, confers the characteristic hypermucoviscous phenotype. This capsule is central to HvKp pathogenesis, as it facilitates evasion of host immune clearance by resisting phagocytosis, complement-mediated opsonization, and direct complement-mediated killing [84].
- Iron Acquisition Systems: HvKp harbors specific genetic determinants encoding highly efficient siderophores, including aerobactin, salmochelin, and

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yersiniabactin. These systems allow the bacterium to scavenge iron in the iron-limited host environment, a defense mechanism known as nutritional immunity. This process is essential for its survival, proliferation, and overall pathogenicity [85].

- Adhesins and Biofilms: Virulence is further enhanced by adhesins and pili (including type 1 and type 3 fimbriae), which mediate attachment to host tissues in the urinary and respiratory tracts [86], and by a robust capacity to form biofilms, which promotes bacterial persistence and resistance to host immune defenses and antibiotics [87].
- Lipopolysaccharide (LPS): As a Gram-negative bacterium, HvKp produces LPS, the lipid A component of which is a potent endotoxin that modulates the host inflammatory response, contributing to tissue damage [88].

Many of these virulence determinants are encoded on large virulence plasmids characteristic of HvKp strains. In summary, these virulence factors collectively enable HvKp to cause severe, invasive, and difficult-to-treat infections [82-88].

Transmission and colonization. HvKp transmission occurs in both community and healthcare settings. In the community, it can be transmitted via respiratory droplets generated when an infected or colonized individual coughs or sneezes, or, more commonly, through the fecal-oral route, with the gastrointestinal tract serving as the primary reservoir. Transmission can also occur through direct contact with contaminated surfaces (fomites) [89]. Following exposure, HvKp can colonize the gastrointestinal tract as well as the upper respiratory tract, particularly the nasopharynx. From this reservoir, HvKp may subsequently be aspirated into the lower respiratory tract, including the lungs, which can result in pneumonia [90]. Notably, community-acquired HvKp infections often occur in otherwise healthy individuals, suggesting efficient transmission and colonization mechanisms distinct from cKP. In healthcare settings, by contrast, invasive medical devices, including intravascular catheters (central and peripheral), urinary catheters, and mechanical ventilators, serve as critical portals of entry, significantly increasing the risk of colonization and eventual nosocomial HvKp infection [91]. In addition, transmission can occur via the hands of healthcare workers, emphasizing the importance of hand hygiene. Risk factors for colonization include prior antibiotic use, prolonged hospitalization, and immunocompromised status. Understanding these transmission routes is essential for implementing effective infection control measures in both community and healthcare settings.

Adherence and invasion. The pathogenesis of HvKp infection begins with adherence to host tissues. Adhesion factors, including pili (such as type 1 and type 3 fimbriae) and outer membrane proteins, mediate the initial attachment of the bacterium to host epithelial cells, including those of the respiratory and urinary tracts. This step is crucial for establishing colonization and is followed by invasion of host cells, where HvKp may survive intracellularly to some extent, further promoting infection and evading immune surveillance [92]. Following successful colonization, HvKp employs multiple strategies to evade host immune defenses.

Immune evasion. A key immune evasion strategy of HvKp is the production of a thick polysaccharide capsule [93]. This capsule functions as a physical barrier that protects the bacterium from phagocytosis by masking key surface antigens from immune cell receptors. The hypermucoviscous phenotype further contributes to immune evasion by impeding neutrophil-mediated killing. Furthermore, the capsule critically interferes with the complement system—an essential component of the innate immune response responsible for pathogen elimination [94]. Specifically, the HvKp capsule inhibits the alternative and lectin complement pathways, a mechanism involving the binding of host factor H, a complement regulatory protein, to reduce C3b deposition on the bacterial surface. This action effectively prevents complement-mediated opsonization and subsequent phagocytosis, allowing the pathogen to survive and proliferate within the host [95]. Additionally, HvKp demonstrates enhanced serum resistance, allowing survival in the bloodstream.

Inflammatory response and tissue damage. Despite its effective immune evasion mechanisms, HvKp infection still elicits a robust inflammatory response in the host [96]. The activation of immune cells, such as neutrophils and macrophages, results in the release of proinflammatory cytokines, including interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α). While this immune response is intended to control the infection, the high bacterial burden often associated with HvKp can trigger excessive or dysregulated cytokine release. This phenomenon, termed a "cytokine storm," can lead to significant immunopathology, tissue damage, and organ injury (including lung and liver damage). Furthermore, this excessive neutrophil recruitment to the site of infection can lead to the formation of abscesses within the lung parenchyma, a hallmark of severe HvKp pneumonia [97].

Toxin production. While HvKp is primarily defined by its capsule and iron acquisition systems, toxin production also contributes to its pathogenicity. Like all strains of *K. pneumoniae*, HvKp possesses LPS, a major component of the outer membrane. The lipid A component of LPS is a potent endotoxin, which can trigger an excessive inflammatory response, leading to septic shock and tissue damage. Furthermore, certain strains of *K. pneumoniae* have been reported to produce toxins, such as colibactin, although CNF1, more commonly associated with *Escherichia coli*, has also been detected in some isolates [98]. Although these toxins are not exclusive to the HvKp pathotype, their expression can exacerbate the

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tissue damage and contribute to the overall severity of the infection. Together, these toxin-mediated effects amplify the host inflammatory response and contribute to disease severity.

Host-pathogen interactions in HvKp infection. Host defense against bacterial invasion relies on phagocytosis by neutrophils (polymorphonuclear granulocytes) and the bactericidal activity of serum, which is largely mediated by the complement system [99]. The complement cascade can be initiated via the classical, alternative, or lectin pathways, all of which converge to promote opsonization and bacterial clearance [100]. However, the pathophysiology of HvKp infection is defined by its remarkable ability to subvert these defenses. The thick, negatively charged polysaccharide capsule characteristic of HvKp is a primary mechanism of evasion; it sterically hinders the deposition of complement component C3b, thereby preventing opsonophagocytosis and formation of the MAC [101]. Furthermore, specific HvKp serotypes, such as K1 and K2, are particularly adept at resisting complement-mediated killing. This enhanced immune evasion allows HvKp to survive in the bloodstream and disseminate to distant sites, a key step in the development of severe, metastatic infections such as liver abscesses and endophthalmitis.

Building on these immune evasion mechanisms, the enhanced virulence of HvKp stems from its ability to manipulate host-pathogen interactions through several synergistic mechanisms. Its thick polysaccharide capsule is a primary tool for subverting host immunity, preventing effective detection and elimination by immune cells [102]. This resistance to clearance allows HvKp to invade host tissues proficiently, leading to invasive disseminated disease such as liver abscesses, even in immunocompetent individuals [103]. The infection is further characterized by a dysregulated inflammatory response, where the potent proinflammatory signals triggered by HvKp overwhelm host regulatory mechanisms, culminating in excessive inflammation and tissue damage [104]. Finally, its capacity for robust biofilm formation promotes persistent colonization on both host tissues and indwelling medical devices, increasing the risk of chronic and refractory infections [105]. Collectively, these strategies enable HvKp to cause distinct, organ-specific diseases that can overwhelm host immune clearance mechanisms, thereby complicating therapeutic interventions [106].

Recent studies have highlighted specific host proteins critical for defense against *K. pneumoniae* infection, which are likely key targets for HvKp immune evasion strategies. Among these are neutrophil myeloperoxidase, which generates reactive oxygen species to kill bacteria and modulate neutrophil elastase activity via oxidative mechanisms [107], and lipopolysaccharide-binding protein (LBP), which facilitates the transfer of bacterial cell wall components to inflammatory cells to initiate an appropriate immune response. The importance of these factors is underscored by experiments in which gene-deficient mice demonstrate increased susceptibility to infection [108]. While these defenses are effective against cKP strains, the potent anti-phagocytic and anti-complement properties of the HvKp capsule may allow the pathogen to evade or overwhelm these specific clearance mechanisms, contributing to its hypervirulent phenotype.

At the molecular level, HvKp employs a multitude of strategies to evade host innate immunity. As described above, a prominent mechanism is the production of its thick polysaccharide capsule, which plays a crucial role in its pathogenicity [109]. This capsule functions as a protective barrier, impeding phagocytosis by neutrophils and interfering with the deposition of complement components, notably C3b. In concert with this protective capsule, surface adhesins are critical for mediating attachment to specific host cells and tissues [110]. Together, these factors are essential for establishing colonization and enabling the progression of invasive HvKp infections.

Beyond physical barriers, HvKp employs other strategies to resist host immunity. The long O-antigen chains of its LPS can activate the complement cascade; however, this structure can sterically hinder the insertion of the functional membrane attack complex (MAC) into the bacterial membrane, thereby preventing cell lysis [111]. Furthermore, HvKp effectively competes for host iron through the secretion of high-affinity siderophores. This competition is crucial for pathogenesis, as the host actively sequesters iron using binding proteins as a form of nutritional immunity to deprive bacteria of this essential nutrient [112].

Clinical manifestations of HvKp infections. HvKp causes a distinctive spectrum of clinical syndromes that differ markedly from those caused by cKP. Community-acquired HvKp infections are being reported with increasing frequency worldwide, though they remain most prevalent in East Asian countries such as Taiwan, China, and South Korea, where the K1 serotype predominates [113]. While HvKp can infect healthy individuals, certain risk factors are associated with increased susceptibility and severity, including diabetes mellitus, alcohol use disorder, malignancies, and immunosuppressive conditions or therapy [114]. Diabetes mellitus, in particular, impairs immune function and creates favorable conditions for bacterial colonization, including impaired neutrophil function and hyperglycemia-associated epithelial damage, significantly elevating the risk of serious clinical outcomes such as liver abscesses [115]. In terms of transmission, community spread, which poses significant public health challenges, is facilitated through person-to-person transmission, environmental reservoirs, and potentially animal vectors (though this route requires further investigation) [116].

Clinically, a defining feature of HvKp is its capacity to cause severe, invasive infections even in previously

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healthy, immunocompetent hosts. This is in stark contrast to cKP, which typically causes opportunistic infections such as healthcare-associated pneumonia and UTIs in immunocompromised individuals. Hallmark clinical manifestations of HvKp include PLA, which can be complicated by metastatic spread leading to pneumonia, meningitis, endophthalmitis, septic arthritis, and osteomyelitis [117]. This ability to cause disseminated, community-acquired infections is a direct result of the distinct virulence factors harbored by HvKp strains [117]. The following sections describe specific clinical syndromes associated with HvKp in both community and healthcare settings.

Community-acquired infections. CA *K. pneumoniae* infections are those acquired outside of healthcare settings. The bacterium is a common commensal of the human gastrointestinal tract and is also found in various environmental niches [118]. While many individuals are susceptible, those with substance use disorders (*e.g.*, alcohol use disorder), tobacco use, and underlying conditions such as diabetes mellitus, COPD, advanced age, or compromised immunity exhibit a heightened risk of infection [119]. When CA infections are caused by HvKp strains, they are typically more severe. For instance, bacteremia can rapidly progress to sepsis and organ failure, with higher mortality rates due to the pathogen's enhanced virulence and immune evasion capabilities. Furthermore, HvKp strains increasingly exhibit multidrug resistance, complicating treatment and making these infections particularly challenging to manage in vulnerable populations [120].

Community-acquired pneumonia (CAP). *K. pneumoniae* is a significant cause of CAP, a lower respiratory tract infection characterized by inflammation of the alveoli [121]. While cKP is a well-known cause of pneumonia, particularly in individuals with underlying conditions such as alcohol use disorder or diabetes, infections caused by HvKp strains present a more serious clinical picture. HvKp pneumonia is often characterized by rapid progression, extensive lung necrosis, cavitary lesions, and the formation of abscesses [122]. Clinical presentation typically includes high fever, productive cough, and hemoptysis, reflecting the necrotizing nature of the infection. Unlike typical cKP infections, HvKp can cause life-threatening pneumonia even in young, previously healthy hosts. Furthermore, HvKp pneumonia frequently results in metastatic spread, leading to secondary complications such as bacteremia, empyema, and distant abscess formation in sites such as the liver or brain, contributing to its high morbidity and mortality, with reported case-fatality rates of 20-50% in severe cases [123].

Community acquired bacteremia (CAB). CAB, the presence of bacteria in the bloodstream confirmed upon or within 48 hours of hospital admission, according to standard epidemiological definitions, is a severe condition, and *K. pneumoniae* is a leading cause worldwide [124]. In the community setting, *K. pneumoniae* bacteremia often arises from the dissemination of primary infections, most commonly from the urinary or respiratory tracts, or from primary liver abscesses in endemic regions [125]. While bacteremia with cKP is a serious concern, infections involving HvKp strains are associated with a dramatically worse prognosis. HvKp bacteremia is characterized by a high bacterial load, rapid progression to septic shock, and a significantly higher mortality rate compared to cKP bacteremia, with reported rates of 20-40% in some studies. Furthermore, a hallmark of HvKp bacteremia is its strong propensity for metastatic spread, often leading to devastating secondary infections such as liver abscesses, endophthalmitis, and meningitis, even in otherwise healthy individuals [126]. Prompt initiation of appropriate empiric antibiotic therapy is critical given the rapid progression of HvKp bacteremia.

Community-acquired UTI. While *Escherichia coli* is the most common cause of community-acquired UTIs, *Klebsiella pneumoniae* is also a significant uropathogen [127]. These infections typically occur when perineal or periurethral flora, including *K. pneumoniae*, ascend via the urethra into the bladder. Although most UTIs caused by cKP are uncomplicated, infections involving HvKp strains can lead to significantly more severe outcomes. HvKp is associated with a higher incidence of complicated UTIs, including pyelonephritis, renal abscesses, and prostatitis (in males). Crucially, due to its enhanced virulence and capacity for systemic invasion, HvKp originating from a UTI can disseminate into the bloodstream, serving as a primary source for secondary bacteremia and disseminated infections in other organs [128]. Therefore, clinicians should maintain a high index of suspicion for HvKp in patients with severe or complicated UTIs.

Community-acquired *K. pneumoniae* meningitis. While meningitis caused by cKP is rare in the community, HvKp is an emerging and life-threatening cause of this central nervous system (CNS) infection [129]. A hallmark of the HvKp pathotype is its capacity for metastatic spread, as discussed above. Consequently, HvKp meningitis typically arises as a devastating complication of bacteremia originating from PLA or severe pneumonia, and may be accompanied by endophthalmitis. Patients typically present with fever, altered mental status, and neck stiffness, often with concurrent signs of the primary infection. This clinical presentation contrasts sharply with that of typical bacterial meningitis pathogens, such as *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae*, which usually present as primary infections without an extracranial source. Given its association with high morbidity and mortality, with case-fatality rates exceeding 30% in some series, a diagnosis of *K. pneumoniae* meningitis, particularly in a patient with a concurrent abscess, should raise a high index of suspicion for HvKp.

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Other community-acquired syndromes. In addition to the classic invasive syndromes, HvKp has been implicated in other serious community-acquired infections. For example, certain HvKp strains have emerged as gastrointestinal pathogens capable of causing severe diarrhea, particularly in immunocompromised individuals such as those with HIV infection [130]. This phenomenon has been reported primarily in endemic regions in Asia. This enteric colonization can serve as a reservoir for subsequent translocation and the development of severe sepsis or septic shock [131]. Additionally, deep-tissue infections, including necrotizing fasciitis (a rare but serious manifestation) and prostatic abscesses, have also been reported as manifestations of community-acquired HvKp infection [132]. These diverse clinical presentations underscore the broad pathogenic potential of HvKp and the need for heightened clinical awareness.

Hospital-acquired HvKp infections. While historically associated with community settings, HvKp is an emerging threat in healthcare environments, causing severe nosocomial infections. Established risk factors for hospital-acquired *K. pneumoniae* infection are particularly relevant for HvKp, including the use of invasive medical devices such as indwelling urinary catheters, central venous catheters, and mechanical ventilators [133]. These devices breach natural host defenses and can become reservoirs for the pathogen. Consequently, breaches in infection control, such as suboptimal device management and inadequate hygiene protocols, are major drivers of device-associated infections, including CLABSIs, catheter-associated urinary tract infections (CAUTIs), surgical site infections (SSIs), and VAP caused by HvKp [134]. Of particular concern is the emergence of multidrug-resistant HvKp strains in healthcare settings, further complicating treatment options.

Hospital acquired pneumonia (HAP). HAP is a lower respiratory tract infection that develops ≥ 48 hours after hospital admission, and is a major cause of morbidity and mortality, particularly among patients who are elderly, immunosuppressed, have prolonged hospitalization, or require mechanical ventilation [135]. *K. pneumoniae* is one of the most common and clinically significant pathogens responsible for HAP. While cKP is a well-established cause, the emergence of HvKp strains in the nosocomial setting is a growing concern. HAP caused by HvKp is often associated with more severe clinical outcomes, including necrotizing pneumonia and abscess formation. Additionally, there is a higher likelihood of progression to bacteremia and sepsis compared to HAP caused by cKP strains. A particularly severe form of HAP is VAP.

Ventilator-associated pneumonia (VAP). VAP is a severe form of HAP that develops ≥ 48 hours after endotracheal intubation and mechanical ventilation. Critically ill individuals in the intensive care unit (ICU) are highly susceptible to airway colonization by opportunistic pathogens, with *K. pneumoniae* being one of the most frequently isolated and clinically significant causative agents. When VAP is caused by HvKp strains, the clinical course is often more severe and associated with higher rates of bacteremia, septic shock, and death compared to VAP caused by cKP strains. The robust biofilm-forming capacity of many HvKp strains, as described earlier, may also contribute to their persistence on endotracheal tubes, making eradication particularly challenging [136].

Pneumonia associated with non-invasive ventilation (NIV). The use of NIV devices, such as continuous positive airway pressure (CPAP) and bilevel positive airway pressure (BiPAP), can also increase the risk of nosocomial pneumonia, particularly in vulnerable immunosuppressed patients [137]. While NIV avoids the complications of an artificial airway, the continuous positive pressure can facilitate the aspiration of oropharyngeal secretions colonized with pathogens. This creates a potential pathway for infection with HvKp, which can lead to aggressive pneumonia even in this setting. Clinicians should be aware of this risk when managing patients on NIV.

Non-ventilator hospital-acquired pneumonia (NV-HAP). Similarly, patients not receiving any ventilatory support remain at risk. NV-HAP refers to pneumonia that develops in hospitalized patients who are not mechanically ventilated and is a growing area of concern [138]. Risk factors include advanced age, postoperative status, and immunosuppression. *K. pneumoniae* is a leading cause of NV-HAP, responsible for a significant proportion of cases [139]. While often caused by cKP strains, the acquisition of HvKp in this setting poses a severe threat. Due to its heightened pathogenicity, HvKp can cause aggressive pneumonia with a high risk of bacteremic dissemination, even in non-ventilated patients who might otherwise be considered at lower risk for severe disease.

Ventilator-associated tracheobronchitis (VAT). VAT is considered a potential precursor to VAP, though not all cases progress to pneumonia. VAT arises from the tracheobronchial colonization by hospital-acquired pathogens following prolonged mechanical ventilation [140]. VAT is distinguished from VAP by the absence of new pulmonary infiltrates on chest imaging. Common causative agents include Gram-negative bacteria such as *Pseudomonas aeruginosa* and *K. pneumoniae*, as well as methicillin-resistant *S. aureus* (MRSA) [141]. However, colonization and subsequent infection with HvKp are of particular concern. Given its increased invasive potential and biofilm-forming capabilities, HvKp-associated VAT may have a higher propensity to progress rapidly to severe, necrotizing VAP, representing a critical stage for intervention in ventilated patients. Therefore, early recognition and treatment of HvKp VAT may prevent progression to life-threatening VAP.

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Catheter-associated urinary tract infections (CAUTIs). CAUTIs are among the most common healthcare-associated infections, and *K. pneumoniae* is a leading causative agent [142]. The presence of an indwelling catheter, particularly with prolonged catheterization, compromises host defenses and provides a surface for bacterial colonization and biofilm formation. While cKP is a frequent cause of CAUTI, the emergence of HvKp strains in this setting represents a significant clinical challenge. HvKp strains often exhibit enhanced biofilm-forming capabilities and possess virulence factors, such as the hypermucoviscosity phenotype and the *rmpA* gene, that are associated with more severe disease [143]. Therefore, CAUTI caused by HvKp may have a higher risk of progressing to complicated outcomes, such as pyelonephritis and bacteremia, thereby transforming a localized device-associated infection into a potentially fatal systemic illness. Adherence to catheter care bundles, early catheter removal, and appropriate antimicrobial therapy are critical for optimal outcomes.

Surgical site infection (SSI). Another significant nosocomial syndrome is SSI. SSIs are infections that develop within 30 days of a surgical procedure, or up to 90 days for procedures involving implants, and HvKp is an increasingly recognized and clinically significant pathogen in this context. The key virulence factors characteristic of HvKp, such as its thick anti-phagocytic capsule and robust biofilm-forming capabilities, as noted above, may allow it to effectively colonize surgical wounds and resist host clearance mechanisms. The predominant K1 and K2 capsular serotypes, particularly the K1-ST23 lineage (a globally disseminated hypervirulent clone), are frequently implicated in severe SSIs [144]. Hepatobiliary and abdominal surgeries may be at particular risk given the association between HvKp and liver abscesses. This threat is further compounded by antimicrobial resistance; an increasing number of nosocomial HvKp strains produce ESBLs or are resistant to carbapenems, severely limiting therapeutic options and highlighting the critical need for stringent infection control, including surgical site bundles and antimicrobial stewardship, in surgical settings [145]. Surveillance for HvKp in surgical patients, particularly those with risk factors, is warranted.

Rising association between HvKp and multidrug resistance. Historically, hypervirulence and antimicrobial resistance were considered mutually exclusive traits in *K. pneumoniae*. However, this paradigm is rapidly changing. The association between hypervirulence and MDR, especially in pathogens such as *Klebsiella pneumoniae*, has created a new class of highly dangerous pathogens, often termed "superbugs," that pose a significant and escalating global public health threat [146]. This phenomenon is driven primarily by mobile genetic elements such as hybrid plasmids (plasmids carrying both resistance and virulence determinants) that can simultaneously transfer resistance and virulence genes. As a result, the historical separation between highly virulent, community-acquired strains and drug-resistant, hospital-acquired strains is eroding [147]. Key resistance determinants include carbapenemases such as KPC (*K. pneumoniae* carbapenemase) and NDM (New Delhi metallo-β-lactamase). This convergence has given rise to specific high-risk clones, such as carbapenem-resistant ST11 and hypervirulent ST23 *K. pneumoniae*, as well as convergent strains combining both phenotypes, that are spreading globally, with particular prevalence in Asia and increasing reports from other regions. These strains, often termed "convergent" or "high-risk" clones, represent a worst-case scenario combining heightened pathogenicity with therapeutic limitations. This is thereby complicating clinical management and resulting in increased patient mortality, treatment failures, and prolonged hospitalizations due to limited effective treatment options [148]. Enhanced infection control measures and antimicrobial stewardship are essential to limit the spread of these strains. Urgent research and surveillance efforts are needed to monitor and combat the emergence of these convergent pathogens.

In summary, while both HvKp and cKP are pathotypes of the same bacterial species, they are distinguished by critical differences. HvKp is characterized by a greater repertoire of virulence factors, encoded by genes such as *rmpA*, *iuc*, and *iro*, particularly the hypermucoviscosity phenotype resulting from elevated capsular polysaccharide production. This heightened virulence enables HvKp to cause severe, invasive infections, such as PLA, meningitis, endophthalmitis, and pneumonia, even in immunocompetent individuals. Conversely, cKP is predominantly implicated in opportunistic infections, typically affecting individuals with compromised immune systems. These pathotypes have traditionally been distinguished by their primary threat: cKP has historically been recognized as a prototypical MDR nosocomial pathogen, while HvKp is defined by its heightened virulence potential. However, the epidemiological landscape is shifting alarmingly as HvKp strains increasingly acquire MDR determinants, creating convergent strains that are both hypervirulent and difficult to treat. Despite these fundamental distinctions, both pathotypes share a common bacterial identity, utilizing similar core pathogenic mechanisms and transmission routes, particularly within healthcare environments.

At the molecular level, the intrinsic characteristics of HvKp determine its heightened pathogenicity and the severe clinical spectrum of infections it causes. Its defining features—including a hypercapsular phenotype (manifesting as hypermucoviscosity) that confers resistance to phagocytosis, enhanced iron acquisition systems (including aerobactin and salmochelin production), and a robust capacity for biofilm formation—act synergistically to enable invasion, persistence, and dissemination, even in immunocompetent hosts. This pathogenic arsenal allows HvKp to cause a wider spectrum of disseminated, metastatic

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diseases compared to cKP, which typically causes more localized, opportunistic infections. The convergence of this hypervirulence with increasing antimicrobial resistance presents a formidable public health threat, demanding urgent development of novel diagnostic approaches, including molecular detection of virulence markers and rapid phenotypic tests such as the string test, preventive, and therapeutic strategies. While cKP has traditionally been characterized by higher rates of antimicrobial resistance [149], recent studies demonstrate the concerning emergence of MDR HvKp strains [150]. Future research should focus on understanding the molecular mechanisms of virulence-resistance convergence. Prevention relies on stringent infection control, early detection, and appropriate antimicrobial therapy. Given the global spread of HvKp, international collaboration in surveillance and research is essential to address this emerging public health threat.

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CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest associated with this manuscript.

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We disclose that Gemini AI was used in gathering related research articles, extraction of data, and summarization for this study. All other parts of the study were written, reviewed, and formatted by the authors following standard publication guidelines.

DATA AVAILABILITY

Not applicable. This is a review article; no original data were generated.

AUTHORS' CONTRIBUTIONS

NIU: Conceptualization; Writing—original draft; Writing—review & editing; Formatting in accordance with the journal guidelines and manuscript revision as required. AFU: Manuscript review and critical revision. MYI: Manuscript review and critical revision. NMA: Literature search and sourcing of relevant research articles; Support for citation and referencing.

ETHICS STATEMENT

As this is a review article based on published literature, formal ethical approval was not required. However, institutional approval was obtained from Abubakar Tafawa Balewa University Teaching Hospital, Bauchi, Nigeria.

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