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Review article

Recent trends to overcome *Klebsiella pneumoniae* infections in the intensive care units

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ABSTRACT

Background: *Klebsiella pneumoniae* (*K. pneumoniae*) is an opportunistic pathogen that frequently causes nosocomial infections and contributes to significant morbidity and mortality. Numerous factors are believed to be associated with the colonization of *K. pneumoniae* in hospital and community settings. *K. pneumoniae* frequently colonizes hospitalized individuals, leading to extraintestinal diseases like bloodstream infections (septicemia), urinary tract infections, and pneumonia. Patients in intensive care units (ICUs) are especially vulnerable to such infections. Infections with *K. pneumoniae* are particularly problematic in the healthcare setting for newborns, the elderly, and people with impaired immune systems. Due to the severity of the diseases, resistance to numerous antibiotics, and difficulty of treatment, *K. pneumoniae* has drawn the interest of researchers worldwide in recent years. *Klebsiella pneumoniae* is a significant global antibiotic resistance source and transmitter. The global rise in resistance highlights the need for novel therapeutic options. The choice of an appropriate antibiotic for hospital-acquired infections is becoming a rising global issue due to this resistance. In this review, we reveal that *K. pneumoniae* is a major threat to patients in intensive care units and we discuss the mechanisms of drug resistance in *K. pneumoniae*. We demonstrate the mechanisms and effects of emerging novel therapeutic strategies for *K. pneumoniae* in recent years to overcome drug resistance in the treatment of *K. pneumoniae* infections for a better future.

Introduction

Klebsiella pneumoniae is a Gram-negative, non-motile bacterium of the *Enterobacteriaceae* family [1]. For an extended period, *K. pneumoniae* has been linked to various diseases, including liver abscesses, respiratory tract infections, and urinary tract infections. This pathogen is a significant cause of nosocomial infections in Egypt. *Klebsiella pneumoniae* has developed various mechanisms for resistance to several antibiotics. Among these mechanisms, the efflux pump and enzymatic degradation systems appear to be crucial, at least in part, in the emergence of multidrug resistance in *K. pneumoniae* [2].

β-lactam antibiotic resistance is primarily indicated by the generation of β-lactamase enzymes due to the presence of β-lactam-insensitive cell wall transpeptidases or the active release of β-lactam molecules from Gram-negative bacteria. Carbapenems are the preferred β-lactams for treating diseases caused by bacteria that synthesize extended-spectrum beta-lactamases (ESBLs) [3].

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However, there is a significant evidence of increased bacterial resistance to carbapenems.

The severity of *K. pneumoniae* infections is influenced by several virulence factors, including siderophores, capsular polysaccharides, both types 1 and 3 fimbriae, and aggregative adhesion. Other factors expected to improve *K. pneumoniae's* pathogenicity include hemolysin, phospholipase synthesis, and biofilm development [4]. The production of biofilms by *Klebsiella* species has been documented for abiotic surfaces such as plastic, indwelling medical devices, catheters, and inside the body. The growth of biofilms increases (by 1000 times) in comparison to planktonic (free-living) cells, helping bacterial populations survive and stay in hospital surroundings and raising the risk of hospital-acquired infections [5]. Biofilm production can lead to resistance to antimicrobials, limiting therapy options.

Due to limited therapeutic choices, new approaches are needed to treat infections caused by this pathogen. It is encouraging development and research of novel antibiotics.

This review was performed to identify the dramatic increase in *K. pneumonia* as a nosocomial pathogen and highlights on certain variations between classical and non-classical subtypes, some epidemiological risk factors, and some virulent factors of this organism. This review also looked at some trends in the novel therapeutic approaches that target *K. pneumoniae*.

From commensal to pathogenic

Klebsiella pneumoniae is ubiquitous and has been isolated from several ecological niches, involving water, the soil, and sewage. It is a commensal in various hosts, including plants and mammals. In humans, it is recognized as an opportunistic pathogen. In the digestive and respiratory systems, commensal colonization is frequent; however, prevalence estimates differ according to age group, geographical location, and recent medical contact [6]. *Klebsiella pneumoniae* is a prevalent hospital-acquired pathogen that causes infections in the urinary tract, lungs, and blood. It has also been related to pyogenic liver abscesses (PLA), which can worsen with endophthalmitis, meningitis, necrotizing fasciitis, and prostatic abscess [7]. Most vulnerable patient groups are at risk, including the immunocompromised, the elderly, neonates, and those with implanted medical devices, where infections are thought to be caused by a lack of immune control and overgrowth of commensal *K. pneumoniae* strains [6]. Therefore, intestinal carriage is a significant risk factor for *K. pneumoniae* HAI, linked to a four-fold higher risk of infection in patients receiving cancer treatment and intensive care.

The classical strain and several subtypes of *Klebsiella pneumoniae*

There are two main subtypes of *Klebsiella pneumoniae*: classical *Klebsiella pneumoniae* (cKp) and non-classical *Klebsiella pneumoniae* (ncKp) [8]. Classical *K. pneumoniae* strains typically infect immunocompromised persons, such as those with diabetes or cancer, and induce severe infections like bacteremia, meningitis, or pneumonia [9]. Several clones of ncKp have been linked to difficult-to-treat and severe infections due to acquisition of transposons and plasmids containing virulent and resistant genes and continual mutation [8]. As a result, strains like hypermucoviscous *Klebsiella pneumoniae* (HMKP) and hypervirulent *Klebsiella pneumoniae* (hvKp) have emerged [8]. HV strains can cause pneumonia, lung abscesses, and other infections but are usually linked to pyogenic liver abscesses. Horizontal plasmid and transposon transfer has led to MDR and XDR subtypes **(Figure 1)** [8].

Epidemiological risk factors linked to infections and colonization by *K. pneumoniae*

Cases of *K. pneumoniae* infections vary by country [8]. According to reports, the colonization rate of Chinese people was 66.0%, compared to Malay people (14.3%), Indian people (7.9%), and other nationals (11.8%). Several sociodemographic variables, such as age, gender, hospitalization status, malnourishment, co-morbidity, and antibiotic abuse, are potential epidemiological risk factors linked to *K. pneumoniae* infections [8]. Primarily, the increased usage of antibiotics is linked to greater colonization rates.

Neonates, especially those who are premature or in the intensive care unit, are at risk because of undeveloped immunological defences, the quite high permeability of the mucosa in the GI tract, and a lack of established microbiota. *K. pneumoniae* mainly causes neonatal sepsis in some developing countries, and it is frequently the cause of sepsis in newborns. *K. pneumoniae* can enter patients through reused scopes, other medical tools, implanted medical devices, or other procedures [10]. Certain strains of *K. pneumoniae* are extremely adhere and sticky to medical equipment, mainly because of their fimbriae. These bacteria can build biofilms on medical devices, evading the immune system and contributing to the failure of antimicrobial therapy **(Figure 2)** [11].

Endotracheal intubation is a common method of catching pneumonia caused by *K. pneumoniae*, raising the chance of acquiring ventilator-associated pneumonia (VAP). This nosocomial pneumonia appears at least forty eight hours after intubation [12]. Another way of transmitting *K. pneumoniae* is by catheter insertion, which provides a substrate for *K. pneumoniae* to produce a biofilm and a point of entry into the urinary system.

Infections caused by *K. pneumoniae*

Generally, pneumonia or UTIs are the primary diseases resulting from classical *K. pneumoniae* strains [10]. *K. pneumoniae* HAPs are significantly more common than *K. pneumoniae* CAPs.

HAPs are defined differently depending on the articles. Still, HAP is commonly described as pneumonia that manifests at least forty eight hours after hospital admission in a person who did not have pneumonia symptoms before admission [10]. Bacterial HAPs are among the most prevalent types of nosocomial infections and the main reason for nosocomial infection-related death [13]. About 11.8% of HAPs are caused by *K. pneumoniae* [13]. Although community-acquired pneumonias (CAPs) are common, they are relatively severe infections that may spread quickly, resulting in hospitalization, stays in intensive care units (ICUs), and elevated mortality and morbidity rates.

Klebsiella pneumoniae is the second most prevalent species, causing urinary tract infections. Urinary tract infections (UTIs) typically begin as bladder infections, frequently progress to impact the kidneys, and can ultimately result in bacteremia, severe sepsis, renal failure, and even death. The most prominent hospital-acquired infections (HAIs) are catheter-associated urinary tract infections (CAUTIs). Indwelling urethral catheters are responsible for approximately eighty percent of UTIs that occur during hospital stays [14].

Mechanism of antibiotic resistance in *Klebsiella pneumoniae* that promotes virulence and weakens host defences

Klebsiella pneumoniae is thought to be a stealth pathogen that doesn't trigger innate immune responses [10]. But there's enough information today to show that *Klebsiella* also actively weakens host defences [1]. *Klebsiella pneumoniae*, like many other bacterial infections, has evolved defense mechanisms against the host's cationic antimicrobial peptides (CAMPs)**,** primary defences [1]. Interestingly, CAMPs and antibiotics like polymyxins and quinolones have the same initial target in Gram-negative bacteria's outer membrane.

Virulence factors

Currently, the four known virulent factors are lipopolysaccharide (LPS), pili, capsule, and iron carriers. To overcome the bactericidal effects of polymyxins and CAMPs, *K. pneumoniae* utilizes the versatility of the LPS and CPS [1]. Remodeling in lipid A leads to resistance to colistin and polymyxin B [15]. Indeed, most of the predominant strains of *K. pneumoniae* may have partially altered LPS, which prevents the host cell from recognizing the pathogen; other strains, on the other hand, may employ the capsule to conceal LPS to evade being recognized by toll-like receptor 4 (TLR4) [16]. These changes decrease clearance of microorganisms and limit the inflammatory response [17].

Like all Gram-negative bacteria, *Klebsiella* produces immunosuppressive lipopolysaccharide (LPS), a capsule that shields it from phagocytosis and other immune responses, and fimbriae that enable attachment to the host mucosal surface. RmpA is a plasmid-located virulence factor in *K. pneumoniae* that controls capsular polysaccharide formation [17]. RmpA-expressing strains were significantly associated with purulent tissue infections, including as liver abscesses, and the high mucus phenotype of hvKP.

Antimicrobial drugs resistance mechanisms

Possible resistance mechanisms of *K. pneumoniae* to several kinds of antimicrobial drugs include variations in membrane permeability, stimulation of efflux pump systems, production of enzymes that break down antimicrobials, modification of metabolic pathways, and modulation of antimicrobial target sites **(Figure 3)** [18].

Promoting of virulence factors

Certain *K. pneumoniae* sequence types classified as "high risk," like the STs11, 15, and 383 clones, exhibited drug resistance and virulence factors [17]. Many components of these strains are carried on a large virulent plasmid (e.g., ST147 with *bla*$_{NDM-1}$), which typically encodes heavy metal resistance genes (e.g., expressing the resistance for copper, silver, lead, and tellurite), capsule up-regulation genes (*rmp*A2 and *rmp*A), and iron vector genes (e.g., enterochelin, aerobactin, and salmochelin) [17]. It's concerning that this resistance and virulence combination is alarming.

Block of the transmission / prevention of transmission route

Direct patient contact or touching polluted hospital surfaces can contaminate the hands of healthcare personnel. Hand washing is regarded as the most important and useful precaution to stop the transmission of infections. Invasive operations and indwelling devices, such as endotracheal tubes and central venous catheters, should be minimized and avoided or utilized for the shortest time [19].

Old available therapeutic options

Colistin

Colistin, an antibiotic identified in 1949, belongs to polymyxins (polymyxin E) [20]. Colistin is commonly used to treat VAP, bacteremia, UTIs, and stomach infections caused by MDRKP and CRKP [21]. However, using colistin monotherapy to treat these infections has been linked to a detrimental effect, including the rise of colistin-resistant CRKP and the development of antibiotic resistance. As a result, colistin is frequently delivered in combination therapeutic protocols with aminoglycosides or tigecycline, triple combined regimens with carbapenems and tigecycline, aminoglycosides or fosfomycin, and quadruple treatment regimens [22]. While colistin is frequently used in clinical settings, it is imperative to note that it is not regarded as a first-line treatment for CRKP infections.

Tigecycline

One member of the glycylcyclines class is tigecycline, which is derived from minocycline [20]. Tigecycline is effective against many anaerobic, Gram-positive, and Gram-negative bacteria, including strains with clearly identified resistance mechanisms. Tigecycline inhibits the synthesis of proteins in bacteria. It has a bactericidal effect on CRKP isolates when paired with colistin [23].

Novel antimicrobial agents

In the past five years, the U.S. Food and Drug Administration have launched and approved several antimicrobials with varying degrees of effectiveness against MDR Gram-negative bacteria.

Plazomicin

Plazomicin is a new aminoglycoside resistant to the activities of all therapeutically significant aminoglycoside-modifying enzymes (AMEs), the main cause of aminoglycoside resistance [24]. Plazomicin is effective against multidrug-resistant *Enterobacteriaceae* and CRE, as well as Gram-positive and Gram-negative bacteria. From a clinical perspective, plazomicin—which is preferred over colistin due to its superior safety profile and efficacy—will likely replace colistin as the cornerstone of antimicrobial combination protocols against life-threatening *K. pneumoniae* infections, based on the early results from the current CARE study [25]. Unfortunately, because many isolates that produce New Delhi metallo-β-lactamases also produce 16S ribosomal RNA methyltransferase, plazomicin is inactive against them.

Eravacycline

Eravacycline is a new synthetic fluorocycline antibiotic, and has strong bactericidal efficacy against most antibiotic-resistant bacteria, according to multiple in vitro studies [26]. Eravacycline attaches directly to the bacterial ribosome to prevent the production of proteins in bacteria. Regarding eravacycline's ideal dispersion in the pulmonary surfactant and the lung, this antibiotic may one day be used to treat pneumonia that is difficult to cure and is acquired in a hospital [27]. However, CRKP has already started to show signs of eravacycline resistance because of over-expression of efflux pumps.

New methods for treating MDR *K. pneumoniae* in the future

Phage therapy

Much has been learned during the last thirty years about the ecological, genetic, structural, and functional characteristics of phages. As a result, phage therapy development has advanced gradually across a wide range of infections **(Table 1)** [31]. Recent improvements in genetic engineering and sequencing technologies have enabled the generation of phages with more predictable therapeutic effects [31]. By decorating phage capsid surfaces with cell-penetrating peptides, a process known as phage display, bacteria that are intracellularly living in mammalian cells can be killed. However, serious challenges must be handled before using the bacteriophage strategy against bacterial diseases, like the lack of ad hoc regulatory requirements, the possibility of rapid development of phage resistance, and the risk of patient immunological response to the introduced phages [32].

Monoclonal antibodies

Monoclonal antibodies can be utilized to prevent or treat sepsis Induced by *Klebsiella pneumoniae*, *Escherichia coli*, *Acinetobacter baumannii*, and other MDR Gram-negative bacteria, a reasonable target that is becoming more realistic [33]. The benefit of monoclonal antibodies is their ability to attach to extremely precise bacterial targets; also, their unique mode of action confers desirable characteristics [33]. Additionally, it has been demonstrated that certain MAbs enhance the antibacterial activity of antibiotics by acting in concert with them [34]. The majority of monoclonal antibody targets are composed of extracellular vesicle components, pilus formation proteins, capsular polysaccharide or exopolysaccharide, and bacterium proteins (i.e., lipopolysaccharide) [33]. The specificity of antibodies makes them a useful treatment [33]. Most monoclonal antibodies (MAbs) may attach to targets specific to the invasive bacteria instead of general bacterial targets [33]. Monoclonal antibodies targeting bacterial pili may provide a possible future method for treating urinary tract infections caused by *K. pneumoniae*, decreasing biofilm formation and bacterial adherence in the urinary tract [33]. These properties show the promise of using MAbs as a novel substitutes for traditional antibiotics once optimum pathogen targets are found [33].

Fecal microbiota transplantation (FMT)

Fecal microbiota transplantation (FMT) normalizes the nature and function of gut microbiota. FMT interacts with commensal bacteria, enhances colonization resistance, and restores gut microbes' diversity. There is increasing proof in the different domains where FMT is applied (from CDI and MDR decolonization to treating autoimmune and chronic bowel diseases, to cancer immunotherapy) [35].

Novel therapeutic approaches to combat *K. pneumoniae*

Antimicrobial nanoparticle technology

Antibiotic conjugated nanoparticles, metal oxide nanoparticles, silver nanoparticles, and photothermal conversion nanoparticles are common forms of antimicrobial nanoparticles. These nanoparticles bind with bacterial DNA or proteins, break down bacterial cell membranes, and indirectly start the formation of reactive oxygen species (ROS) to produce their antimicrobial effects [36]. Researchers investigated zinc ferrate nanoparticles' (ZnFeO NPs) antibiofilm and antibacterial efficacy against *K. pneumoniae*. The findings demonstrated that ZnFeO nanoparticles had remarkable anti-biofilm properties and demonstrated excellent antibacterial efficacy, causing bacterial destruction by (ROS) [37]. In general, antimicrobial nanoparticle technology exhibits promise in treating *K. pneumoniae* infections, providing novel therapeutic choices and encouraging pathways to overcome drugs resistance.

QS Inhibitors

The discovery of novel drugs that target bacterial activities, such as quorum sensing **(Figure 4)** and biofilm development, is the result of recent efforts to create alternative techniques to combat bacterial infections. QS Inhibitors exert antimicrobial effects by reducing signaling molecular communication between bacteria and regulating physiological functions, such as biofilm formation, pathogenicity, and bacterial metabolism [38]. For example, it has been found that a "quorum quenching" enzyme that deactivates AI-2 molecules prevents the development of *K. pneumoniae* biofilm.

Vaccines

Currently, research and development is going on for vaccines against *K. pneumoniae* infections. Strategies include whole cell vaccines, polysaccharides, lipopolysaccharides (LPS), ribosomes, outer membrane vesicles (OMVs), and protein vaccine formulations [39]. These strategies aim to successfully combat *K. pneumoniae* as a pathogen by inducing cell-mediated immune responses and antibodies [39].

Table 1. A concise summary of clinical and experimental trials on phage therapy with *K. pneumoniae* as a host.

Disease type	Object (n)	Disease	Type of study / location	Result	Reference
Urinary tract infection	Human (1)	Recurrent urinary tract infection	Case report / China	The phage cocktail com-bind with (Sulfamethoxazole –trimethoprim) Effectively treated the patient's urinary tract infection and prevented the occurrence of phage resistance mutants in vitro.	[28]
Urinary tract infection	Human (1)	Chronic urinary tract infection after post-transplant	Case report / Netherlands	Meropenem and phages were effective in treating the infection, which ultimately developed into epididymitis.	[29]
Respiratory infection	Swiss Webster mice (20)	Pneumonia	Animal experiment / China	Comparing the lungs of the phage-treated mice to those of the untreated control, the former showed a reduced load of *Klebsiella pneumoniae.*	[30]

Figure 1. Essential mechanisms for transfer of mobile genetic elements.

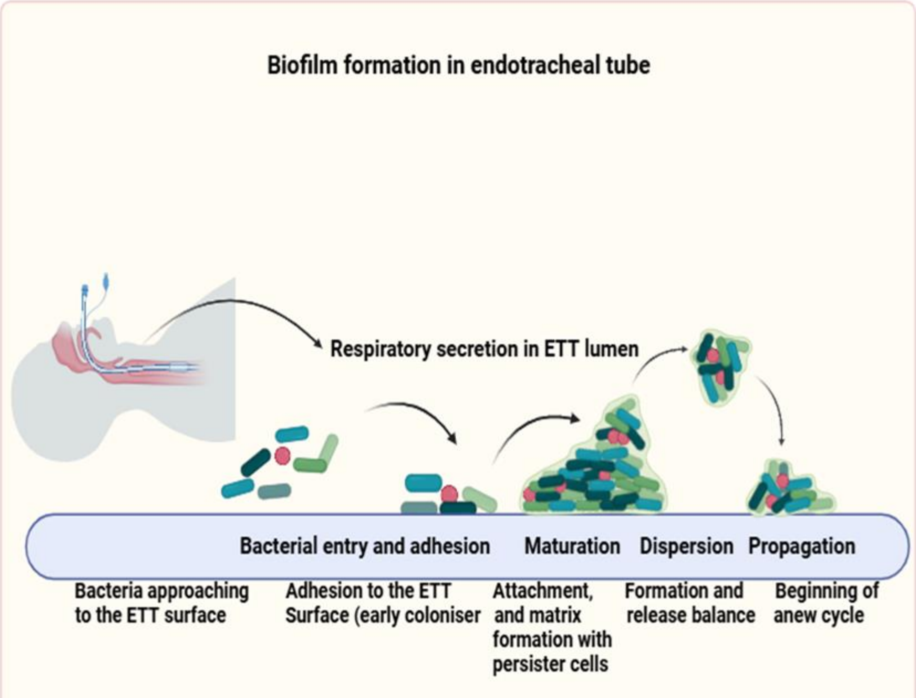


Figure 2. Life-cycle of biofilm formation in the endotracheal tube (ETT) lumen.

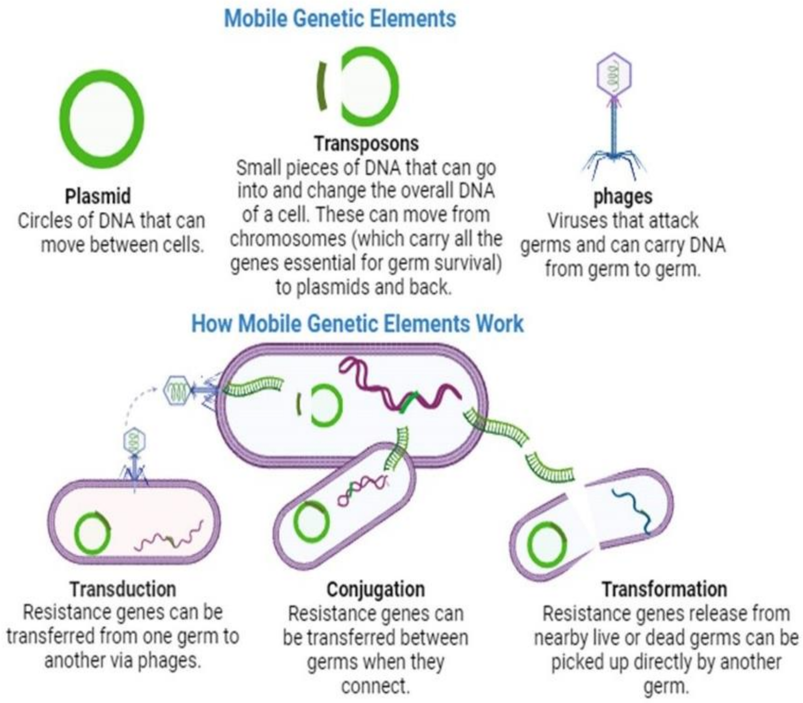


Figure 3. Different mechanisms conferring antibiotic resistance to *K. pneumoniae*.

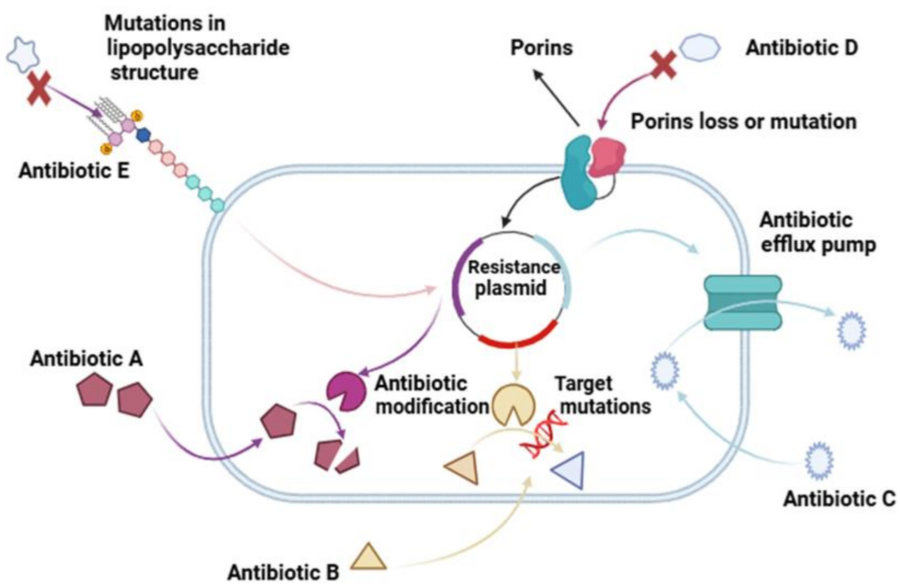
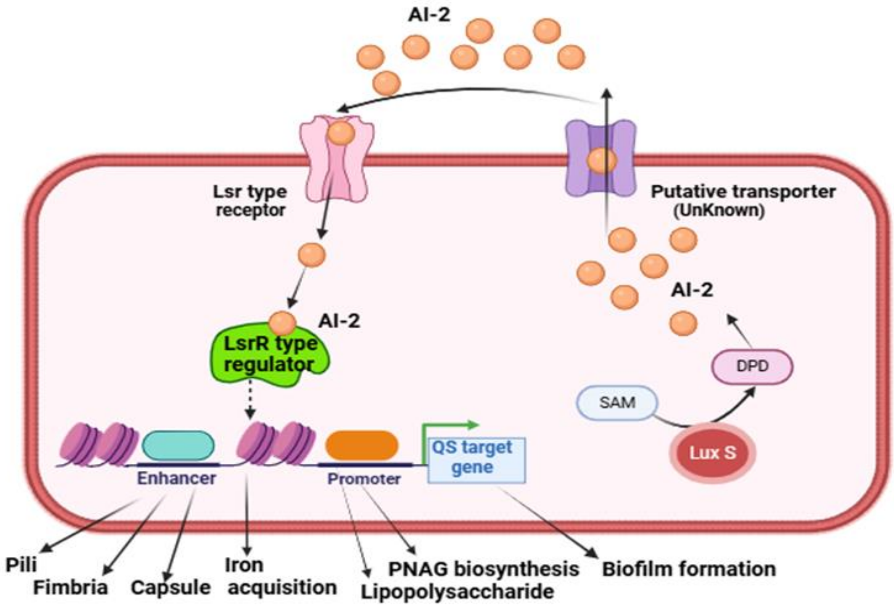


Figure 4. Quorum sensing signaling in *K. pneumoniae*.



Conclusions

Worldwide, multidrug-resistant (MDR) strains of *K. pneumoniae* are a major contributor to several infections that require life-saving treatments. MRKP outbreaks most commonly begin in ICUs. So, to eradicate this this bacteria from Critical Care Units, we should follow antibiotic guidelines and policies to prevent such outbreaks in the future. In addition to that, infection control measures need to involve untraditional plans arranged by domestic health officials in the medical fields. In light of sermons old is gold and the new is innovation, novel therapeutic alternatives needed to represent a promising future approach to fight *K. pneumoniae*. Meanwhile concerted efforts between infection control and environmental sanitation are other players to combat the same problem.

Competing interests

None.

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None.

Data availability

All data generated or analyzed during this study are included in this puplished article.

Authors' contribution

All authors made significant contributions to the work presented, including study design, data collection, analysis, and interpretation. They also contributed to the article's writing, revising, or critical evaluation, gave final approval for the version to be published.

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