Context-dependent virulence in *Klebsiella pneumoniae*: deciphering niche-specific adaptation and virulence-resistance interplay

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Hypervirulent *Klebsiella pneumoniae* (hvKp) can cause severe infections mediated by a virulence plasmid (KpVP) that encodes aerobactin (*iuc*), salmochelin (*iro*), and the capsule regulator *rmpA*. While these factors are known to drive systemic infection, their niche-specific roles remain unclear. Aerobactin facilitates gut colonization primarily by overcoming iron competition from the microbiota,[1] whereas salmochelin promotes bloodstream survival by evading host-derived lipocalin-2.[2] Despite extensive research on strain-specific virulence determinants,[3] relatively few studies have examined the regulation of these virulence factors across distinct infection sites, such as the gut versus the bloodstream. Moreover, much of the research on hvKp in Asia has focused predominantly on the convergence of carbapenem resistance, rather than niche-specific adaptation.[4] Since hvKp frequently originate within the gut prior to systemic dissemination, clarifying how these virulence determinants influence disease progression is crucial for the development of targeted therapeutic interventions.

In this issue of *eBioMedicine*, Lim et al. (2025)[5] systematically examined the niche-specific roles of virulence plasmid-encoded factors in hvKp pathogenesis using the well-characterized ST23 K1 strain, SGH10. Using isogenic mutants and various murine infection models, they identified distinct functional roles for aerobactin, salmochelin, and *rmpA* in bacterial colonization and systemic infection. A key novel finding of their study is that salmochelin plays a pivotal role in bloodstream dissemination, a role often overshadowed by the established importance of aerobactin in facilitating iron acquisition.[6] The study further confirms that aerobactin is indispensable for stable gut colonization, emphasizing its role in outcompeting the host microbiota during iron sequestration. Furthermore, bioinformatics analyses demonstrate a strong co-inheritance pattern of *iro* and *iuc* loci, suggesting their combined presence confers a selective advantage across host niches. These findings extend previous research indicating that *rmpA* enhances bacterial dissemination through increased capsule production but is dispensable for gut colonization. By systematically dissecting the contributions of multiple virulence factors across distinct infection models. This work provides a refined perspective on niche-specific virulence and highlight critical targets for therapeutic intervention.[5]

Moreover, Lim et al.[5] establish an important framework for understanding the mechanisms through which *K. pneumoniae* adapts to distinct host niches, reinforcing the concept of niche-specific virulence programs. Their findings on siderophore prioritization underscore the necessity of investigating how factors such as pH, iron availability, and immune pressure modulate virulence expression.[3] The co-inheritance of *iro* and *iuc* in hypervirulent strains indicates a potential evolutionary advantage; however, the mechanisms by which these genetic elements persist under antibiotic selection pressures remain unclear. Emerging evidence suggests that multidrug-resistant (MDR) *K. pneumoniae* strains are increasingly acquiring hypervirulent traits, prompting concerns regarding the emergence of "convergent strains" possessing both enhanced virulence and resistance.[7] Investigating whether MDR strains trade virulence for resistance or maintain both through adaptive mechanisms could provide critical insights into *K. pneumoniae* evolution and antimicrobial resistance strategies. Another key implication of Lim et al.'s work is the observed dispensability of *rmpA*-mediated hypermucoviscosity in gut colonization despite its critical role in systemic dissemination. This observation challenges the conventional perspective of capsule production as an indispensable virulence factor across all infection stages.[8] One possible explanation is that capsule expression imposes a metabolic burden in the gut, where nutrient competition is high. Additionally, the interplay between virulence and antibiotic resistance in

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hvKp remains an important research priority. Studies suggest that aerobactin may confer a survival advantage beyond facilitating iron uptake, potentially protecting bacteria from antibiotic-induced oxidative stress. Examining this potential interplay between virulence and antibiotic resistance mechanisms could yield novel insights into hvKp adaptability and persistence.

While the study offers valuable insights, several key questions remain unresolved. The precise mechanisms governing niche-specific roles of aerobactin and salmochelin, including how host immunity or bacterial regulatory networks modulate siderophore expression, require further investigation. Additionally, the limited role of the hypermucoviscous capsule in gut colonization compared to its established systemic functions raises questions about whether capsule downregulation enhances bacterial fitness by reducing metabolic costs or enabling alternative survival strategies. Another critical issue is the convergence of virulence and antibiotic resistance, exemplified by ST11 strains harboring both virulence and resistance determinants.[9] Clarifying if virulence traits, such as enhanced iron acquisition via aerobactin, confer advantages under antibiotic stress could significantly advance our understanding of *K. pneumoniae* adaptability and inform targeted therapeutic strategies.

The study by Lim et al. significantly advances our understanding of the requirements for niche-specific virulence factors in hvKp. By demonstrating how different host environments shape the necessity of aerobactin, salmochelin, and *rmpA*, this work provides a refined perspective on bacterial pathogenesis and highlights the importance of infection site-specific therapeutic approaches. Future research should explore how virulence-resistance convergence, such as ST11-CRKP with *rmpA*/*iucA*, is shaped by host-microbe-environment interactions.[10] An integrated approach combining genomic analyses, ecological studies, and infection models will be critical for developing precision therapeutics aimed at disrupting the adaptation of *K. pneumoniae* during critical stages of infection.

Contributors
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Declaration of interests
The authors declare no conflicts of interest.

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