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CONFRONTING HYPERVIRULENT KLEBSIELLA PNEUMONIAE: INSIGHTS INTO PATHOGENICITY, RESISTANCE, AND INTERVENTION STRATEGIES

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ABSTRACT

Community-acquired infections caused by Klebsiella pneumoniae (K. pneumoniae) have emerged as a major global health concern, particularly with the rise of hypervirulent strains (hvKP). These strains are capable of causing severe infections-such as pyogenic liver abscesses-even in otherwise healthy individuals. First identified in Taiwan in the 1980s, hvKP has since achieved worldwide distribution. Its heightened pathogenicity is driven by a diverse repertoire of virulence factors that facilitate host colonization and enable evasion of immune defenses. The recent convergence of hypervirulence with antimicrobial resistance has further complicated clinical management. As a member of the ESKAPE group of pathogens, K. pneumoniae demonstrates high-level resistance to multiple antibiotics, posing significant therapeutic challenges in healthcare settings.

This review presents an in-depth analysis of hvKP, examining its structural and pathogenic distinctions from classical K. pneumoniae strains, major virulence determinants, and mechanisms underlying antimicrobial resistance. We also address the escalating threat of multidrug-resistant hvKP and evaluate both current treatment recommendations and emerging therapeutic approaches aimed at mitigating the impact of this formidable pathogen.

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Introduction

Klebsiella pneumoniae (*K. pneumoniae*) is a Gram-negative, encapsulated, non-motile bacterium from the *Enterobacteriaceae* family. It is a well-known opportunistic pathogen and a major cause of nosocomial infections, particularly in immunocompromised patients. This organism is implicated in a broad range of diseases, including pneumonia, urinary tract infections, bacteremia, and liver abscesses (Magill et al., 2014; Makharita et al., 2020; Paczosa & Mecsas, 2016).

In recent years, the emergence of hypervirulent *K. pneumoniae* (hvKP) has significantly increased the threat of severe invasive infections, affecting not only immunocompromised patients but also healthy individuals. While classical *K. pneumoniae* (cKP) primarily targets hospitalized or immunocompromised patients-especially those with underlying conditions such as diabetes, malignancy, or recent surgical procedures-hvKP demonstrates a distinct ability to cause aggressive, community-acquired infections in individuals without known risk factors. This remarkable pathogenicity is linked to its enhanced virulence arsenal, which includes a hypermucoviscous capsule, overproduction of siderophores, and resistance to phagocytosis, enabling it to penetrate host barriers and evade immune responses more effectively than cKP

(Al Ismail et al., 2024; Fazili et al., 2016; Kareem et al., 2021; Lin, Siu, et al., 2012; Nadasy et al., 2007; Shon et al., 2013).

Unlike cKP, which is largely associated with hospital-acquired infections, hvKP is more frequently linked to community-acquired disease and is capable of causing a broader spectrum of systemic illnesses, such as pneumonia, hepatic abscesses, meningitis, and necrotizing fasciitis.

One of hvKP's hallmark traits is the hypermucoviscous phenotype, traditionally identified via the "string test" (>5 mm viscous string formation) (Fang et al., 2004). However, this phenotypic marker is not entirely reliable-some hvKP strains do not display hypermucoviscosity, while certain cKP strains do (Mai et al., 2023; Nannini et al., 2025; Pu et al., 2023; Russo & Marr, 2019). Consequently, molecular biomarkers such as *iucA*, *rmpA*, *rmpA2*, and *peg-344* have become essential for accurate identification (Chen et al., 2024; García-Cobos et al., 2025).

The recent rise of antibiotic-resistant hvKP strains has further intensified the clinical challenge. As part of the ESKAPE group, *K. pneumoniae* exhibits resistance to multiple antibiotic classes, including carbapenems and colistin, making treatment increasingly difficult (Algammal et al., 2023). The convergence of hypervirulence and multidrug resistance in hvKP represents a major public health concern, underscoring the urgent need for novel therapeutic approaches (García-Cobos et al., 2025).

This review provides an in-depth examination of hvKP, focusing on its structural and pathogenic differences from cKP, mechanisms of antimicrobial resistance, and the growing concern over multidrug-resistant hvKP. Additionally, we discuss current and emerging treatment strategies to counter this highly virulent and drug-resistant pathogen.

2. Differences Between Classical and Hypervirulent *K. pneumoniae*

K. pneumoniae exists in two major pathotypes: classical (cKP) and hypervirulent (hvKP), which differ significantly in epidemiology, host susceptibility, molecular characteristics, and virulence mechanisms. Understanding these distinctions is crucial for accurate diagnosis, infection control, and tailored therapy.

cKP is predominantly a healthcare-associated pathogen, infecting immunocompromised or hospitalized patients, and is a frequent cause of hospital-acquired pneumonia, urinary tract infections, and bloodstream infections (Chew et al., 2017). In contrast, hvKP has emerged as a more aggressive variant capable of causing severe, community-acquired infections in otherwise healthy individuals. It is linked to a wider range of invasive diseases, including pyogenic liver abscess, meningitis, endophthalmitis, and necrotizing fasciitis (Catalán-Nájera et al., 2017; Russo & Marr, 2019; Zhu et al., 2021).

Hypermucoviscosity was historically used to distinguish hvKP from cKP via the string test (>5 mm viscous string) (Fang et al., 2004; Russo et al., 2018). However, its limited specificity-due to overlap between strains-has diminished its diagnostic reliability (Catalán-Nájera et al., 2017; Russo et al., 2018), prompting a shift toward molecular markers.

hvKP harbors additional virulence genes, often plasmid-encoded, including *rmpA* and *rmpA2* (capsule overproduction), *iucA* (aerobactin siderophore synthesis), and *peg-344* (linked to enhanced in vivo virulence) (Russo et al., 2018). These genes are absent in most cKP strains and have high predictive accuracy (>95%) for hvKP. A chromosomal *rmpA* (*crmpA*) variant can also drive capsule overexpression and immune evasion.

Capsular types K1, K2, K5, K20, K54, and K57 are strongly associated with hvKP (Shon et al., 2013; Yu et al., 2008). The K1 serotype, often linked to sequence type ST23, is especially associated with liver abscesses, while K2 occurs in multiple sequence types such as ST65 and ST86. These serotypes enhance resistance to phagocytosis and complement-mediated killing, aiding hvKP survival in the bloodstream and deep tissues. A notable virulence feature of hvKP is its superior iron uptake, particularly via elevated production of aerobactin - a siderophore crucial for bacterial growth in iron-limited environments like the human host (Russo et al., 2015).

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hvKP strains exhibit heightened resistance to neutrophil phagocytosis and complement activation compared to cKP (L. Wang et al., 2017), promoting rapid systemic spread and a higher risk of metastatic infection.

Beyond the string test, functional assays such as centrifugation-based mucoviscosity tests have been proposed, where hvKP typically resists sedimentation, leaving a turbid supernatant (Walker et al., 2020). Nevertheless, molecular genotyping remains the gold standard for definitive differentiation. While cKP remains a significant cause of nosocomial infections, hvKP poses a growing global health threat due to its ability to cause severe, often metastatic, community-acquired infections in healthy individuals. Accurate differentiation requires integrating clinical, phenotypic, and molecular diagnostic approaches to guide timely and effective management.

3. Diseases Caused by Hypervirulent *Klebsiella pneumoniae* (hvKP)

The first recognized syndrome linked to hvKP was cryptogenic hepatic abscess, reported in 1980 (J.-H. Wang et al., 1998; Liu et al., 1986, 1991). Clinically, hvKP infections typically present with fever, abdominal pain, leukocytosis, and chills (Kong et al., 2017). Hepatic abscess caused by hypervirulent strains is regarded as a distinct clinical entity due to its unique features (Liu et al., 1991; Oikonomou & Aye, 2017). Unlike other hepatic abscesses-commonly associated with biliary tract disease or prior invasive procedures-those caused by hvKP often occur in individuals with normal liver function and intact biliary systems (Zhang et al., 2016).

The most common route of hvKP entry is via the oropharynx through inhalation, leading to pneumonia. In the 1990s, community-acquired *K. pneumoniae* pneumonia accounted for less than 1% of pneumonia cases requiring hospitalization in Argentina, Australia, Europe, and North America (Carpenter, 1990; Ko et al., 2002; Marrie et al., 1989; Vergis et al., 2000).

Endophthalmitis is a severe complication of hvKP infection and one of the earliest distinguishing features between classical *K. pneumoniae* (cKP) and hvKP (Liu et al., 1986). Endogenous endophthalmitis caused by Gram-negative bacilli was rare in healthy individuals prior to the emergence of hvKP, but it is now recognized as a relatively frequent complication, affecting approximately 5% of hvKP-infected patients (Lee et al., 2006). Exogenous endophthalmitis-arising from trauma or surgery-remains rare in hvKP cases. Symptoms of endogenous hvKP endophthalmitis typically include sudden-onset blurred vision, ocular redness, and periocular swelling (Kishibe et al., 2016).

In Asia, *K. pneumoniae* has been identified as a leading cause of community-acquired meningitis in patients without prior head injury or neurosurgical intervention (Chang et al., 2012; Fang, Chang, et al., 2000; Jang et al., 1993; Tang et al., 1997). With the global spread of hvKP, such cases are now reported worldwide (Durand et al., 1993). hvKP meningitis can occur as a primary infection or as a metastatic complication (Fang, Chen, et al., 2000; Lin, Liu, et al., 2012), and some cases present with multiple, diffuse brain abscesses (Hentzien et al., 2017; Yoon, 2013). The infection may also involve ventriculitis (Yoon, 2013), epidural abscess, or subdural empyema (Doud et al., 2009; Hentzien et al., 2017; Hsieh et al., 2009; Kuramochi et al., 2005; Liu et al., 1986; Russo & Marr, 2019).

In Taiwan, hvKP is among the principal causes of necrotizing fasciitis, which carries a high mortality rate (Cheng et al., 2012). Although initially concentrated in Southeast Asia, cases have now been reported globally (Gunnarsson et al., 2009; Ng & Frazee, 2015; Ye et al., 2016). Presentations may include intramuscular abscesses-either alone or in combination with necrotizing fasciitis (Liu et al., 1991; Mgbemena et al., 2017)-as well as pyomyositis (commonly affecting the lower extremities), sometimes accompanied by septic arthritis (Kishibe et al., 2016). Osteomyelitis may also occur and, when multifocal, can mimic malignancy until progressing to necrotizing fasciitis (Prokesch et al., 2016).

Deep neck infections may be primary or secondary to metastatic spread (Frazee et al., 2009; Nadasy et al., 2007), and can lead to septic thrombophlebitis as a complication (McCabe et al., 2010). hvKP can

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also cause superficial skin and soft tissue infections through systemic dissemination (Paraschiv et al., 2018).

Although rare, urinary tract involvement can occur following ascending colonization (Shon et al., 2013). In some patients, hvKP infection is found concurrently with both hepatic abscess and colon cancer (Qu et al., 2012).

Bacteremia is a frequent complication of hvKP infection, most often originating from pyogenic hepatic abscess (Lee et al., 2006). In many cases, bacteremia has no identifiable primary focus. While hvKP-associated endocarditis is rare, purulent endocarditis is the most common form linked to this pathogen (Rivero et al., 2010), with hepatic abscess or hematogenous spread (Hentzien et al., 2017) being possible sources (Figure 1).

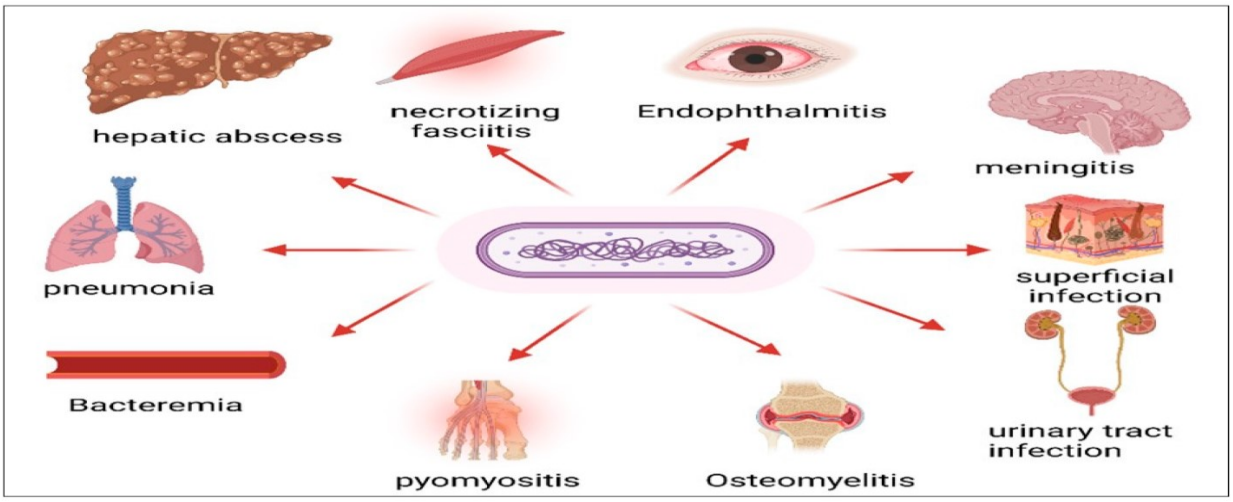


Figure 1. Diseases caused by hvKP. It affects almost all systems and causes endophthalmitis, meningitis, necrotizing fasciitis, pyomylitis, osteomyelitis, pneumonia, bacteremia, hepatic abscess, urinary tract infection, and superficial infection.

4. Discovery and Epidemiology of hvKP

The hypervirulent *Klebsiella pneumoniae* (hvKP) strain was first described in 1986 by Liu et al. in Taiwan. They reported seven cases of community-acquired *K. pneumoniae* infections presenting with liver abscesses and severe extrahepatic complications, including prostate abscess, endophthalmitis, and purulent meningitis. Despite receiving aggressive antimicrobial therapy, several patients experienced permanent vision loss, underscoring the high pathogenic potential of hvKP (Liu et al., 1986).

Since its initial identification, hvKP infections have been increasingly reported across the globe, including in Europe, Australia, and North America. Epidemiologically, East and Southeast Asia remain the primary epicenters, with Taiwan, South Korea, Iran, and China accounting for a large proportion of documented cases (Al Ismail et al., 2024). In a multicenter study conducted in China, 22.8% of invasive *K. pneumoniae* infections were attributed to hvKP. Another regional study revealed that hvKP was responsible for 90.9% of pyogenic liver abscess cases (Ye et al., 2016).

While prevalence in Western countries is lower, it is steadily increasing. In the United States, hvKP has been detected in approximately 6–8% of clinical *K. pneumoniae* isolates, often linked to severe disease and cases involving recent international travel (Russo & Marr, 2019).

The emergence of novel sequence types (STs)-notably ST23, ST65, and ST86-demonstrates the ongoing evolution and adaptation of hvKP. In China, multidrug-resistant hvKP (MDR-hvKP) strains are increasingly observed, with ST11 being the predominant lineage associated with carbapenem resistance. This convergence of hypervirulence and multidrug resistance poses a dual threat to public health, emphasizing the need for comprehensive epidemiological surveillance and genomic monitoring.

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In early 2024, the World Health Organization (WHO) reported the global emergence of hvKP ST23 strains carrying carbapenemase genes, conferring resistance to last-line antibiotics. These strains have been detected in at least one country within each of the six WHO regions, including Algeria, Argentina, Australia, Canada, India, Iran, Japan, Oman, the Philippines, Switzerland, Thailand, the United Kingdom, and the United States. The co-occurrence of hypervirulence and extensive drug resistance in these strains presents major challenges for both treatment and infection control. The WHO has stressed the urgent need to strengthen laboratory diagnostic capabilities, expand molecular testing, and implement robust surveillance systems to track and mitigate the spread of these high-risk pathogens.

5. Bacterial Structure

Similar to other members of the *Enterobacteriaceae* family, hvKP possesses a lipid bilayer outer membrane composed of lipopolysaccharides, lipoproteins, and proteins. Surrounding this outer membrane is a polysaccharide capsule (Figure 2). While both hvKP and classical *K. pneumoniae* (cKP) possess capsules, certain serotypes-K1, K2, K5, K20, K54, and K57-are more prevalent in hvKP, with K1 and K2 together accounting for approximately 70% of hvKP isolates (Russo et al., 2018; Shon et al., 2013; Yu et al., 2008).

However, other capsular types, such as K47 or K64, may emerge in hypervirulent strains if classical variants acquire plasmids carrying virulence-associated genes, a phenomenon observed in recent years. The O-antigen (O-Ag) of the lipopolysaccharide is also an important structural feature, with K1 and K2 capsule types most frequently occurring alongside the O1 O-Ag, making it the most common combination in hvKP.

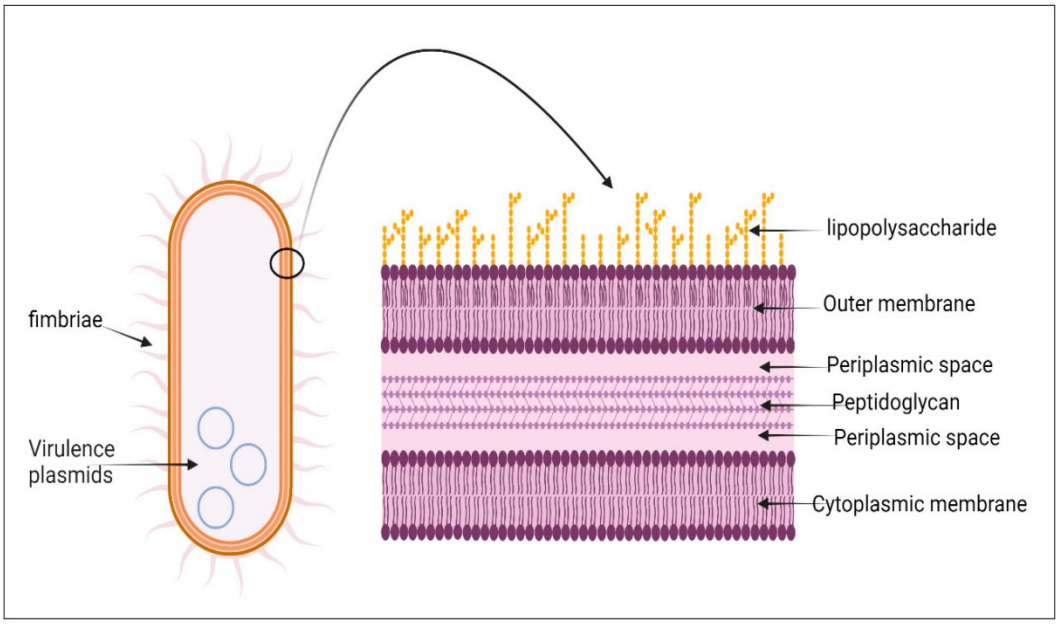


Figure 2. The cell wall structure of *K. pneumoniae*. Like most other gram-negative bacteria, it is composed of an outer membrane that contains lipopolysaccharide, periplasmic spaces, a thin layer of peptidoglycan, and a cytoplasmic membrane.

Both the outer membrane and the capsule play critical roles in pathogen–host and pathogen–environment interactions. These structures contribute to antimicrobial resistance-via permeability barriers and efflux pump mechanisms-and to pathogenesis, particularly through immune evasion mediated by the capsule. A notable feature of hvKP is the rmpA- and/or rmpA2-mediated overproduction of capsular polysaccharides, which significantly enhances systemic virulence (Fang et al., 2004).

Additionally, hvKP produces specialized components that aid in environmental survival, colonization, and host infection. These include the type VI secretion system, which facilitates bacterial

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competition and persistence, and iron-acquisition systems such as siderophores, which are essential for bacterial growth in iron-limited host environments.

6. Pathogenesis of hvKP

Klebsiella pneumoniae readily colonizes human skin and mucosal surfaces, including the oropharynx and gastrointestinal (GI) tract, where colonization is typically benign. However, under certain conditions, it can breach these barriers and cause severe invasive infections. In hospital-acquired cases, the most common routes of invasion are through disrupted epithelial or mucosal integrity-such as surgical wounds, indwelling catheters, or endotracheal tubes. In community-acquired infections, including those affecting otherwise healthy individuals, alternative mechanisms of tissue invasion are likely involved. The frequent occurrence of pyogenic liver abscesses in hvKP infections suggests that these strains can penetrate the intestinal mucosa and disseminate to the liver via the portal circulation.

In hvKP, genes encoding colibactin are located on the integrative and conjugative element ICEKp10, which also harbors genes for microcin E492 and yersiniabactin production. Colibactin is most commonly found in capsule type K1, particularly within clonal group CG23, but occurs less frequently in other hypervirulent strains. Notably, CG23-I sublineages that acquired ICEKp10 in 1928 have since achieved global dissemination, indicating a significant role of colibactin in hvKP evolutionary success.

Microcin E492 is an 8-kDa bacteriocin with potent activity against members of the *Enterobacteriaceae* family. Its function requires salmochelin attachment, enabling uptake by target bacteria. The combined production of salmochelin, microcin E492, and colibactin enhances hvKP's competitive colonization capacity within the intestinal environment.

Additional structural modifications-such as glucuronic acid pyruvation and fucose acetylation-further protect hvKP from phagocytosis. Even after engulfment by neutrophils, hvKP strains, particularly those with the K1 capsule type, can evade intracellular killing, facilitating systemic spread to distant sites like the liver, where they induce abscess formation.

Iron acquisition is another key factor in hvKP pathogenesis. Bacterial growth in vivo and in vitro is highly dependent on iron availability. Hypervirulent strains possess approximately 12 distinct iron uptake systems, including three siderophore-based pathways-iroA, the *Yersinia* high-pathogenicity island, and iuc -as well as two ATP-binding cassette (ABC) transporters, Sit and Kfu. These systems play a crucial role in the pathogen's ability to thrive in iron-restricted host environments.

7. Virulence Factors and Genes

7.1. Capsule

The polysaccharide capsule is a central virulence determinant present in all *K. pneumoniae* strains. Forming a dense, sugar-rich layer around the bacterial cell, it contributes to the organism's mucoid phenotype and provides robust protection against host immune defenses. The capsule inhibits phagocytosis, neutralizes the antimicrobial activity of host peptides, and suppresses inflammatory signaling by downregulating key cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) (Figure 3).

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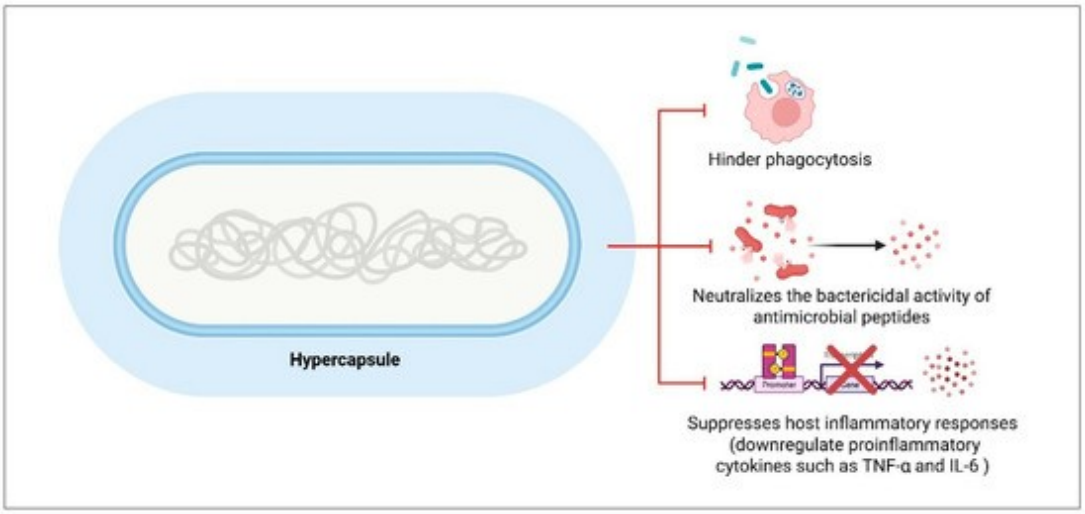


Figure 3. Protective functions of the hypercapsule in hypervirulent *K. pneumoniae* (hvKP). The hypercapsule in hvKP serves as a multifunctional defense structure, contributing to immune evasion and enhanced survival. It impairs phagocytic clearance, reduces susceptibility to host-derived antimicrobial peptides and therapeutic agents, and attenuates inflammatory responses by modulating cytokine production.

Recent research has shown that the hypercapsule of hvKP strains promotes immunosuppression not only by physically masking bacterial antigens but also by disrupting host pattern recognition receptors (PRRs), particularly Toll-like receptors (TLRs). This disruption dampens the activation of the nuclear factor-kappa B (NF-κB) signaling pathway, reducing the transcription of key proinflammatory mediators. The dense polysaccharide layer also inhibits complement activation and impairs immune cell recruitment, further weakening local inflammatory responses. Together, these mechanisms contribute to the subdued innate immune activation observed in hvKP infections, allowing systemic dissemination with minimal early detection.

Compared to classical *K. pneumoniae* (cKP), hvKP strains typically possess larger, more robust capsules that provide enhanced protection and survival. However, this enlarged capsule may also act as a physical barrier to horizontal gene transfer, limiting DNA uptake and possibly explaining the lower prevalence of antimicrobial resistance genes in hvKP relative to cKP.

Capsule biosynthesis is chromosomally encoded, with at least 79 distinct K-antigen types identified based on polysaccharide composition and antigenic structure. Among hvKP isolates, eight capsule types predominate-K1, K2, K5, K16, K20, K54, K57, and KN1-with K1 and K2 collectively accounting for about 70% of strains (Russo et al., 2018; Shon et al., 2013). Multiple studies have shown that these two serotypes exhibit significantly higher virulence than other capsule types (L. Wang et al., 2017).

Multilocus sequence typing (MLST) reveals that K1 is strongly associated with sequence type (ST) 23, while K2 displays greater genetic diversity, being linked to ST25, ST86, ST375, and ST380. Notably, K1 and K2 lack mannose and rhamnose residues-sugars recognized by macrophage lectin receptors-which may reduce phagocytic uptake.

Additional virulence-enhancing mechanisms have been identified. In K1 strains, the surface protein fructose-1,6-bisphosphate aldolase (FBA) can protect neutrophils from cell death under hyperglycemic conditions by upregulating its expression. Moreover, sialic acid residues in K1 and K2 capsular polysaccharides contribute to the hypermucoviscous phenotype and play a role in their antiphagocytic properties.

7.2 Siderophores

For *K. pneumoniae* to thrive during infection, it must acquire iron-a scarce nutrient tightly sequestered by host iron-binding proteins as part of nutritional immunity. To overcome this restriction, the

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bacterium produces siderophores-low-molecular-weight, high-affinity iron chelators that extract iron from host proteins.

Siderophores outcompete host proteins for iron binding and are subsequently internalized by the bacterial cell via specific receptors such as YbtQ, IutA, FepA, and IroN (Figure 4). hvKP produces four major siderophores: yersiniabactin (Ybt), enterobactin (Ent), salmochelin (Iro), and aerobactin (Iuc). The latter two are considered more characteristic of hvKP, with aerobactin being the most critical for systemic infection, accounting for nearly 90% of siderophore activity in laboratory studies (Russo et al., 2015).

While yersiniabactin is a key virulence factor in cKP, its role in hvKP pathogenesis remains less clear (Russo et al., 2018). The host innate immune system can partially neutralize siderophore activity-e.g., aerobactin can be bound by the antimicrobial peptide LL-37, and lipocalin-2 can sequester enterobactin, preventing its uptake. To counteract this, hvKP produces multiple siderophores simultaneously, ensuring iron acquisition across diverse tissue niches and reducing the risk of neutralization by host defenses.

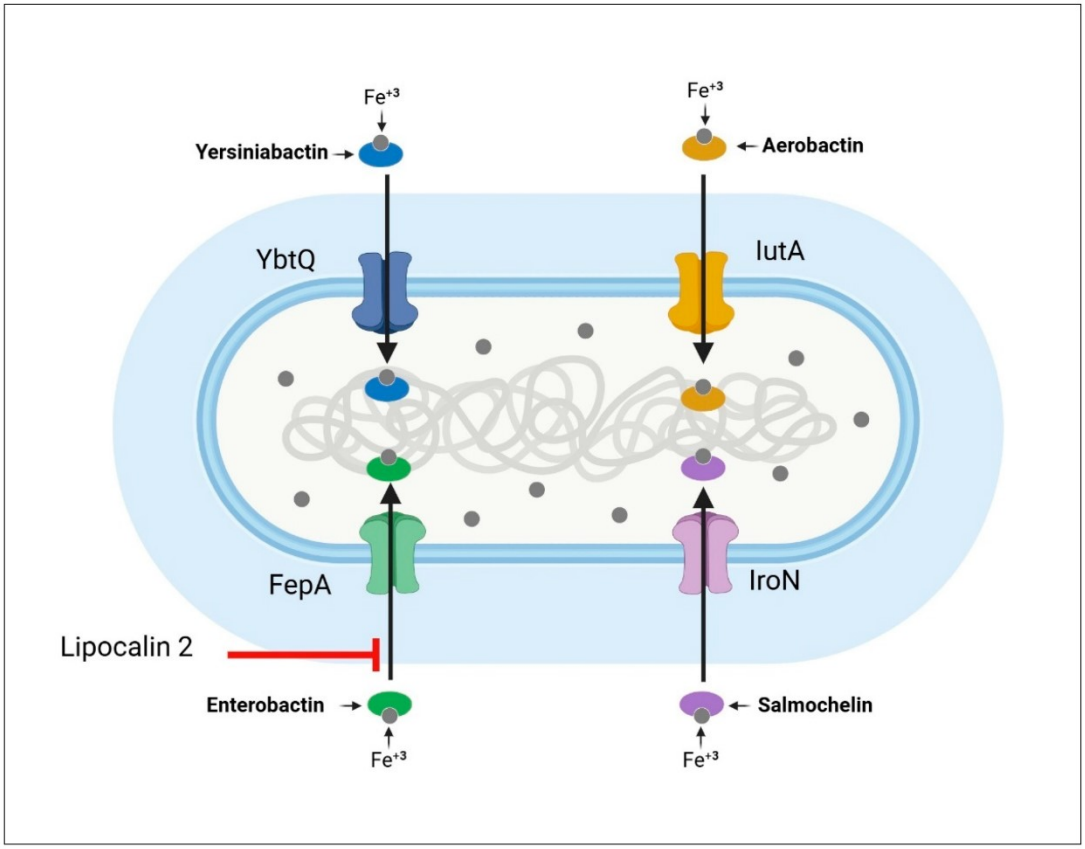


Figure 4. Iron acquisition by siderophores in hypervirulent Klebsiella pneumoniae (hvKP). Siderophores enable hvKP to overcome host nutritional immunity by sequestering iron from host iron-binding proteins. With superior iron-binding affinity, these molecules outcompete host proteins and facilitate iron uptake through dedicated bacterial receptors, supporting growth and virulence within the iron-limited environment of the host.

7.3. Lipopolysaccharide (LPS)

Lipopolysaccharide (LPS) is a fundamental structural element of the outer membrane in all Gram-negative bacteria, including both classical *K. pneumoniae* (cKP) and hypervirulent (hvKP) strains. It plays a pivotal role in virulence and immune evasion. LPS is composed of three distinct regions: lipid A, which anchors the molecule to the bacterial membrane and is responsible for its endotoxic activity; the core oligosaccharide; and the O-antigen, the most exposed portion on the bacterial surface.

The O-antigen acts as a defensive barrier against host immunity by binding complement component C3b, thereby blocking complement-mediated killing, preventing membrane attack complex (MAC)

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formation, and reducing phagocytosis. Of the eight recognized O-antigen serotypes, O1 is the most common among clinical *K. pneumoniae* isolates and is frequently linked to enhanced virulence.

Experimental studies have shown that O1-negative strains exhibit reduced pathogenicity compared to their O1-positive counterparts. However, in K1 hvKP strains, the role of the O1 antigen is less defined, as it is likely masked by the prominent hypercapsule, limiting its interaction with host immune components. This concealment raises questions about the true contribution of the O1 antigen in hvKP pathogenesis.

7.4. Fimbriae

Fimbriae are hair-like appendages on the bacterial surface that mediate adhesion to host cells and abiotic surfaces, facilitating colonization and biofilm development. In *K. pneumoniae*, two main fimbrial types are well characterized: type 1 fimbriae, which are mannose-sensitive and promote attachment to epithelial cells, and type 3 fimbriae, which are mannose-resistant and primarily support biofilm formation on non-living surfaces. While type 3 fimbriae are established contributors to biofilm development in cKP, their exact significance in hvKP remains uncertain.

Comparative genomics has revealed at least seven fimbrial gene clusters in *K. pneumoniae*-kpa, kpb, kpc, kpd, kpe, kpf, and kfg-with kpc being the most prevalent in hvKP, especially in K1 serotype strains. Functional analysis of strain CG43 demonstrated that type 3 fimbrial expression and biofilm formation are regulated by the ferric uptake regulator (Fur) and influenced by environmental iron availability. This suggests that under the iron-limited conditions encountered in vivo, type 3 fimbriae may have a reduced role in hvKP virulence (Shon et al., 2013).

7.5. Allantoin Metabolism

While most bacterial species utilize allantoin as a nitrogen source, *K. pneumoniae* can exploit it as both a nitrogen and carbon source. In hvKP, allantoin metabolism is mediated by the allantoinase (allB) enzyme, the negative regulator (allR), the transcriptional activator (allS), and allantoin permease (ybbW).

Deletion of *allS*, a key activator of the allantoin operon, has been shown to significantly reduce hvKP pathogenicity in in vivo models. Moreover, previous studies have reported that the allantoin operon occurs at higher frequencies in liver abscess-associated hvKP strains than in cKP, suggesting a role in tissue-specific adaptation and virulence.

7.6. Colibactin

Colibactin is a genotoxic secondary metabolite synthesized by *K. pneumoniae* strains harboring the pks genomic island. Its biosynthesis involves the coordinated function of non-ribosomal peptide synthetases (NRPSs), polyketide synthases (PKSs), and accessory enzymes encoded within the pks cluster.

The *pks* locus is particularly prevalent among hypervirulent K1 serotype strains, with detection rates reported between 66% and 100% in various studies. Although the exact contribution of colibactin to hvKP pathogenesis is not yet fully defined, its DNA-damaging activity is believed to facilitate tissue invasion, disrupt host cellular defenses, and enhance bacterial persistence. This genotoxic effect may provide hvKP with a competitive advantage during systemic infection.

7.7. Peg-344

Peg-344 is a genetic marker strongly linked to hypervirulent *K. pneumoniae* (hvKP) and is believed to play a role in the enhanced pathogenic potential of these strains. Although its precise biochemical function remains uncertain, it is predicted to encode an inner membrane transporter. In vivo studies have demonstrated that peg-344 is essential for full hvKP virulence, particularly in lung and liver infections. Interestingly, deletion of this gene does not significantly impair the bacterium's ability to cause systemic infections, suggesting that peg-344 may be more critical for organ-specific pathogenesis rather than for widespread dissemination (Russo et al., 2018).

7.8. Type VI Secretion System (T6SS)

The type VI secretion system (T6SS) is a recently identified virulence mechanism in hvKP. Structurally resembling a contractile nanosyringe, the T6SS delivers toxic effector proteins directly into

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neighboring bacterial competitors or host eukaryotic cells. This contact-dependent system contributes to interbacterial competition, host cell damage, and enhanced colonization under hostile environmental conditions. While still under investigation, the presence of a functional T6SS in hvKP is increasingly recognized as an important factor in its pathogenic arsenal.

8. Convergence of Hypervirulence and Multidrug Resistance (MDR) in *K. pneumoniae*

Reports of multidrug-resistant hypervirulent *K. pneumoniae* (MDR-hvKP) are increasing. MDR-hvKP can emerge via two primary pathways:

1. **Type I MDR-hvKP** – hvKP strains acquire antimicrobial resistance genes or plasmids via horizontal gene transfer. For example, a K2 ST86 MDR-hvKP strain was found to carry two carbapenemase plasmids simultaneously: a *bla_{NDM-1}*-bearing IncN plasmid and a *bla_{KPC-2}*-bearing IncFIIK plasmid.
2. **Type II MDR-hvKP** – classical MDR *K. pneumoniae* strains acquire pLVPK-like virulence plasmids. A notable example is a fatal outbreak in China caused by a KPC-producing ST11 strain that had gained such a virulence plasmid.

Peg-344, present on the virulence plasmid, serves as a valuable diagnostic marker for both Type I and Type II MDR-hvKP. A peg-344 loop-mediated isothermal amplification assay has been developed to enable rapid detection.

9. The Escalating Threat of Antibiotic Resistance in hvKP

K. pneumoniae has developed an extraordinary ability to acquire antibiotic resistance, prompting the World Health Organization (WHO) to classify it as a **"critical" priority pathogen** and list it among the ESKAPE group of bacteria (including *Enterococcus faecium*, *Staphylococcus aureus*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter spp.*) that are responsible for most hospital-acquired drug-resistant infections.

The bacterium commonly acquires antimicrobial resistance (AMR) genes via **horizontal gene transfer,** facilitated by plasmids, integrons, and transposons. Many *K. pneumoniae* strains harbor three or more stable AMR plasmids-often more stable than those in *E. coli*. Mobile genetic elements such as **integrons (**e.g., integron 1), **insertion sequences** (e.g., IS26), and **transposons** (e.g., Tn4401a) further promote the spread of resistance genes between plasmids and the chromosome.

Mechanisms of Resistance

1. **Plasmid-mediated resistance** – hvKP can acquire AMR genes through conjugative plasmids.
2. **Integration of AMR determinants into virulence elements** – integrative and conjugative elements (ICEs) carrying resistance genes may insert into virulence plasmids or the chromosome.
3. **Chromosomal mutations** – particularly in outer membrane proteins (OMPs), which can alter permeability and reduce drug uptake.
4. **Convergence events** – MDR or extensively drug-resistant (XDR) cKP strains acquiring hvKP virulence plasmids.

A proposed mechanism suggests that conjugative plasmids carrying *bla_{KPC}* carbapenemase genes share an 11.2-kb homologous region with certain hvKP virulence plasmids, facilitating recombination and gene exchange-though this requires further experimental confirmation.

Intrinsic and Acquired Resistance Profiles

- **Intrinsic resistance** – All *K. pneumoniae* strains, including hvKP, are naturally resistant to ticarcillin and ampicillin, and display variable susceptibility to nitrofurantoin.
- **β-lactam and carbapenem resistance** – Carbapenemase- or ESBL-producing strains carry plasmids conferring resistance to tetracyclines, aminoglycosides, fluoroquinolones, and trimethoprim-sulfamethoxazole.
- **ESBLs** such as TEM, CTX-M, and SHV hydrolyze 3rd/4th-generation cephalosporins and aztreonam, reducing the efficacy of β-lactam/β-lactamase inhibitor combinations (Kong et al., 2017).

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- Some hvKP strains also produce **AmpC β-lactamases**, extending resistance to cephamycins like cefotetan and cefoxitin.
- **Carbapenemases** – The main classes are KPC (Class A), NDM and IMP (Class B metallo-β-lactamases), and OXA (Class D). Among these, **KPC-type** enzymes are the most common.
- **Polymyxin resistance** – Often plasmid-mediated via *mcr-1*, or through lipid A modification by the PhoP–PhoQ–Arn pathway. Inactivation of *mgrB*, a negative regulator of this pathway, has been linked to colistin resistance.
- **Tigecycline resistance** – Associated with overexpression of the efflux pump regulator *ramA* and its repressor *acrR*. cKP strains that acquire hvKP virulence plasmids may also gain tigecycline resistance.

10. Clinical and Epidemiological Risk Factors

The presence of K1 or K2 capsular serotypes and other virulence determinants does not appear to directly influence patient mortality. Instead, several **clinical parameters** have been identified as significant predictors of increased mortality, including:

- Bacteremia
- Respiratory distress (respiratory rate > 30 breaths/min)
- Altered mental status
- Septic shock
- Arterial pH < 7.35
- Tachycardia (heart rate > 125 beats/min)
- Hematocrit < 30%
- Elevated blood urea nitrogen (>10.71 mmol/L).

Mortality risk is generally comparable between infections caused by hvKP and those caused by cKP. However, **cKP infections** are more frequently observed in hospitalized cancer patients, likely reflecting the higher prevalence of immunosuppression in this population.

In bloodstream infections (BSIs), patients with hvKP-BSI are **more likely** to have diabetes mellitus (DM) and **less likely** to be immunocompromised compared to those with cKP-BSI. Pyogenic liver abscesses represent a more frequent source of hvKP-BSIs than cKP-BSIs. Established risk factors for hvKP infection include DM, community-acquired infection, solid malignancies, and hypertension, whereas immunosuppression appears to be paradoxically protective against hvKP-BSI.

Although hvKP infections can occur across all ethnic groups, they are reported more frequently in **Asian**, **Hispanic**, and **Pacific Island** populations-possibly due to higher colonization rates and environmental exposure (Fazili et al., 2016; McCabe et al., 2010; Nadasy et al., 2007). Regarding gender differences, some studies suggest a higher infection rate among males, while others report no significant sex-based variation (Ye et al., 2016).

11. Association with Malignancy

Multiple studies have demonstrated a **higher incidence of colorectal cancer** in patients with *K. pneumoniae* liver abscess compared to those without liver abscess or with abscesses caused by other pathogens. This association is thought to be linked to **colibactin**, a genotoxic metabolite produced by certain *Klebsiella* strains. Colibactin-induced DNA damage may contribute to tumorigenesis, supporting the hypothesis that liver abscess caused by hvKP could represent a **precancerous condition**.

Given this association, **colonoscopy screening** should be considered for all patients with hvKP-related liver abscess-particularly those with additional risk factors such as family history of colorectal cancer or older age.

12. Clinical Challenges in hvKP Infection

12.1. Diagnostic Challenges

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A major hurdle in hvKP management is **accurate strain identification**. In China, hvKP was detected in 22.8% (84/369) of *K. pneumoniae* isolates linked to invasive infections. Compared to cKP, hvKP is more prone to causing **multifocal, invasive disease**, often leading to higher mortality. However, there is **no standardized clinical definition** for hvKP, and classification criteria vary widely between studies.

Traditional phenotypic tests-such as the **string test** and **aerobactin detection**-have shown limited reliability, often resulting in inconsistent clinical interpretations (Zhang et al., 2016). In practice, diagnosis often relies on **clinical suspicion**, especially in cases of metastatic infection in otherwise healthy individuals. While hvKP was initially considered a disease of young adults, recent findings-such as the 45.7% prevalence reported by Liu et al. in older patients-highlight its wider demographic impact.

Molecular diagnostics offer a more precise approach, distinguishing hvKP from cKP through genotypic and phenotypic markers. Key hypervirulence-associated markers include **mobile genetic element-associated genes** and **virulence plasmid genes** such as *iroB*, *peg-344*, *iucA*, *prmpA2*, and *rmpA*. Certain combinations-particularly *iuc* plus total siderophore production, along with *rmpA*/*rmpA2*-are considered among the most sensitive and specific for hvKP identification (Russo et al., 2018). Despite their diagnostic potential, the **routine clinical use** of such molecular tools remains limited by cost and logistical challenges, maintaining a gap in hvKP–cKP differentiation in many healthcare settings.

12.2. Antibiotic Resistance and Treatment Challenges

One of the most pressing obstacles in hvKP management is the **escalating problem of antimicrobial resistance**. Many hvKP strains now exhibit **multidrug resistance (MDR)**, severely restricting therapeutic options. The prevalence of resistant hvKP isolates has risen markedly in recent years, especially in endemic regions such as China (Zhang et al., 2016). In a study by Zhang et al. (2016), 37% of clinical *K. pneumoniae* isolates were classified as hvKP based on the presence of *rmpA*, and 13% of these also produced extended-spectrum β-lactamases (ESBLs).

Resistance acquisition in hvKP occurs via **multiple mechanisms**, including horizontal gene transfer and the acquisition of resistance-encoding plasmids (Khujaeva, 2024a, 2024b; Russo & Marr, 2019). The convergence of hypervirulence and MDR creates significant clinical challenges, as standard antibiotic regimens often fail. These limitations underscore the need for **alternative therapeutic strategies** such as bacteriophage therapy, combination antibiotic regimens, and the development of novel antimicrobial compounds.

Given these trends, **rigorous infection control and active surveillance** are crucial to preventing hvKP spread within healthcare environments. Strong antimicrobial stewardship programs must also be implemented to curb inappropriate antibiotic use, which accelerates resistance development. An effective hvKP management strategy should integrate **rapid diagnostics**, optimized antimicrobial therapy, and strict infection prevention protocols.

13. Strategies for Controlling hvKP Infections

A comprehensive control plan for hvKP should combine **traditional measures** with **innovative interventions**. Key components include infection monitoring, targeted antibiotic therapy, phage therapy, biofilm disruption strategies, monoclonal antibodies, and vaccine development.

Prompt **radiological assessment** and **abscess drainage** are central to treatment, given the high incidence of abscess formation in hvKP infections. The hypermucoviscous (HMV) phenotype produces **highly viscous pus**, which complicates drainage procedures. Antimicrobial therapy alone may suffice for abscesses < 5 cm, but larger abscesses typically require intervention. Long-term follow-up is essential, as reinfections have been reported months or years after initial treatment (Shon et al., 2013).

Empirical antibiotic selection should reflect **local resistance profiles**. While *K. pneumoniae* is inherently resistant to ampicillin, there is no universally accepted regimen for hvKP. For central nervous system (CNS) infections, **meropenem plus ceftriaxone** has been suggested, whereas ocular infections

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may require systemic and local administration of cefazolin, ceftazidime, aminoglycosides, or imipenem . Treatment duration often extends to six weeks, depending on infection site and severity (Shon et al., 2013).

- **Phage therapy:** Promising results have been achieved when bacteriophages are combined with antibiotics, particularly for treating carbapenem-resistant hvKP. Phages active against MDR *K. pneumoniae* have been identified, highlighting their potential as adjunctive therapy.
- **Vaccines:** A bivalent bioconjugate vaccine targeting K1/K2 serotypes has been developed using genetically engineered *E. coli*. Vaccines incorporating B-cell epitopes from type 1 fimbrial antigens have also shown protective effects.
- **Monoclonal antibodies:** Experimental models indicate that monoclonal antibodies can reduce intestinal hvKP colonization, preventing systemic spread.

Biofilm formation enhances hvKP persistence and **reduces antibiotic penetration**. Potential biofilm-disruption strategies include:

- **Quorum-sensing (QS) inhibitors** (furans, pyridines, phenyl acyl alkaloids, fatty acids) to block bacterial signaling and biofilm maturation.
- **Enzymatic degradation** of extracellular polymeric substances using dispersin B or DNase, improving antibiotic efficacy.
- **Synthetic polymers and antimicrobial peptides** (e.g., polymyxin, polyalanine) to prevent or dismantle biofilms.
- **Metal-based nanotherapies** with copper or gold nanoparticles, which disrupt bacterial membranes and interfere with metabolism .
- **Combination therapies** integrating multiple anti-biofilm agents, producing synergistic eradication effects.

Priorities include the development of **rapid molecular diagnostics** for hvKP detection and resistance profiling, potentially integrating whole-genome sequencing with AI-based predictive models. Preventive measures-such as vaccines and monoclonal antibodies-require further refinement for durable protection. Enhancing anti-biofilm strategies will also be essential for managing persistent infections.

Ultimately, a **global, multidisciplinary approach**-integrating antimicrobial stewardship, infection prevention, rapid diagnostics, and novel therapeutics-will be key to mitigating the expanding threat posed by hvKP.

14. Conclusions

Klebsiella pneumoniae remains one of the leading causes of **nosocomial infections**, particularly among immunocompromised patients. The emergence of **hypervirulent subtypes (hvKP)** has elevated this pathogen to a critical public health concern, as it now affects not only vulnerable hospital populations but also otherwise healthy individuals. hvKP can cause severe, often life-threatening infections involving multiple organ systems, with **hepatic abscesses** being among the earliest and most characteristic presentations.

Accurate differentiation between **classical K. pneumoniae (cKP)** and hvKP is essential, relying on the detection of specific **molecular and phenotypic biomarkers** to ensure precise diagnosis. The pathogen's capacity to acquire a wide range of **antimicrobial resistance (AMR) genes**-facilitated by its presence in diverse environmental and host reservoirs-further compounds the challenge. In recognition of its escalating drug resistance, the **World Health Organization (WHO)** has designated *K. pneumoniae* as a "critical priority pathogen." The rapid dissemination of resistance determinants has resulted in the alarming emergence of **multidrug-resistant (MDR)** and **extensively drug-resistant (XDR)** hvKP strains, which are refractory to most conventional antibiotics.

In response to these challenges, research has increasingly focused on **innovative therapeutic strategies**, including bacteriophage therapy, biofilm-disrupting agents, monoclonal antibodies, and vaccine development. The integration of **nanotechnology-based approaches** holds additional promise for

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improving prevention and treatment outcomes. Moving forward, sustained **global collaboration** will be indispensable to advancing these novel interventions, enhancing early diagnostic capabilities, and implementing effective infection control measures to curb the growing threat posed by this highly virulent and drug-resistant pathogen.

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