Infection and Drug Resistance

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REVIEW

# Interactions and Implications of *Klebsiella pneumoniae* with Human Immune Responses and Metabolic Pathways: A Comprehensive Review

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**Abstract:** *Klebsiella pneumoniae* (*K. pneumoniae*), a significant contributor to the global challenge of antibiotic resistance, is not only a ubiquitous component of the human microbiome but also a potent pathogen capable of causing a spectrum of diseases. This review provides a thorough analysis of the intricate interactions between *K. pneumoniae* and the human immune system, elucidating its substantial impact on metabolic processes. We explore the mechanisms employed by *K. pneumoniae* to evade and manipulate immune responses, including molecular mimicry, immune modulation, and biofilm formation. The review further investigates the bacterium's influence on metabolic pathways, particularly glycolysis, highlighting how these interactions exacerbate disease severity. The emergence of multidrug-resistant and extremely drug-resistant strains within the Enterobacteriaceae family has heightened the public health crisis, underscoring the urgency for comprehensive research. We investigate the roles of the host's complement system, autophagy, cell death mechanisms, and various cytokines in combating *K. pneumoniae* infections, shedding light on areas that warrant further academic investigation. Additionally, the review discusses the challenges posed by K1- and K2-capsule polysaccharides in vaccine development due to their complex molecular structures and adhesive properties. Acknowledging the limited availability of effective antimicrobials, this review advocates for exploring alternative approaches such as immunotherapeutics, vaccinations, and phage therapy. We consolidate current knowledge on *K. pneumoniae*, covering classical and non-classical subtypes, antimicrobial resistance-mediated genes, virulence factors, and epidemiological trends in isolation and antibiotic resistance rates. This comprehensive review not only advances our understanding of *K. pneumoniae* but also underscores the imperative for ongoing research and collaborative efforts to develop new prevention and treatment strategies against this formidable pathogen.

**Keywords:** *Klebsiella pneumoniae*, complement system, pathogenic mechanism, drug-resistant, treatment strategy

## Introduction

Antibiotic resistance remains one of the most pressing global health challenges, significantly impeding our ability to effectively treat various infections. A prominent culprit in this crisis is *Klebsiella pneumoniae* (*K. pneumoniae*), a prevalent gram-negative bacterium. While often considered a benign component of the human microbiome, it can initiate a spectrum of diseases, ranging from urinary tract infections to severe conditions such as necrotizing pneumonia and pyogenic liver abscesses.[1] It predominantly impacts neonates, the elderly, and individuals with compromised immune systems.[2] Accounting for approximately one-third of all Gram-negative infections, the role of *K. pneumoniae* in the escalating antibiotic resistance crisis is paramount.[3]

The emergence of multidrug-resistant (MDR) and extremely drug-resistant (XDR) strains within the Enterobacteriaceae family has significantly intensified the public health crisis, carrying substantial economic implications.[3] This review seeks to synthesize our current understanding of *K. pneumoniae*, with a particular focus on its interactions with the human immune system and the resulting implications on metabolic processes. Such comprehension is essential for formulating comprehensive strategies to counter the escalating threat posed by this bacterium.[4]

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*K. pneumoniae*'s sophisticated survival strategies within the human host, including molecular mimicry, immune modulation, and biofilm formation, pose considerable challenges in clinical and infection control settings. Further scholarly inquiry is warranted into the roles of the host's complement system, autophagy, cell death mechanisms, and various cytokines in combating *K. pneumoniae* infections. Additionally, the bacterium's impact on human metabolic pathways, especially the glycolytic pathway, and its implications in exacerbating disease severity underscore the need for in-depth investigation into these intersections of metabolism and immunity.

Considering the scarcity of effective antimicrobials in the current pharmaceutical landscape, there is an increasing urgency to explore alternative approaches such as immunotherapeutics, vaccinations, and phage therapy. This review consolidates existing knowledge on *K. pneumoniae*, examining differences between classical and non-classical subtypes, antimicrobial resistance genes, virulence factors, and epidemiological trends. Emphasizing the necessity for ongoing research and collaboration between clinicians and researchers, the review underscores the importance of developing novel prevention and treatment strategies against this formidable pathogen.

## Interaction Between *K. pneumoniae* Infection and the Human Immune System

*K. pneumoniae* can employ various virulence factors for survival and pathogenesis, including the capsule, siderophores, lipopolysaccharide (LPS), fimbriae, outer membrane proteins (OMPs), and the type 6 secretion system.[5] Among these, the capsule emerges as a prominent virulence factor of *K. pneumoniae*, providing protection against complement and phagocytosis. This defense mechanism facilitates bacterial colonization and dissemination within host tissues. Currently, over 80 different capsular types (K types) are recognized, with K1 and K2 being the most prevalent pathogenic types.[6] Upon entering the host's body, the bacteria trigger immune responses aimed at eliminating the infection. Throughout this process, the capsule plays a pivotal role by shielding the bacteria from complement and phagocytosis attacks, thereby enabling their colonization and spread within host tissues.[6] This section will delve into the mechanisms through which *K. pneumoniae* evades the host's immune response.

### Complement System's Response to K. Pneumoniae

#### Overview of the Complement System

The complement system represents a critical component of the immune defense, specifically engineered to identify and eliminate bacterial invaders. This system consists of an intricate network of inactive proteins that, upon activation, participate in a cascade-like sequence of reactions. This proteolytic cascade is initiated in response to various microbial patterns, ultimately leading to the deposition of complement proteins on bacterial surfaces. This process effectively labels the bacteria for phagocytosis and subsequent destruction, playing a pivotal role in immune defense mechanisms.[7–9]

Three distinct pathways can initiate the complement system: the classical pathway, the mannose-binding lectin pathway, and the alternative pathway. Each pathway converges at a critical step—the cleavage of the C3 protein into C3a and C3b fragments. C3b, in particular, binds to the bacterial surface, forming a C3 convertase that amplifies the response by cleaving additional C3 molecules. Moreover, C3b can associate with C3 convertase to create a C5 convertase, which further cleaves C5 into C5a and C5b. Subsequent formation of the membrane attack complex (MAC), involving C5b, C6, C7, C8, and multiple C9 molecules, leads to the creation of pores in the bacterial membrane, disrupting cellular exchange and resulting in cell lysis and death. In addition to these direct attack mechanisms, the complement system serves broader roles in immune defense, including opsonization for phagocytosis, regulation of inflammation, and stimulation of other immune responses.[8]

#### Resistance Mechanisms of *K. Pneumoniae*

Despite the remarkable strength of the complement system, certain pathogens, such as *K. pneumoniae*, have evolved intricate strategies to evade its impact. Upon invasion by *K. pneumoniae*, the host's complement system promptly initiates a counterattack against this bacterial intruder. However, *K. pneumoniae* has adeptly adapted to resist and elude these immune responses, showcasing a sophisticated level of evolutionary defense mechanisms.

*K. pneumoniae*'s resistance is multifaceted, involving its unique capsule structure, an array of virulence factors, and complex colonization mechanisms. The capsule, characterized by a dense matrix of polysaccharide fibers, plays a critical role in impeding the formation and action of MAC. This structure effectively shields the bacterium from various immune responses, including phagocytosis, the action of antimicrobial peptides, and complement-mediated lysis.[10] The polysaccharide composition of the capsule varies between strains, contributing to the diversity in immune evasion strategies. For instance, strains with inadequate encapsulation tend to exhibit increased C3b deposition, rendering them more vulnerable to phagocytic uptake by lung epithelial cells.[11]

In individuals with robust immune systems, innate immune defenses, particularly the serum complement system and phagocytic leukocytes such as neutrophils and macrophages, play a significant role in combating *K. pneumoniae* infection and preventing severe illness. This dynamic interplay underscores the importance of understanding the complement system's mechanisms and the bacterial strategies that challenge its efficacy.[12,13]

## Capsule Structure and Its Role in Immune Evasion

A critical element in the defense mechanisms of *K. pneumoniae* is its unique capsule structure. Comprising a dense matrix of polysaccharide fibers, this capsule establishes an impervious barrier against the host's immune responses. The efficiency of this capsule in obstructing the formation and function of the MAC is particularly noteworthy. Not only does this barrier impede MAC, but it also provides substantial resistance against other immune mechanisms, including phagocytosis, the activity of antimicrobial peptides, and complement-mediated lysis.[11]

The variability in the polysaccharide composition of *K. pneumoniae* capsules among different strains is a critical determinant of their immune evasion capabilities. Some strains demonstrate a remarkable ability to dynamically modify their polysaccharide structures, allowing them to evade detection via the lectin pathway of the complement system. This adaptive capability underscores the complexity of the immune evasion strategies employed by various *K. pneumoniae* strains. Strains with less effective encapsulation, for example, show increased deposition of C3b on their surfaces, rendering them more susceptible to phagocytosis by lung epithelial cells.[11]

## Virulence Factors and Iron Acquisition

The virulence of *K. pneumoniae* is significantly augmented by various factors, particularly in hypervirulent strains, such as those associated with clonal complex 23. These strains possess a substantial virulence plasmid encoding several key virulence factors.[14] Among these factors, the ability of *K. pneumoniae* to acquire iron from its environment is crucial for its survival and pathogenicity within the host organism. The bacterium relies on siderophores, high-affinity iron-chelating compounds that are essential for both growth and virulence. Studies have shown that the deletion of genes responsible for producing specific siderophores, such as aerobactin, results in reduced growth and virulence, particularly in lung infection models.[10]

## Colonization Mechanisms

For successful colonization, *K. pneumoniae* employs Type I pili, which are essential for the bacterium's adherence to various surfaces, including mucosal membranes.[15,16] This adherence capability facilitates the establishment of the bacterium within the host, enabling it to maintain a presence inside specialized cells like alveolar macrophages and effectively evade destruction within the phagosome.[17] This strategic colonization is a testament to the adaptive capabilities of *K. pneumoniae*, allowing it to persist and thrive within the host environment.

## Antagonistic Role of OMPs and Interference of LPS

OMPs of *K. pneumoniae* play a pivotal role in mediating its resistance to various components of the host immune system. These proteins are particularly significant in conferring resistance to antimicrobial peptides, a crucial component of the broad-spectrum antibiotics within the host defense system.[18] Over time, *K. pneumoniae* and other bacteria have developed sophisticated mechanisms to resist these peptides, with OMPs being central to this resistance.

For example, OmpK36, a specific outer membrane porin of *K. pneumoniae*, adeptly activates the classical pathway of the complement system, providing serum resistance. This protein achieves this by binding directly to C1q, effectively inhibiting the activation of the complement system and enhancing the bacterium's resilience against host immune

responses.[7] Interestingly, strains deficient in OmpK36 exhibit increased resistance to serum, indicating a complex interplay and critical role of these proteins in *K. pneumoniae*'s survival.[19]

LPS, another major component of *K. pneumoniae*'s outer membrane, significantly contributes to the bacterium's evasion of the host's immune responses. LPS can inhibit the complement system in various ways. One notable mechanism involves the release of membrane vesicles containing LPS, which can absorb complement proteins, thereby reducing complement deposition on the bacterial surface.[20] This process effectively shields *K. pneumoniae* from recognition and elimination by the complement system, enhancing its survival within the host. The special outer membrane properties of *K. pneumoniae*, from its resistant capsule structure to its effective evasion mechanisms involving OMPs and LPS, establish this bacterium as a challenging pathogen to treat.

## Impact of Autophagy and PANoptosis Mechanisms

Cell death is a fundamental process in all living organisms, and autophagy serves as a crucial defense mechanism against invading bacteria. Moreover, various PANoptosis mechanisms exist through which cells can undergo death, including apoptosis, pyroptosis, and necrosis. Each of these mechanisms has a distinct impact on the immune response to *K. pneumoniae* infection. This section will delve into an in-depth exploration of how *K. pneumoniae* interacts with the host immune system, disrupting autophagy, and activating PANoptosis.

### Autophagy

*K. pneumoniae* has the ability to activate autophagy, promoting the formation of neutrophil extracellular traps (NETs), a process that enhances the bactericidal effect of neutrophils.[21] However, *K. pneumoniae* also possesses the capability to interfere with the fusion of phagosomes and lysosomes, creating a relatively safe habitat within host cells.

Autophagy promotion by *K. pneumoniae* can occur through surface recognition or cytoplasmic sensing, although the specific signaling molecules and receptors involved are not fully understood. Toll-like receptor 4 (TLR4), a protein recognizing *K. pneumoniae*'s LPS, is considered a crucial receptor in *K. pneumoniae*-induced autophagy.[22] Additionally, transient receptor potential melastatin 2 (TRPM2) and macrophage-inducible C-type lectin (Mincle) are thought to be key molecules involved in the formation of NETs.[21]

Throughout *K. pneumoniae* infection, the PI3K-AKT-Rab14 signaling pathway emerges as a vital regulator of phagosome maturation.[21] This pathway influences the fusion of phagosomes and lysosomes, thereby impacting the survival of *K. pneumoniae* within host cells.

### Apoptosis

Apoptosis is a programmed cell death (PCD) process that allows an organism to eliminate unwanted or defective cells in an orderly manner, avoiding an undesirable inflammatory response.[23] These orchestrated changes are mediated by a family of proteins known as caspases (Casp).

*K. pneumoniae*, a bacterium causing various infections, influences the apoptosis of host cells through diverse mechanisms. On one hand, *K. pneumoniae* can induce apoptosis in macrophages,[17] hepatocellular carcinoma cells (HepG2),[24] platelets,[25] and epithelial cells,[26] enabling the bacterium to evade immune clearance or facilitate its spread. Additionally, *K. pneumoniae* can inhibit apoptotic signaling pathways through factors such as capsules, which down-regulate the Bax/Bcl-2 ratio and up-regulate Mcl-1 expression, thereby resisting the bactericidal effect of the host.[27] The capsule, a crucial virulence factor, also plays a role in delaying neutrophil apoptosis. Compared to acapsular mutants, strains with a K1-type capsule significantly delay the apoptosis of infected neutrophils.[27] Therefore, the interaction between *K. pneumoniae* and host cell apoptosis is complex, potentially influencing the severity and prognosis of infection.

### Pyroptosis/Pyronecrosis

Pyroptosis is a form of PCD that relies on inflammatory caspases, specifically human caspases-1, −4, and −5, and their murine equivalents. These caspases are key components of the innate immune defense, with caspase-1 activated by canonical inflammasome ligands and caspase-4, −5, and −11 recognizing bacterial LPS, ultimately leading to pyroptosis. This process is characterized by the cleavage of gasdermin D (GSDMD), which drives the release of pro-inflammatory

cytokines like IL-1β and IL-18, playing a crucial role in the body's response to invading pathogens.[28] Cytokines like IL-1β and IL-18 are processed and released in a caspase-1-dependent manner during pyroptosis, although the exact mechanisms of their secretion are still under investigation.[29]

Pyronecrosis, a related cell death pathway, is a caspase-independent and cathepsin B-dependent cell death pathway. Resembling necrosis in its morphological features, pyronecrosis is associated with genetically induced auto-inflammatory diseases and infections by certain microbial pathogens. Unlike pyroptosis, which relies on caspases, pyronecrosis depends on cathepsin B for cell death.[30] In the context of *K. pneumoniae* infections, studies have demonstrated that *K. pneumoniae* can induce pyroptosis through the increased expression of NLRP3, ASC, caspase-1, and GSDMD in macrophages and lung tissues. Specifically, NLRP3/ASC-mediated pyroptosis in alveolar macrophages has been shown to enhance the secretion of high-mobility group box 1 protein (HMGB1), indicating a significant role in the immune response to *K. pneumoniae* infection.[21]

The factors within *K. pneumoniae* that trigger pyroptosis/pyronecrosis remain elusive, but K1-CPS has emerged as a key contributor. In mouse J774A.1 macrophages, K1-CPS induced caspase-1 activation and IL-1β secretion in the presence of ATP.[31] Moreover, K1-CPS-induced NLRP3 expression was markedly lower in TLR4 knockdown cells than in control cells, suggesting TLR4 involvement in the NLRP3 inflammasome activation triggered by K1-CPS.[31] Furthermore, K1-CPS induced NLRP3 inflammasome activation was also associated with reactive oxygen species (ROS) generation, mitogen-activated protein kinase phosphorylation, and NF-κB activation.[31] These forms of cell death play a significant role in host anti-infection responses by eliminating the protective intracellular niche of pathogens and promoting neutrophil-mediated killing.

### Necrosis

*K. pneumoniae* infection induces two main forms of cell death: necrosis and necroptosis. Necrosis, a lytic cell death mechanism, is utilized by certain bacteria for in vivo dissemination and evasion of host immune responses. In contrast, necroptosis is a programmed cell death that also facilitates pathogen transition.

In the presence of *K. pneumoniae* infection, apoptotic HepG2 cells undergo progression to secondary necrosis and primary necrosis, involving the inactivation of PARP by caspase 7.[21] With the persistence of the infection, Endo G, AIF, and DFF40 relocate from the mitochondria to the nucleus, initiating DNA fragmentation.[24] Subsequent DNA damage activates PARP, depleting ATP and triggering increased expression of calpain-2. This sequence of events culminates in the breakdown of cellular components, ultimately inducing necrosis and facilitating the dissemination of *K. pneumoniae*.[21]

Concurrently, *K. pneumoniae* activates cell necroptosis through the RIPK1/RIPK3/MLKL cascade to evade host defenses.[32] Additionally, it interferes with apoptosis activation to inhibit efferocytosis. In vitro studies suggest that inhibiting necroptosis via RIPK1 and RIPK3 can restore the efferocytic uptake of *K. pneumoniae*-infected neutrophils by macrophages, indicating that *K. pneumoniae* induces neutrophil necroptosis.[33] Therefore, inhibiting necroptosis could potentially enhance efferocytic uptake for *K. pneumoniae*-infected neutrophils.

In contrast to wild-type mice, Ripk3$^{-/-}$ mice exhibited improved bacterial clearance from the bronchoalveolar lavage fluid (BALF) and lungs 96 h post-infection.[32] These results indicate that necroptosis supports *K. pneumoniae* survival within the host by diminishing macrophage-mediated efferocytic uptake of infected neutrophils. Therefore, inhibiting necrosis/necroptosis could potentially serve as an adjunctive treatment for *K. pneumoniae* infection.

In summary, *K. pneumoniae* infection can trigger cell death via multiple mechanisms, each exerting unique influences on the immune response and the ultimate result of the infection. Exploration of these mechanisms could potentially lead to the development of more effective treatment strategies against *K. pneumoniae* infection.

## Cytokines Involved

Cytokines, small proteins crucial for orchestrating the immune response, function as signaling molecules released by immune cells. These molecules play a pivotal role in facilitating communication and coordination among various cells to effectively counteract invading pathogens. In the context of *K. pneumoniae* infection, a complex interplay of both pro-inflammatory and anti-inflammatory cytokines contributes to the intricate immune response.

### Pro-Inflammatory Cytokines

*K. pneumoniae* infection triggers the host cells to secrete a variety of pro-inflammatory cytokines, including IL-1β, IL-6, IL-8, TNF-α, and IL-17.[21] These cytokines play a crucial role in activating and recruiting immune cells, thereby enhancing the host's antibacterial ability. Virulence factors of *K. pneumoniae*, like K1-CPS and LPS, can activate inflammasomes through TLR4 or NLRP3 signaling, resulting in the production of mature cytokines.

Primarily generated by activated macrophages, pro-inflammatory cytokines boost inflammatory responses and aid in pathogen elimination. For example, *K. pneumoniae* induces the production of chemokines such as CXCL15, MIP-1α/CCL3, CXCL1, CXCL8 (IL-8), and CXCL5, promoting the movement and bactericidal activity of neutrophils.[34] Moreover, *K. pneumoniae* activates inflammasomes like NLRP3 and NLRC4, leading to the activation of Caspase-1 /Interleukin-1 converting enzyme (ICE) and subsequent secretion of pro-inflammatory cytokines like IL-1β and IL-18. While these cytokines enhance host immune defenses, they may also cause excessive inflammatory responses and tissue damage.[21]

Pro-inflammatory cytokines induced by *K. pneumoniae* can also lead to severe complications such as lung injury, sepsis, and multiple organ failure. Therefore, understanding the role of these cytokines in the immune response to *K. pneumoniae* infection is crucial for developing effective therapeutic strategies.[21]

### Anti-Inflammatory Cytokines

In *K. pneumoniae* infection, the bacterium intricately interacts with anti-inflammatory factors to manipulate the host's immune system. One strategy employed by *K. pneumoniae* is the reduction of CXCL8 secretion via the TLR4 signaling pathway.[21] This reduction effectively diminishes the recruitment of neutrophils, crucial white blood cells in the body's defense against bacterial infections.

Additionally, *K. pneumoniae* can induce the production of IL-10 in myeloid-derived suppressor cells (MDSCs).[34] IL-10 is an anti-inflammatory cytokine that shields the host from damage caused by excessive inflammation.[21] However, these anti-inflammatory effects can also be exploited by *K. pneumoniae* to evade host defense mechanisms and promote its survival within the host. For instance, IL-10 has been shown to inhibit pyroptosis and efferocytosis of infected cells.[35] By inhibiting these processes, IL-10 reduces bacterial clearance, ultimately boosting their survival. Moreover, IL-22, another anti-inflammatory factor, collaborates with IFN-λ to maintain the integrity of the epithelial barrier. This collaboration inhibits neutrophil migration and prevents bacterial invasion.[21] Crucial to the host's defense against *K. pneumoniae*, specific cytokines like IL-10 and IL-4 orchestrate anti-inflammatory effects. These cytokines are known for their anti-inflammatory properties and their ability to inhibit the production of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6.[21]

The equilibrium between pro-inflammatory and anti-inflammatory responses is pivotal in regulating the progression of the infection. Pro-inflammatory responses activate the immune system to defend against the invader, while anti-inflammatory responses prevent excessive inflammation, averting tissue damage and complications.[21] Anti-inflammatory cytokines not only inhibit pro-inflammatory responses but also modulate the expression of adhesion molecules and chemokines, which are vital for recruiting and activating immune cells at the infection site. By controlling their expression, anti-inflammatory cytokines can manage the influx of immune cells, influencing the outcome of the immune response.

In summary, the intricate interplay between pro-inflammatory and anti-inflammatory cytokines significantly influences the clinical course of *K. pneumoniae* infections. Maintaining a delicate equilibrium between these opposing forces is essential for mounting a strong immune response without causing additional tissue damage. Future research is needed to unravel the complex molecular mechanisms and regulatory pathways within this intricate cytokine landscape during *K. pneumoniae* infections.

## Impact of *K. pneumoniae* Infection on Human Metabolism and Research Progress

The complex network of metabolic pathways forms the basis of biological processes, orchestrating cellular functions and maintaining balance within the body. In this system, the metabolism of the host's immune system plays a vital role in overseeing the biochemical reactions of immune cells. These reactions encompass energy production, the creation of large molecules, and signal transduction—all crucial for normal immune cell function and effective responses to

infections. Unfortunately, this delicate balance is often disrupted during infections, especially those caused by bacteria like *K. pneumoniae*.

Understanding the relationship between *K. pneumoniae* and host immune metabolism is critical for deciphering the pathogenic mechanisms of this bacterium. *K. pneumoniae* can manipulate the host's metabolic processes, including glycolysis, citrate cycle, amino acid and fatty acid metabolism.[36] This allows it to avoid immune responses and thrive within the host. This chapter will delve into the significant impact of *K. pneumoniae* infection on human metabolism, focusing on the changes in enzymes it induces and the consequences of these alterations for disease progression. Insights from this exploration may guide potential therapeutic interventions.

## K. Pneumoniae and Glycolysis

Glycolysis, a fundamental metabolic pathway within host cells, is a common target for exploitation by pathogens like *K. pneumoniae* to ensure their survival and proliferation. This phenomenon becomes particularly evident during *K. pneumoniae*-induced bacteremia, where the pathogen triggers a notable increase in the host's glycolytic activity.[37] This induction of glycolysis serves a dual purpose: initially, it provides the energy required for the host's immune response to counteract the infection, as evidenced by a significant decrease in glucose levels and an increase in lactate and pyruvate in infected hosts. Subsequently, it provides the pathogen with vital nutrients and energy. The elevated urinary levels of tricarboxylic acid (TCA) cycle intermediates like 2-oxoglutarate and citrate, in infected rats suggest that this intensified glycolysis also accelerates the TCA cycle, further signifying the high energy demands imposed by the infection. Consequently, the host's glycolytic pathway plays a crucial role in both energizing the immune response and sustaining the pathogen, underscoring the intricate nature of host-pathogen interactions.[37] This complex relationship emphasizes the potential of targeting glycolysis in therapeutic strategies against *K. pneumoniae* infections.

The interaction between the bacterium and the host's glycolytic pathway can impact both the host's immune response and the pathogen's survival within the host. However, the specific mechanisms by which *K. pneumoniae* interacts with and influences glycolysis in the host cells are still under investigation. This suggests that the glycolytic pathway might contribute to providing the necessary energy for the host's defense mechanisms against the infection.

## K. Pneumoniae and Amino Acid Metabolism

Amino acids serve as pivotal elements in bacterial growth, functioning as essential building blocks for proteins and energy sources. *K. pneumoniae* intricately engages with the host's amino acid metabolism, exerting influence over immune responses and its own survival. Notably, *K. pneumoniae* has the capacity to modulate the degradation of specific amino acids, such as histidine.[38] This interplay bears significant implications for both the host's immune response dynamics and the pathogen's viability within the host environment.[39] However, The specific mechanisms underlying this interaction, particularly its impact on the overall outcome of *K. pneumoniae* infections, warrant further comprehensive investigation.

## K. Pneumoniae and Lipid Metabolism

*K. pneumoniae*'s interaction with the host's lipid metabolism, specifically its involvement with cholesterol in membrane-associated lipid rafts, has been well-documented.[40] This interaction exerts a profound influence on the host's immune response dynamics and significantly impacts the bacterium's survival.

A study investigating the role of cholesterol in the expression of *K. pneumoniae*'s capsular polysaccharide genes revealed its implications in resisting phagocytosis.[40] The data indicate that supplementing *K. pneumoniae* with exogenous cholesterol leads to an augmentation in macrophage-mediated phagocytosis. Furthermore, the study elucidated that cholesterol-mediated suppression of capsular gene expression is contingent on the global regulators RcsA and H-NS. Cholesterol also downregulates gene expression responsible for LPS core oligosaccharide production and OMP. These insightful findings highlight the pivotal role of cholesterol within the host, diminishing the anti-phagocytic capability of *K. pneumoniae*'s capsule. This, in turn, promotes the efficient engulfment of bacteria by macrophages during interactions between bacteria and eukaryotic cells facilitated by lipid rafts.

A recent investigation has shed light on the metabolic repercussions of *Klebsiella pneumoniae*-induced bacteremia, characterized by the presence of bacteria in the bloodstream. Beyond the well-documented stimulation of glycolysis and the tricarboxylic acid cycle, this study underscores an additional facet—enhanced oxidation of fatty acids,[37] a process vital for meeting the heightened energy demands of the host's response to infection. In the context of a *K. pneumoniae* infection, there is increased breakdown of fats, providing energy for the host's immune response. Intriguingly, the study suggests that a diet rich in glucose, fats, and choline might hold the potential to alleviate challenges associated with bacteremia. This implies that a nutritionally balanced diet might enhance the body's energy reserves during infection, potentially leading to better outcomes.

*K. pneumoniae* infections induce profound changes in human metabolism, reshaping enzyme activities, gene expressions, and cellular metabolic strategies. These alterations provide valuable insights into the pathogenic mechanisms of the bacterium, unveiling novel therapeutic targets for managing *K. pneumoniae* infections. In summary, infections induced by *K. pneumoniae* lead to extensive alterations in human metabolism, impacting enzyme activities, gene expression profiles, nutrient distributions, and overall cellular metabolic strategies. These changes shed light on the underlying mechanisms of the disease and hold promise for guiding future therapeutic strategies. Comprehensive research is required to unravel the complex interplay between *K. pneumoniae* infections and human metabolic pathways, with a particular focus on the potential for targeted metabolic interventions.

## The Imperative of Developing Novel Therapeutic Strategies for *K. pneumoniae* Infections

*K. pneumoniae* demonstrates a multitude of resistance mechanisms against a variety of antimicrobial agents, orchestrated by specific genes that confer resistance and provide the bacterium with robust defenses against medical interventions, especially antibiotic therapies. Extended-spectrum β-lactamase (ESBL)-associated genes, such as bla_SHV, bla_TEM, bla_CTX-M-1, and bla_OXA48, are commonly identified in *K. pneumoniae*, conferring resistance to β-lactam antibiotics, a class of antibiotics frequently used as the first line therapy against bacterial infections. Additionally, the presence of genes conferring resistance to quinolones (eg, aac(6)-Ib-cr, qnrB), aminoglycosides (aadB), and sulfonamides (sul1 and sul2) indicate a broad spectrum of antimicrobial resistance capabilities.[41]

In addition to resistance genes, *K. pneumoniae* isolates often harbor genes encoding various virulence factors, such as adhesins (fimH, mrkD), siderophores (entB, iucA, irp2, ybtS, fyuA, iroN), and capsule production (wcaG, rmpA). These virulence factors enhance the pathogenicity of the bacterium and contribute to its resilience against antimicrobial agents. The presence of these genes boosts the bacterium's ability to initiate an infection and strengthens its resistance to certain antimicrobial agents. Recent literature emphasizes the significance of these virulence genes, particularly in the context of hypervirulence exhibited by strains capable of causing severe infections across various environments.[5,42,43]

Transferable plasmids in *K. pneumoniae* play a crucial role in the spread of antimicrobial resistance genes, facilitating their transfer among different *K. pneumoniae* strains and even to other bacterial species, such as *Escherichia coli* (*E. coli*). The noteworthy feature of these plasmids, encompassing a substantial proportion of both antimicrobial resistance genes and virulence genes, underscores their significance in the pathogen's adaptability and persistence within clinical environments.[44]

*K. pneumoniae* employs adaptive resistance as another strategy, showcasing its capability to withstand antibiotics through modifications in outer membrane proteins, particularly porins like OmpK35 and OmpK36. Deficiency or alteration of these porins can lead to increased resistance to β-lactams, including carbapenems. Research has also unveiled the emergence of ceftazidime/avibactam resistance in clinical strains during antimicrobial treatment, attributed to specific mutations in the bla_KPC gene.[45]

One of the most alarming aspects of *K. pneumoniae* antimicrobial resistance is the existence of carbapenem resistance genes. These genes render one of the most potent classes of antibiotics ineffective, posing a significant threat in hospital settings where carbapenem-resistant *K. pneumoniae* (CRKP) can lead to severe and difficult-to-treat infections.[46]

In the realm of clinical management, ongoing research and development are imperative to address the mounting challenge posed by antibiotic-resistant bacteria. Given the dynamic nature of resistance patterns in *Klebsiella*

*pneumoniae*, sustained research efforts are urgently needed to innovate novel therapeutic agents and devise effective prevention strategies. A comprehensive understanding of resistance mechanisms, particularly the virulence factors and their genetic underpinnings, is crucial for formulating advanced treatment approaches to combat *K. pneumoniae* infections.

## Treatment Strategies for *K. pneumoniae* Infection

The rise of multidrug-resistant and highly virulent strains of *K. pneumoniae* poses a substantial challenge in effectively treating these infections. As antibiotic resistance in *K. pneumoniae* continues to escalate, it is crucial to comprehend the associated risk factors, implement preventive measures, and explore alternative therapeutic approaches to address these severe infections. This section will delve into four promising strategies for the treatment or prevention of *K. pneumoniae* infections, encompassing pharmaceutical intervention, immunological therapy, biological treatment, and vaccination.

### Application of EDTA and Its Salt

The formation of biofilms by *K. pneumoniae* on medical devices, such as catheters, significantly contributes to their pathogenesis and the development of antibiotic resistance.[47] In a study by Shein et al in 2021,[48] a novel combination of colistin and Ethylenediamine tetra-acetic acid (EDTA) was explored for eradicating colistin-resistant KP in catheter-related biofilm infections. This combination demonstrated potent synergistic activity against both planktonic and biofilm forms of KP, offering a promising therapeutic approach for such infections.

Another study by Shein et al in 2022,[49] the high prevalence of mgrB-mediated colistin resistance among carbapenem-resistant KP was addressed. The study underscored the effectiveness of the colistin-EDTA combination in overcoming this resistance, particularly in biofilm formation, suggesting a potential strategy for tackling resistant KP strains.

In a study by Wannigama et al in 2023,[50] the use of Calcium-EDTA (Ca-EDTA) in combination with either ceftazidime-avibactam or aztreonam was investigated. This study focused on restoring the activity of these antibiotics against carbapenemase-producing KP, highlighting the potential of Ca-EDTA as an adjuvant in antibiotic therapy. These collective findings indicate promising avenues for future research and potential treatments for *K. pneumoniae* infections.

### Antibody Therapy

Antibody therapy, a promising approach for treating multidrug-resistant *K. pneumoniae* infections, is currently under active research. This innovative method employs antibodies to specifically target the protective capsule polysaccharide of *K. pneumoniae*. Such targeted precision allows immune system cells, specifically neutrophils, to discern, assail, and ultimately eliminate the bacteria.[12]

Recent studies highlight the potential of monoclonal antibodies in treating diseases caused by *K. pneumoniae*. Monoclonal antibodies, meticulously crafted in laboratories, serve as synthetic counterparts that either mimic or augment the immune system's assault on this bacterial strain.[51] Engineered to bind to specific receptors on the bacterial cell surface, these antibodies impede the bacteria's ability to infect host cells.

However, the path toward effective antibody therapy encounters challenges, with bacterial resistance standing out prominently. Over time, bacteria like *K. pneumoniae* can develop resistance to treatments, including antibiotics and potentially antibody therapies. This resistance can diminish the effectiveness of treatments and complicate disease management.[52]

To overcome these challenges and fully realize the potential of antibody therapy for *K. pneumoniae* infections, further research is crucial. Scientists are actively investigating bacterial resistance mechanisms and developing strategies to address them. The objective extends beyond merely creating effective antibody therapies; it includes ensuring their sustained efficacy amid the continual evolution of bacterial resistance.[52]

Apart from these efforts, researchers are exploring other innovative strategies such as combination therapies, incorporating both antibiotics and antibodies to elicit a more robust response. Concurrently, there is active investigation into the development of vaccines against *K. pneumoniae*, aiming to offer long-term protection.

The future of antibody therapy for *K. pneumoniae* infections is promising but requires continued research and innovation. As our comprehension of this complex bacterium and its interactions with the immune system deepens, we move closer to the development of effective treatments capable of saving lives.

## Bacteriophage Therapy

Bacteriophage therapy, an alternative to traditional antibiotics for treating bacterial infections such as those caused by *K. pneumoniae*, has been gaining attention in the scientific community. This innovative approach uses bacteriophages, viruses that specifically target bacteria, to selectively eliminate harmful bacterial cells, emphasizing the potential of lytic phages, which induce bacterial cell lysis, in combatting pathogenic *K. pneumoniae* strains.[53]

Recent studies using mouse models have provided valuable in vivo evidence of the effectiveness of phage therapy against virulent *K. pneumoniae* infections. These studies underscore the potential of phage therapy as a viable alternative to antibiotics, especially against emerging antibiotic-resistant strains.[54,55] Moving from animal models to human clinical settings, notable progress has been achieved. For instance, the use of phage M1, isolated from sewage water, in combination with antibiotics, has shown promise in treating infections caused by pandrug-resistant *K. pneumoniae*. This approach has significantly reduced the incidence of bacterial phage resistance, demonstrating its potential effectiveness in clinical settings.[56] Additionally, research focusing on primary sclerosing cholangitis (PSC) patients highlighted the therapeutic potential of bacteriophage combinations in suppressing the growth of specific *K. pneumoniae* strains.[57] Additionally, a study investigating CRKP strains from COVID-19 patients with ventilator-associated pneumonia underscores the importance of developing targeted bacteriophage therapies for complex infections.[52]

While phage therapy shows considerable promise, it is not without its challenges, and one significant hurdle is the emergence of phage resistance in bacteria. As bacteria undergo evolutionary changes, they may develop mechanisms to resist bacteriophages, potentially diminishing the efficacy of this treatment. Current research is actively seeking ways to overcome this challenge and enhance the effectiveness of phage therapy. Successful application of phage therapy requires a comprehensive understanding of the diversity of both *K. pneumoniae* pathogens and phages. This involves characterizing different strains of *K. pneumoniae* and identifying suitable bacteriophages that can effectively target these strains.[53] Regulatory and manufacturing complexities also pose significant challenges. Given the high specificity of each bacteriophage to its host bacteria, the production and approval of a broad spectrum of bacteriophages for therapeutic use present considerable difficulties.

Despite these scientific obstacles, phage therapy holds significant promise as a potential treatment for bacterial infections, including those caused by *K. pneumoniae*. Continuous research and development in this field are crucial to overcoming these challenges, paving the way for more effective and reliable phage therapies in the future. As our understanding of this complex bacterium and its interaction with bacteriophages advances, we approach the development of treatments capable of saving lives. This is especially important in the context of multidrug-resistant infections, where current treatment options are limited. The promise of phage therapy underscores the importance of sustained research efforts in this field.

## Vaccination

Currently, there are no approved vaccines for *K. pneumoniae* infection, but active research is underway to develop effective vaccines.[58] Potential targets for vaccine development include capsular polysaccharides (K-antigen) and LPS (O-antigen) of *K. pneumoniae*.[58] Various strategies are being pursued, such as live attenuated vaccines based on genetically modified bacteria, inactivated whole cell vaccines, outer membrane vesicles containing numerous virulence factors, polysaccharide and LPS-based vaccines, protein-based vaccines, and conjugate vaccines including PS-protein or LPS-protein fusions.[59]

Significant progress was made with the initial reports of designing a *K. pneumoniae* K1 capsule polysaccharide (CPS) vaccine in 198,5[60] and subsequent reports of developing polyvalent *K. pneumoniae* CPS vaccines in 1986 (six-valent) and 1988 (24-valent).[60,61] However, despite these advancements, no vaccine has yet been approved for clinical use. The polysaccharide vaccine only induced T-cell-independent immunity, failing to generate immunological memory or high-affinity antibodies.[62] Nevertheless, a *K. pneumoniae* CPS-protein-conjugated vaccine could potentially offer improved

protection. It's worth noting that the depolymerization of CPS for protein conjugation, while necessary, may remove crucial CPS modifications (acetylation or pyruvation), potentially influencing the vaccine's efficacy.[63]

Recent advancements in vaccine development against drug-resistant *K. pneumoniae* include the utilization of innovative vesicle production technology. This approach focuses on creating biomimetic vesicles under high pressure and homogenization to develop a nano-vaccine targeting drug resistance.[59] Additionally, the use of phage depolymerases in the preparation of K1 and K2 CPS-conjugated vaccines ensures the preservation of CPS modifications, contributing to an effective immunogenic response.[64,65]

The recent adoption by the US Food and Drug Administration (FDA) of new pneumococcal conjugate vaccines (PCVs), namely PCV15 (Vaxneuvance) and PCV20 (Prevnar 20),[66] targeting *Streptococcus pneumoniae*, may offer valuable insights for potential application against *K. pneumoniae* in the future. Current research is exploring factors involved in biofilm formation as potential vaccine candidates against *K. pneumoniae*, with a focus on the anti-biofilm properties of induced antibodies.[67] An experimental formulation, incorporating key components of outer membrane proteins (AK36), has undergone testing in a mouse model of systemic infection.[67] Furthermore, the development of a maternal vaccine targeting *K. pneumoniae*, providing protection to newborns through transplacental antibody transfer, holds promise for reducing the burden of neonatal sepsis. However, the extent of sepsis reduction remains to be fully determined.[58] These findings suggest promising avenues for vaccine development against *K. pneumoniae*. Nevertheless, further research is crucial to thoroughly assess the potential effectiveness and safety of these vaccine candidates.

## Conclusion and Future Prospects

The intricate interplay between *K. pneumoniae* infection, the human immune system, and metabolism represents a rapidly evolving field, marked by significant advancements and substantial challenges. A deeper comprehension of the mechanisms by which *K. pneumoniae* interacts with immune defenses and alters metabolic pathways holds promise for guiding the development of more effective treatments. Investigating specific interactions of *K. pneumoniae* with the immune system and its impact on metabolic processes is a promising research direction. Advanced techniques such as transcriptomics, proteomics, and metabolomics could be instrumental in elucidating molecular changes during infection. Additionally, the development of accurate animal models and in vitro systems that mimic human infection could offer crucial insights into disease progression.

An imperative focus of current research involves the development of novel treatment strategies for *K. pneumoniae* infections. This encompasses the exploration of innovative immunotherapeutic approaches, including antibody therapy, vaccination, and phage therapy. The increasing prevalence of antibiotic-resistant strains highlights the urgent need for new antibiotics targeting *K. pneumoniae*. The identification of novel drug targets and the development of innovative drug delivery systems hold substantial promise for significantly enhancing treatment outcomes. While progress has been made in understanding *K. pneumoniae* infections, challenges remain in deciphering the complex interactions between immune responses, metabolism, and other physiological processes during infection. Addressing these challenges requires a multidisciplinary approach, integrating insights from immunology, microbiology, biochemistry, and related fields. Bridging the gap between fundamental research findings and their clinical application is crucial, necessitating close collaboration between researchers and clinicians to swiftly translate new discoveries into improved patient care.

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