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REVIEW

Capsular Polysaccharide as a Potential Target in Hypervirulent and Drug-Resistant *Klebsiella pneumoniae* Treatment

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Abstract: *Klebsiella pneumoniae* is a common cause of antimicrobial-resistant opportunistic infections in hospitalized patients. Hypervirulent *Klebsiella pneumoniae* (hvKP) acquiring exogenous resistance-encoding and hypervirulence-encoding genetic elements tend to develop both high virulence and resistance. The management of hvKP has also been made more difficult. Capsular polysaccharide (CPS) is the most important virulent factor of hvKP. The high degree of heterogeneity of the CPS and its hindering function adds difficulties in finding a general therapeutic approach. Thus, it is imperative to develop effective ways to target the CPS. The development of CPS-targeting phage treatment has spurred scientific interest. CPS relative vaccines show great potential as therapeutic alternatives to the currently ineffective antibiotics. To find out new ideas for clinical practice, we reviewed the molecular pathogenesis of *K. pneumoniae*, discussed the biological functions and regulatory factors of CPS. We studied the roles of CPS in virulence, drug resistance, and treatment of *K. pneumoniae*, and preliminarily investigated the viability of CPS as a target for prevention and therapy of *K. pneumoniae* infection.

Keywords: capsular polysaccharide, hypervirulent, *Klebsiella pneumoniae*, drug-resistance, bacteriophages

Introduction

Hypervirulent *Klebsiella pneumoniae* (hvKP) is an invasive variant that differs from classical *Klebsiella pneumoniae* (cKP). It exhibits hypermucoviscosity and hypervirulence, causing community-acquired infections such as pyogenic liver abscess, pneumonia, meningitis, and endophthalmitis. Since hvKP was initially discovered in Taiwan, China in 1986, it has spread throughout Southeast Asia, South Africa, Australia, Europe, and the United States.[1] Reports of antibiotic-resistant hvKP isolates have been increasing over the past few years.[2] More and more studies have shown that hvKP resistance and CPS presence are positively associated.[3]

CPS is a thick and dense covering enveloping the bacteria's surface. CPS is an essential virulent factor of hvKP, which shields bacteria from the host immune system phagocytes (such as neutrophils and macrophages) and prevents them from being identified and destroyed. In addition, CPS helps hvKP develop biofilms, which strengthen their resistance to antibiotics.[4] CPS also plays an unignorable role in bacterial pathogenesis by preventing antibodies and complementing components of the immune system from binding to antigens on the bacterial surface, thereby interfering with the immune response.[5]

Therefore, CPS impacts drug resistance and pathogenesis of *K. pneumoniae* in medical research and clinical treatment. Developing immunoprophylactic and immunotherapeutic approaches is one of the key ways to combat *K. pneumoniae* infection. This review aims to summarize the existing literature on the pathogenesis of hvKP infections and clarify the role of CPS in it. By doing so, it is expected to provide a theoretical foundation for more effective preventions and treatments of *K. pneumoniae*.

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Characteristics and Serotypes

Function and Regulators

CPS can be found in cKP and hvKP, but it is thicker in hvKP. The physical barrier effect of CPS and other properties of CPS as a bioactive components carrier, make CPS the most important virulence factor of hvKP, surpassing iron carriers, biofilms, flagella, and other structures. CPS production is known to be transcriptionally regulated by several regulators, but very little is known about how these regulators collectively control CPS production. It is acknowledged that genes located in the chromosomal *rmp* locus encode expression of the hypermucoviscosity (HMV) phenotype and CPS biosynthesis in *K. pneumoniae*. Previous research has shown that the homologs of *rmp, rmpA*, and *rmpA2*, promote CPS synthesis by enhancing the expression of CPS synthetic genes.[6] It has been reported that *rmpC* affects CPS production without changing the HMV phenotype, proving that CPS production and the HMV phenotype are distinct processes.[7] *RmpD* is independent of other CPS regulators, which changes the distribution of CPS chain lengths and confers the HMV phenotype in various species by binding to *wzc*.[8] MarR-like proteins *kvrA* and *kvrB* can regulate CPS synthesis in hypervirulent strains.[9] Homologous response regulators *kvgA, kvhA*, and *kvhR* regulate the synthesis of CPS in *K. pneumoniae* CG43 in a coordinated manner.[10] Studies implicate that *rcsAB*,[11] H-NS,[12] CRP,[13] iron-responsive regulator *IcrR*,[14] *kbvR*[15] can regulate CPS production positively. Also, *fur*[16] and fumarate nitrate reduction regulator (FNR) decreases the amount of CPS.[17] Moreover, OmpR can regulate the energy level of *K. pneumoniae* and affect hyperviscosity simultaneously by overexpressing the genes associated with energy production and metabolism.[18] All the above regulators are listed (Table 1).

Table 1 Summary of CPS Regulators

Regulator	Function	Mechanism	Reference
Direct regulator			
rmpA/A2	Enhance expression of CPS synthesis genes	Activate CPS synthesis genes, like *galF* and *wzi*	[19]
rcsAB	Enhance CPS biosynthesis	*RcsAB*-complex proteins could directly bind to the *galF* promoter and positively regulate the transcription of *galF*	[11]
rmpC	Enhance CPS gene expression	Regulate *manC* and *galF* promoter expression	[7]
rmpD	Confer the HMV phenotype by regulating the chain-length distribution of CPS	Interact with *wzc*	[8]
CRP	Repress CPS biosynthesis	Putative CRP binding sites located in the promoter region of *rcsA*, which encodes CPS transcriptional activator	[20]
IcrR	Enhance CPS biosynthesis	Activate the transcription of CPS genes in a Fe-S cluster-dependent manner.	[14]
kvhR, kvhA, kvgA	Enhance CPS biosynthesis	Three homologous response regulators interact to control, in coordination, the bacterial CPS biosynthesis.	[10]
kbvR	Enhance CPS biosynthesis	Regulate mRNA levels of genes associated with CPS synthesis	[15]
kvrA, kvrB (MarR-like proteins)	Enhance CPS biosynthesis	Regulate transcription from *galF* and *manC* promoters that drive expression of CPS synthesis genes	[9]
Indirect regulator			
H-NS	Repress CPS biosynthesis	Repress expression levels of *rcsA, galF, wzi*, and *manC*	[12]
Fumarate nitrate reduction regulator (FNR)	Repress CPS biosynthesis	Repress the transcription of *rmpA* and *rmpA2*	[17]
fur	Repress CPS biosynthesis	Repress *rcsA* expression	[16]

Notes: *RmpA, RmpA2, RmpC*, and *RmpD* are family of regulators mucoid phenotype; *RcsAB*, two-component regulatory system; CRP, catabolite activator protein; *IcrR*, an Fe–S cluster-containing transcriptional factor; *KbvR*, transcription regulator KP1_RS12260; *KvhR, KvhA* and *KvgA* are homologous response regulators; *KvrA* and *KvrB* are *marR* homologs; H-NS, histone-like nucleoid-structuring protein; FNR, fumarate nitrate reduction regulator; *Fur*, a ferric uptake regulation protein.

The formation and management of CPS in *K. pneumoniae* are highly regulated procedures that involve several signaling pathways and regulatory networks. The performance of these regulators affects the bacteria pathogenicity, physical characteristics, and ability to resist antibiotics and evade the immune system. Although most of the CPS regulatory variable mechanisms are not yet understood, their significance suggests that CPS is essential for *K. pneumoniae* survival. Understanding these systems is necessary to develop new therapeutic and antibacterial treatments. The molecular mechanism of the CPS regulator is presented in Figure 1.

Serotypes

HvKP has been reported worldwide but is mainly prevalent in Asia Pacific, especially in China. A multi-center study revealed that out of 230 K. *pneumoniae* isolates from 10 cities in China, 37.8% were hvKP.[21] However, the rates were generally below 10% in some countries in America and Africa.[22,23] A meta-analysis showed that 394 hvKP isolates were grouped into 50 sequence types (STs). ST23, ST11, ST65, and ST86 were the main strains.[24] In Taiwan, Singapore, and mainland China, 37%~64% of hvKP isolates mainly include ST23, ST26, ST57, and ST163.[25] Moreover, hvKP can acquire carbapenemase genes, resulting in carbapenem-resistant hypervirulent K. *pneumoniae* (CR-hvKP), which possesses high virulence and drug resistance capabilities.[26] CR-hvKP has emerged with distinct sequence types compared to hvKP and shows regional variations. Researchers found that eighteen CR-hvKP isolates were predominantly ST23 and ST65 in Singapore.[27] ST11, ST23, and ST258 were prevalent in the USA, India, Russia, Egypt, and Italy. In China, 80% of CR-hvKP isolates were associated with ST11.[28–30]

K. pneumoniae has also been classified historically by CPS (K antigen) serotyping. To date, 79 CPS types have been identified.[31] Variations in the nucleotide sequence and number of CPS genes account for the differences in *K. pneumoniae* CPS types.[32] K1 and K2 are common in hvKP. The report has found other K16, K28, K54, K63, and KN1 in hvKP.[33] Several sequence types (ST) are associated with hvKP. For example, K1 serotype is most associated with the ST23. A study in China found that 96.2% of ST23 hvKP isolates belonged to K1 serotype and were closely associated with the formation of liver abscess.[34] The STs of K2 serotype isolates exhibited a range of diversity, including ST65, ST66, ST86, ST373, ST374, ST375, ST380, and ST434, of which ST65 and ST86 predominated, associating with invasive infection.[35] Recognizing hvKP strain types is necessary to assist epidemiological investigations and link genetic diversity with pathophysiological specificities.

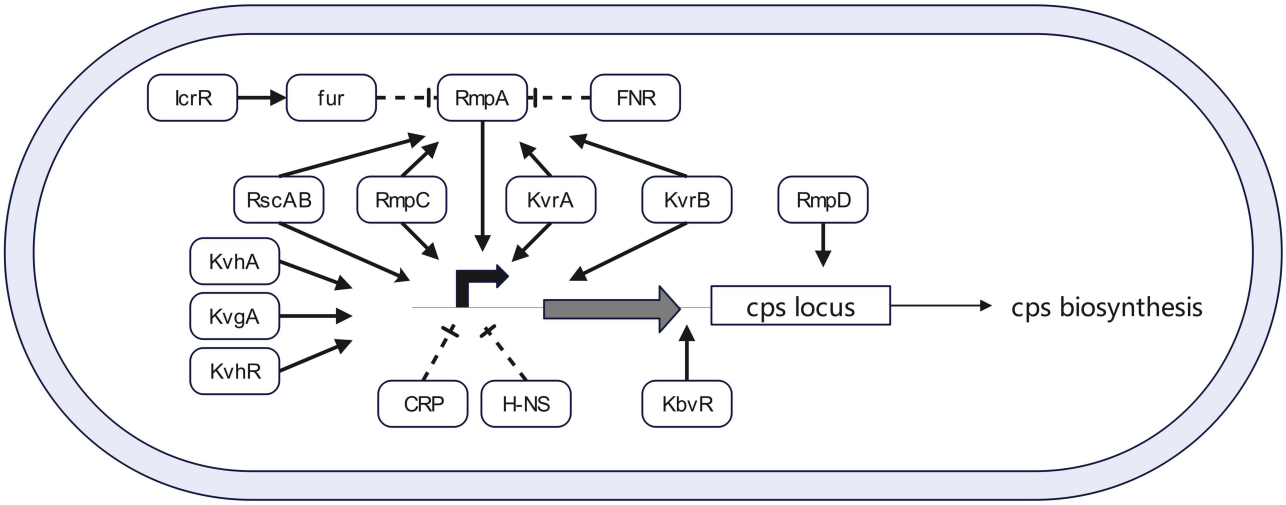

Figure 1 Regulatory factors of CPS in *Klebsiella pneumoniae*. The right-turn arrows indicate the three known upstream promoters of the CPS synthesis region. Solid arrows denote promotion, and dashed arrows indicate repression.
Note: Reproduced from Xu, L., Li, J., Wu, W., Wu, X., & Ren, J. (2024). Klebsiella pneumoniae capsular polysaccharide: Mechanism in regulation of synthesis, virulence, and pathogenicity. Virulence, 15(1). https://doi.org/10.1080/21505594.2024.2439509.

Pathogenicity of Capsule Polysaccharide

In recent years, much attention has been paid to the emergence of hvKP due to its significant clinical risks. Even though the explanation of the pathogenicity of hvKP has been identified, it remains to be fully understood. CPS is a potential target in immunotherapy.[36] However, Diverse K antigen types and the high multidrug resistance make it difficult to provide broad coverage.[37] Hence, research into the effects of CPS on hvKP is important.

Adaption

It has been reported that the adaptive evolution of *K. pneumoniae* is partly attributed to CPS production.[38] The study found after 47 days of antibiotic therapy, the carbapenem-resistant *K. pneumoniae* (CRKP) underwent adaptive evolution, including tigecycline resistance, CPS reduction, and virulence attenuation. The acyltransferase (*act*) gene was mutated in the process. *Act* deficiency reduced CPS production, enhanced biofilm formation, weakened CPS protection, and decreased induction of pro-inflammatory cytokines.[38] It helps CRKP develop adaptive evolution in hostile environments.

Another research suggests that the ST11-KL64 CRKP strain modifies CPS through conflicting evolutionary methods to develop pathogenicity. *Wzc* and *wcaj* genes are CPS biosynthesis proteins. Mutations in them are associated with the mucoid phenotypes. A mutation in S682N *wzc* causes a high-mucus-like phenotype that impacts biofilm formation, epithelial cell adhesion, virulence, macrophage phagocytosis, and mortality. However, the mutation in the *wcaJ* gene results in a non-mucus-like phenotype.[39] Bloodstream infections are linked to a high mucus-like phenotype, while urinary tract infections are linked to a mutant with a non-mucus-like phenotype.[40] The two phenotypes make *K. pneumoniae* infect differently in two situations. In the latter scenario, drug-resistant *K. pneumoniae* may adapt to the environment, continue to grow, and cause infections that might not be cured.

Immunological Responses

K. pneumoniae evades phagocytosis, complement, and antimicrobial peptides by using the bioactive components of CPS to make it difficult for bacteria to be bound. It also affects the immune response of host to the bacteria by interacting with immune factors.

Over 20 years ago, it was discovered that certain *K. pneumoniae* CPS could impede the phagocytosis of host cells.[41] Further research revealed that CPS bearing the Man-α-2-Man sequence exhibited increased sensitivity to phagocytosis and binding, a process known as agglutination phagocytosis.[42] The K1 and K2 CPS also contain sialic acid, contributing to the hypermucoviscosity phenotype and hampers phagocytosis.[43]

Hypermucoviscosity plays a crucial role in the pathogenesis of the organism, as it confers lower adherence to different types of human cells and the ability to avoid neutrophil binding and phagocytosis.[44] In addition, CPS-containing di-Man/Rha epitopes are less likely to be detected by polymorphonuclear leukocytes. Several components of the innate immune system, such as phagocyte mannose receptors, lung surface-activating proteins, mannose-binding lectins, and alternative complement-activating components, are unable to detect these epitopes. As a result, CPS can directly control phagocytosis and enhance survival by preventing bacterial-phagocytic interactions. The CPS of serum-resistant *K. pneumoniae* isolates is a defense mechanism against complement-mediated lysis.[45] The deposition of complement components in the CPS results in morphological changes. However, it does not seem to destroy the bacteria or cause any observable membrane damage.

In addition to interacting with immune cells, CPS can affect immune factors. Studies have shown that CPS can reduce CD14 production, increase the expression of TLR4, CD83, and CD86 markers, and promote dendritic cell maturation.[46] Also, CPS regulates inflammation through the innate immune protein SARM1, which controls TLR to decrease innate responses. Through the TLR4-TRAMIF-IRF3-IFNAR1 pathway, *K. pneumoniae* induces SARM1 in a CPS and lipopolysaccharide O-polysaccharide-dependent manner. This inhibits *Klebsiella*-induced activation of melanosome to inflammasome deletion, limits the production of IL-1β, and suppresses further inflammation.[47]

The Drug-Resistance of Capsule Polysaccharide

Due to the widespread use of antibiotics, hvKP can acquire antimicrobial resistance through several mechanisms.[48] These strains are not only hypervirulent and multidrug-resistant (MDR) but also highly transmissible, causing severe and fatal infections in both hospital settings and the community. The combination of multidrug resistance and enhanced virulence can potentially cause a clinical crisis shortly. Therefore, an immediate response to recognize the global dissemination of this hypervirulent strain with resistance determinants is an urgent priority.

Physical Barrier

According to Campos et al (2004), CPS serves as a physical barrier to reduce external damage to the bacterium and provide protection against *K. pneumoniae*.[49] They discovered that *K. pneumoniae* overexpressed CPS when exposed to polymyxin. Moreover, CPS increases growth rate and population yield, providing a clear health advantage under unfavorable environmental conditions for survival.[50]

Mobile genetic elements (MGEs) must physically interact with the cell envelope during genetic transfer. CPS is the first point of contact between the cells. It can act as a barrier for MGEs but also evolves rapidly through horizontal gene transfer (HGT). When the CPS is inactivated by phage treatment, it can facilitate the acquisition of antibiotic resistance genes (ARGs) through coupling with the resistant plasmid. This leads to the loss of the barrier and subsequent reacquisition of the resistant plasmid. Therefore, phage treatment may inadvertently lead to the acquisition of antibiotic-resistance genes while inactivating the CPS, making the bacteria more resistant.[5]

Neutralize Antimicrobial Peptide

Polymyxin can bind to the anionic outer membrane of bacteria, destroy the integrity of the bacterial outer membrane, and neutralize bacterial virulence. It is increasingly used as a last-line therapeutic option against several multidrug-resistant bacteria. However, *K. pneumoniae* is gradually developing resistance to it. CPS is stably bound to the LPS in the form of ionic interactions, and when polymyxin is present in the environment, the ionic interaction would be disturbed by the charge carried by polymyxin, so CPS could detach from LPS and bind to polymyxin, thus reducing the damage of polymyxin to the outer membrane of *K. pneumoniae*.[49,51]

The above studies present novel approaches to combat bacterial drug resistance, including inhibiting CPS binding and decreasing the expression of CPS. Polycationic polysaccharides such as DEAE-dextran and chitosan can prevent anionic CPS from binding to polymyxins, thereby restoring the antibacterial activity of antimicrobial peptides.[52] Another study found that the deletion of OmpA, an outer membrane protein, increased the susceptibility of *K. pneumoniae* to polymyxin B by causing a decrease in the expression of CPS.[53] To alleviate resistance, it is possible to inhibit OmpA.

Bacteriophage Acts with CPS

The potential of bacteriophage (phage) therapy in addressing stubborn infections is generating significant interest. Phages can evoke the lysis of bacterial cells with polysaccharide depolymerase enzymes. This enzyme can combine with CPS, degrading CPS and making the bacteria more vulnerable to serum-induced death. It makes phages typically specific for one bacterial strain and its CPS type.[54] However, there are more important molecular mechanisms involved in the phage-host bacterial interactions. Further study in this field is required to improve the efficacy of phage therapy.

Phages showed great ability to kill *K. pneumoniae* and have been regarded as a potential alternative for hvKP infections. In the intractable biofilm-associated prosthetic knee infection, phage therapy resolved local symptoms and signs of disease and recovered function.[55] PlyKp104 exhibited significant killing activity against clinical and drug-resistant *K. pneumoniae* isolates without additional outer membrane permeabilizers in burn and wound infections, pneumonia, urinary tract infections, and more severe invasive diseases.[56] Two bacteriophages, vB_KpnP_K3-ULINTkp1, and vB_KpnP_K3-ULINTkp2, were newly isolated against an ST13 *K. pneumoniae* strain isolated from a UTI.[57] Lytic bacteriophage (phage) Kp_Pokalde_002 was isolated against carbapenem-resistant *K. pneumoniae* (Kp56).[58] Other novel bacteriophages, including vB_KleM_KB2, PSKP16, vB_KpnP_ZX1, and Klebsiella Phage K5, were found against the multidrug-resistant

Table 2 Summary of K. Pneumoniae Phage

Phage	Strain	Enzyme	Reference
Kp_Pokalde_002	Kp56	Depolymerase	[58]
NTUH-K2044-K1-1	K1	K1 CPS-specific depolymerase	[63]
PlyKp104	Strain HM_4.	Lyase	[56]
ΦFK1979	K2	K2 CPS-specific depolymerase	[64]
B1	K2	Recombinant B1dep depolymerase	[65]
vB_KpnP_K3-ULINTkp1	K3	Exopolysaccharide-degrading enzyme	[57]
vB_KpnP_K3-ULINTkp2	K3	Exopolysaccharide-degrading enzyme	[57]
vB_KpnM-20	K7,K20,K27	K7dep, K20dep, K27dep depolymerase	[66]
K5	K21	Receptor-binding proteins (RBPs)	[62]
KL-2146	BAA2146	Lyase	[67]
SRD2021	K47	Depolymerase	[68]
SH-KP156570	K19	Depolymerase K19-Dpo41	[69]
KpV79	K57	Depolymerase Dep_kpv79 and Dep_kpv767	[70]
vB_KpnP_ZX1	K57	Depolymerase Dep_ZX1 e	[61]

clinical isolates of *K. pneumoniae*.[59–62] Novel phages have been reported recently (Table 2). Generally, lytic phage therapy is considered one of the best alternatives for treating infections caused by MDR bacterial pathogens.

Phages can also be utilized as tools for vaccine preparation. CPS depolymerase from phage can successfully identify and cleave K1 and K2 CPS into intact oligosaccharide structural units that maintain immunogenicity with intact modifications. The K1 and K2 oligosaccharides were then coupled with CRM197 carrier protein to prepare CPS-coupled vaccines. The K1 or K2 CPS conjugate vaccines and bivalent vaccines (mixtures of the K1 and K2 CPS conjugate vaccines) protected mice against *K. pneumoniae* infections caused by their respective CPS types. K1 and K2 CPS-conjugate vaccines prepared by CPS depolymerization enzymes are promising candidates for developing vaccines against human *K. pneumoniae* infections.[71]

However, the evolution of phage resistance poses an inevitable threat to the efficacy of phage therapy. Researchers revealed numerous defense mechanisms for bacteria against phage infection (prophage, plasmid, defense/virulence/resistance, and oxidative stress proteins).[72] The most common reason for phage resistance is mutations affecting phage receptors such as CPS. HvKpP3 can lyse a hvKP strain of serotype K2. Spontaneous mutant hvKpP3R15, developed from hvKpLS8 strains, showed strong resistance to the lysing phage hvKpP3. Sequence analysis revealed that nucleotide deletion mutations in the *wcaJ* gene of the CPS gene cluster caused phage resistance. The *wcaJ* mutations inhibit phage adsorption by affecting the synthesis of CPS of hvKpP3R15.[73] Another kKBO-1 phage-resistant mutant BO-FR-1 was mutating in the CPS synthesis gene cluster *wbaP* gene, which is responsible for producing a glycosyltransferase in the initial stage of CPS biosynthesis. K2 capsule type sequence 86 hvKP FK1979, one of the main pandemic lineages of hvKP with thick CPS, developed resistance to a K2-specific lysis phage FK1979 by decreasing CPS expression. *RfaH* and *galU* were further identified as required for CPS production and phage sensitivity.[64] However, there might be an advantage in developing the resistance to phage. When mutations decrease CPS production, the bacteria become more susceptible to the immunity system.[74]

Investigators have modified recombinant lysins to better penetrate the outer membrane through genetic and protein engineering strategies. *K. pneumoniae* 52145 strain was originally resistant to phage 731 due to the lack of K2 capsule. Recent research demonstrated that B1dep-phage 731, the combination of recombinant K2 depolymerase (B1dep) and phage 731, allows the lysis of the wild-type strain.[75] Strategically selecting combinations of phages can also help prevent the evolution of phage resistance. When phages that target different host receptors are combined, the incidence of resistance is reduced. They can infect phage-resistant mutants, which can slow down the development of resistance. Conversely, when a three-phage cocktail contains two phages that target the same receptor, the incidence of resistance is increased.[76] Moreover, combining phages with antibiotics is more effective than using a single drug. The combination can enhance bacterial inhibition, penetrate biofilms more effectively, and reduce the chances of phage resistance emerging.[77] The polymyxin-phage combination can enhance bacterial killing.[78] Combining phage vB_KpnM_P-KP2 and gentamicin completely rescued the acute pneumonia mice caused by K47 Serotype K. *pneumoniae*.[79] Despite the

positive outcomes, the interactions between phages and hosts are more complex and require further study. Clinical trials are necessary to develop treatments widely available to humans.

Conclusion

CPS is the dominant surface structure of the bacteria. And It's unignorable in different strains, including *Streptococcus pneumoniae, Mycobacterium tuberculosis, Cryptococcus neoformans*.[80–82] It can protect bacteria from the phages and antibiotics. Particularly, it is important in aiding immune evasion during initial infection and bloodstream survival. In *K. pneumoniae* CPS serves as the main virulence factor associated with the viscous phenotype. It has been widely accepted that the hypermucoviscosity phenotype of *K. pneumoniae* and the hypervirulent characteristics of the strains are often positively correlated, albeit with a few exceptions. In the first few decades after the emergence of hvKP, widespread antibiotic susceptibility of hvKP isolates allowed for uncomplicated treatment. However, recent studies have reported a convergence of hvKP, with isolates often accompanied by chromosomal resistance genes or carrying plasmids encoding resistance genes. The healthcare community is currently facing a serious challenge due to the increasing prevalence of drug-resistant hvKP. These highly pathogenic virulent strains carry multiple antibiotic-resistance genes, which makes it difficult to select effective antibiotics for infection management. Various mechanisms have been proposed for hvKP to acquire resistance, including the acquisition of coupled plasmids with antimicrobial resistance determinants by hvKP strains[83] and the acquisition and integration of integrally conjugated elements (ICE) containing antimicrobial drug resistance determinants in hvKP strains.[29] The thick hypercapsule could serve as a physical barrier and impair the DNA uptake, consequently limiting the horizontal gene transfer in this mechanism.[84]

Therefore, targeting the CPS could be a potential treatment strategy. It has been proven to be an optimal target for bacterial vaccine development. Pneumococcal conjugate vaccine (PCV), which can prevent pneumococcal disease effectively, is included in the national immunization programs in most countries worldwide.[85] But no hvKP vaccine has been marketed. The traditional method of obtaining CPS for vaccine preparation has limitations due to loss of immunogenicity. There are also challenges related to the variety of CPS serotypes and antigenic diversity caused by chromosomal reorganization. Phage therapy has gained attention in the prevention and treatment of hvKP infection. HvKP is characterized by high production of CPS, one of the most important serum antigens in hvKP, and has been described as the phage absorption receptor. Phages can directly remove the CPS. Due to its bacteriolytic activity and bacterial host specificity, phage therapy can simultaneously overcome two serious side effects: drug resistance emergence and symbiont disorders. It is a promising choice. However, phage resistance has been illustrated as a threat to undermine phage therapy and seems inevitable Engineering sustainable phage-based anti-virulence approaches or phage cocktails to fight hvKP infections might be the solution. Additionally, CPS-targeting therapies can reduce virulence and lead to serum-induced killing, reducing susceptibility to polymyxins. Thus, strengthening infection control and prevention, improving strategies for antibiotic use, and developing novel antibiotics to combat the bacteria are extremely urgent.

The relationship between CPS and *K. pneumoniae* virulence and resistance remains under constant research. Continued research is needed to understand the regulation and resistant mechanisms. Developing therapeutic agents capable of inhibiting or removing CPS from *K. pneumoniae* is of great clinical importance. Phage-antibiotic combinations have broad application areas and hold potential value as a future direction for targeting drug-resistant and hypervirulent *K. pneumoniae*.

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Disclosure

Their authors declare that there are no conflicts of interest.

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