Artykuł przeglądowy *Review*

Cross-transmission of *Klebsiella pneumoniae* across ecological niches, potential hazards and prevention and control strategies*

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Received 19.05.2026 *Accepted 30.07.2026*

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Summary

The increasing antibiotic resistance of *Klebsiella pneumoniae* (KP) has become a global public health issue. This bacterium is an opportunistic zoonotic pathogen capable of causing various infectious diseases. It primarily infects the respiratory, digestive, and urinary tracts, as well as wounds or soft tissues, in both animals and humans, leading to conditions such as pneumonia, urinary tract infections, sepsis, and liver abscesses. This review focuses on the hazards of KP in human, animal, food and environmental transmission, as well as the relationships between these factors. It also briefly describes strategies for the prevention and control of KP. This review aims to enhance awareness of the risks associated with KP, provide a theoretical basis for source control and public health risk early warning, and is of significant importance for safeguarding human and animal health, environmental hygiene, and food safety.

Keywords: *Klebsiella pneumoniae*, hazard, treatment, prevention and Ccontrol strategy, cross-transmission

Klebsiella pneumoniae (KP) is an opportunistic zoonotic pathogen belonging to the genus *Klebsiella* within the family Enterobacteriaceae. In 1882, KP was first described as a bacterium by Carl Friedlander, who isolated it from the lungs of patients who had died of pneumonia. Therefore, it was initially called Friedlander's bacteria (9). It is commonly found in the environment (such as water, sewage, soil and the surfaces of plants), the respiratory tracts, intestines, urinary tracts, skin and other tissues of humans and animals, as well as food and other places (35). Pathogenic KP can be classified into classical *Klebsiella pneumoniae* (cKP) and highly virulent *Klebsiella pneumoniae* (hvKP) (15, 69). They can cause various diseases in humans and animals when the body is weakened, the immune system is compromised, or there is prolonged use of antimicrobial drugs. They can lead to infections in common sites, such as respiratory tract infections, urinary tract infections and sepsis, etc. They can also cause pulmonary and extrapulmonary infections, leading to KP pneumonia, abdominal infections, and urinary tract infections, etc. In severe cases, they can result in sepsis and shock (34, 39).

The pathogenic factors of KP mainly include capsular polysaccharide (CPS), lipopolysaccharide (LPS), iron carrier and outer membrane protein, among which capsular polysaccharide is the core structure mediating its pathogenic process. Currently, at least 78 serotypes of the capsular polysaccharide of this bacterium have been discovered, with K1, K2 types showing the stron-

* This work was supported by the Expert Workstation of Yunnan (202505AF350101), the Talent Plans for Young Topnotch Talents of Yunnan (YNWR-QNBJ-2020-154), Mengla Field Scientific Observation and Research Station for Major Animal Disease Prevention and Control in Yunnan Province (202505AM340007) and Yunnan Key Laboratory of Veterinary Etiological Biology (202449CE340019). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

gest correlation with hvKP. Hypermucoviscosity is the most classic and readily detectable phenotype of hvKP. Domestic clinical data show that among the highly viscous isolates that cause invasive infections such as suppurative liver abscesses, the K2 serotype accounts for 42.9%, and the K1 type accounts for 23.8% (16). In Singapore and the Taiwan region of China, a total of 73 pathogen strains were tested, K1 was detected in 34 strains (46.6%), followed by K2 with 15 strains (20.5%) (67). Among KP strains recovered from hospitalized patients in Poland, the K1 capsular serotype was identified in 19.2% of isolates, while 22.9% belonged to the K2 serotype (24). The sequence type (ST) is the core typing unit in the bacterial multilocus sequence typing (MLST) system, it is used to precisely define the clonal lineages and genetic relationships of bacterial strains at the species level. Globally recognized core hypervirulent clones comprise ST23, ST86, ST65 and ST375. Of these, ST23 is the predominant epidemic lineage of liver abscess-associated hypervirulent strains. Harboring the pLVPK virulence plasmid, ST23 isolates exhibit high invasiveness, are capable of causing community-acquired invasive infections in otherwise healthy individuals, and are associated with an elevated risk of distant metastasis (51). The ST23 clone is strongly associated with the K1 capsular serotype: 85.1% of 47 K1 serotype isolates are assigned to ST23 (53). Studies conducted in China have demonstrated that 57.8% of isolates recovered from liver abscess patients belong to ST23, and 96.2% of ST23 strains correspond to the K1 serotype (42). In South Korea, the ST23 strain accounted for 97.3% of the hvKP strains of the K1 serotype that were collected from patients with acquired hepatic abscesses in the population (8). In contrast, hypervirulent K2 serotype strains exhibit a more diverse genetic background. K2 isolates from three regions in Asia encompass 8 sequence types including ST65 and ST86, which fall into two major clonal groups: ST65-like (42%) and ST86-like (46%) (30). Relevant clinical cases have also been documented in Europe. In France, a patient of Algerian origin was found to have a hvKP strain that produces extended-spectrum β-lactamase (ESBL). This strain is a ST86 clone carrying the K2 serotype (55).

Currently, KP is receiving widespread attention worldwide, mainly due to the escalating issue of antimicrobial resistance (AMR) which has become a major challenge in global health, affecting the health and safety of both humans and animals. The improper and excessive use of antibiotics in medical institutions and the livestock industry is a significant factor contributing to the global spread of AMR, and it has also led to a decreasing effectiveness of antibiotic treatment for diseases. In summary, the inappropriate use of antibiotics poses serious risks to humans, animals, and the environment, damaging human health, affecting the development of the livestock industry, and damaging the natural environment. This review focuses on providing a detailed description of the hazards posed by KP in humans, animals, food, and the environment, providing a detailed description for subsequent research and prevention of KP and serving as a reference for future studies.

The hazards of *Klebsiella pneumoniae* in multiple ecological niches

The hazards of *Klebsiella pneumoniae* to humans. KP is commonly found in the human gastrointestinal tract. As one of the most common pathogenic bacteria causing nosocomial and community-acquired infections, it has strong pathogenicity and widespread antibiotic resistance (26). In recent years, the prevalence of highly virulent KP and multidrug-resistant (MDR) strains has further exacerbated the threat posed by KP to human public health. The harmful effects of highly virulent KP have gone beyond the perception that it only infects immunocompromised individuals, and can also infect healthy individuals, Characterized by rapid metastasis and dissemination, it induces a variety of invasive infections and can affect virtually any part of the body, leading to a range of syndromes, including endophthalmitis, meningitis, C-type brain abscess, necrotizing fasciitis, splenic abscess, and epidural abscess. KP also causes certain infectious diseases, including liver abscesses, pneumonia, and sepsis, etc. The mortality rate and infection rate have significantly increased (13, 46). Among Asian populations, approximately 10% of those colonized with KP carry the highly virulent strain hvKP (31).

Among liver abscesses caused by KP, the K1 and K2 capsular types exhibit the highest virulence; K1 is the predominant serotype in Asian strains, and in Taiwan, K1 accounts for 63.4% of the causative pathogens in liver abscesses, while K2 accounts for 14.2% (12). Liver abscesses are difficult to be treated with antibiotics, so they are prone to spread, causing serious harm, leading to blindness and death. The mortality rate of liver abscesses ranges from 5% to 40% (2). In Germany, relevant studies have shown that KP is a major cause of liver abscesses and fatal pneumonia. Through CT imaging, pneumonia and liver abscesses were observed, and the patient died three days after hospitalization and initiation of treatment. The experiment proved that this was a fatal case of pneumonia caused by highly pathogenic KP ST23 (14).

Studies have shown that KP accounts for 5% to 20% of cases of Gram-negative sepsis, with a mortality rate ranging from 27.4% to 37% (33). In the United States, KP is a major and common pathogen causing hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP); it is also a common cause of community-acquired pneumonia (CAP) in Asia. Surveillance data from eight Asian regions indicate that KP accounts for 15.4% of CAP cases, ranking as the second largest cause of CAP after *Streptococcus pneumoniae* (29.2%) (23, 54).

Data on KP strains isolated from inpatients of a certain tertiary hospital in China from 2016 to 2024 were analyzed. After eliminating duplicate strains, a total of 5,607 strains were included in the study. It was found that KP still showed a relatively high level of resistance in high-risk departments such as the ICU, respiratory medicine department, and neurosurgery department (62). Li et al. established a model in mice by inoculating them with KP to investigate whether KP is a pathogenic factor for the development of hypertension. The results showed that the enrichment of KP directly promoted an increase in blood pressure and the onset of hypertension (27).

The hazards of *Klebsiella pneumoniae* to animals. In recent years, cases of KP infection have been reported in various poultry, livestock and wild animals have been reported both domestically and internationally. The incidence and mortality rates are relatively high, and the hazards of KP to animals cannot be underestimated. KP can cause respiratory diseases and diarrhea in pigs, posing a significant threat to the health of pig herds. From 2013 to 2020, autopsy of pigs from 15 different farms yielded 61 KP strains, which were sequenced to determine that sequence type (ST) 25 was the predominant *Klebsiella* species associated with sepsis in the pig population (accounting for 67%, 10/15 farms) (37). In 2024, a pig farm in Xinjiang, China, isolated a strain of KP from piglets that had died from PRRSV infection. This strain exhibited resistance to multiple antibiotics and was highly pathogenic to BALB/c mice, with a 100% mortality rate at a challenge concentration of 7.0×10^8 CFU/mL (6). In 2024, Gram-positive, short, rod-shaped bacteria were isolated from the mesenteric lymph nodes of newborn piglets that had died from severe diarrhea at a pig farm in Hunan, China. The bacteria were identified as KP through 16S rRNA sequencing and mass spectrometry (66). Wang et al. collected 763 milk samples from dairy farms in provinces such as Jiangsu, Anhui, Hebei, Fujian, Guangdong, Shanxi and Zhejiang in China, and isolated 108 strains of KP. These KP strains exhibited MDR, and some of them showed high toxicity (61). Saddam et al. screened 700 milk samples from symptomatic cows with mastitis at dairy farms in the Peshawar district of Pakistan for MDR KP. The detection rate of KP in these samples was 180/700 (25.7%), while the detection rate of MDR KP was 80/180 (44.4%) (48). Timofte D et al. conducted a test on 17 breast milk samples from dairy cows suffering from mastitis at a dairy farm in northwest England in 2010. Eventually, two strains of *Escherichia coli* and three strains of KP subsp. *pneumoniae* with ESBLs were isolated (58). Wang et al. conducted pathogen isolation and culture, 16S rRNA sequencing, virulence gene testing, antimicrobial susceptibility testing, and pathogenicity assays on aborted fetuses from a fox breeding farm in Hebei Province, China. The KP strain isolated in this study exhibited certain pathogenicity and antimicrobial resistance, and carried multiple virulence genes; it may be one of the factors contributing to fetal abortion and mortality in foxes (63). Shen et al. used zebrafish as the model organism and infected zebrafish larvae with two strains of KP of different virulence to observe their mobility. They found that the highly virulent strain of KP significantly reduced the behavioral ability of the zebrafish larvae, whereas the low-virulence strain had a lesser effect (50). KP can also cause other diseases in livestock and poultry, such as respiratory diseases in cattle and sheep, uterine inflammation in horses, septicemia in pigs, and suppurative inflammation in rabbits, etc., causing losses to the livestock industry. This bacterium can also infect wild animals such as giant pandas, sea lions.

The hazards of *Klebsiella pneumoniae* in food. In 1998, KP was officially recognized as a type of intestinal invasive food borne pathogen, originating from contaminated hamburgers (47). KP is an important microorganism causing food borne infections. It is widely present in food processing stages, including raw material contamination, food processing, and food packaging, and can invade various foods through these pathways. Not only does this compromise food quality and safety, but also transmits the toxicity and antibiotic resistance of KP through food borne foods to humans and animals, causing food poisoning and the spread of antibiotic-resistant genes, posing threats to food safety and public health.

Current studies have found that KP infections can be detected in milk, fresh meat, vegetables, shrimp, and fruits. Wu et al. reported detection rates ranging from 16.51% to 33.73% in milk samples from five dairy farms in Hubei Province, China, and multiple highly virulent strains were also isolated from milk samples associated with mastitis (64). Ma et al. conducted a study and isolated a K2-type highly virulent *Pasteurella multocida* strain from milk samples. Subsequently, researchers isolated multiple strains of K1, K2, K3, K5, K54, and K57 types from milk samples of cows with mastitis. These strains all exhibited strong pathogenicity in mouse infection tests. The *Pasteurella multocida* strains from dairy cows' mastitis, as food borne pathogenic bacteria, pose a risk of zoonotic transmission (32). The detection rate of *Klebsiella pneumoniae* species complex (KPSC) were observed in chicken and salad samples from five European countries. The KPSC was screened using traditional culture method and zur-khe intergenic region (ZKIR) fluorescence quantitative PCR method. The detection rates of the two methods in chicken were 60% and 52% respectively, while in salad they were 30% and 21% respectively (43). In Greece, the detection rate of this bacterium reached as high as 81.8% in 110 meat product samples; most of the strains carried both drug resistance genes and virulence genes, with the detection rate of New Delhi metallo-β-lactamase-

like (blaNDM-like) genes reaching 61.5%, posing a significant threat to human health (57). Sixty-seven MDR KP strains were isolated from shrimp samples imported from Thailand (38). KP has been detected in raw vegetables, fruits, meat, and dairy products sold in the Indian market (49).

The hazards of *Klebsiella pneumoniae* in the environment. KP can survive for a long time in natural environments such as water, sewage, soil and air, and its survival is closely related to environmental temperature and humidity. The direct discharge of untreated medical wastewater, domestic sewage, and livestock and poultry waste can lead to persistent contamination of water bodies such as rivers, lakes, and groundwater, resulting in a continuous increase in the abundance, antibiotic resistance, and virulence of KP, which poses a serious threat to environmental health and public health. Jelić M. et al. were the first to report the detection of carbapenemase production by KP in the water of the Croatian River. KP can survive in river water for up to 50 days, confirming its ability to survive and spread in the environment (21). Campana et al. reported the discovery of KP strains capable of producing New Delhi metallo-β-lactamase (NDM) on a recreational beach (4). Wu et al. collected a total of 887 samples from 5 dairy farms in Hubei Province, China from 2019 to 2020. The samples were sourced from healthy cows, cows with mastitis, as well as bedding materials, feed, feces, air, drinking water, spray water, cleaning water, and milk cup swabs. The samples were identified through PCR of the *khe* gene and 16S rDNA sequencing. The isolation rate of environmental samples (such as nipple cups, bedding materials, feces, etc.) ranged from 15.79% to 47.83%, revealing the environmental transmission and drug resistance/toxicity characteristics (64). Montenegro et al. investigated the prevalence of carbapenem-resistant *Klebsiella pneumoniae* (CRKP) in hospitals and municipal wastewater treatment plants (WWTPs) in Brazil and found that 83.3% exhibited carbapenemase activity (36). From 2014 to 2020, the China Antimicrobial Resistance Surveillance System (CARSS) collected AMR data from 31 provinces. The statistics revealed that for every 1°C increase in the annual average temperature, the detection rate of third-generation cephalosporin-resistant *Klebsiella pneumoniae* (3GCRKP) increased by 4.7%, and the detection rate of CRKP increased by 10.7%. This indicates a positive correlation between ambient temperature and AMR in KP (70). Barnes NM et al. suspended KP in synthetic saliva, placed it in a nebulizer, and after 5 minutes of nebulization, introduced it into an aerosol chamber, where it remained for an additional 15 minutes during the aerosolization phase. This was conducted under four different conditions: 20°C, 50% relative humidity; 20°C, 80% relative humidity; 30°C, 50% relative humidity; and 30°C, 80% relative humidity. Samples were collected for viability analysis and comparative transcriptomic analysis. It was found that higher humidity and lower temperature were conducive to the airborne survival of KP (3).

Cross-transmission chain of *Klebsiella pneumoniae* between humans, animals, food and the environment. Under the concept of "One World, One Health," the health of humans, animals, and the environment is inextricably linked, and KP is a zoonotic pathogen. As a colonizing bacteria in humans, animals, and the environment, KP infection poses a significant threat to global health. It is necessary to implement the „One Health" strategy, acknowledging the interconnections among human health, animal health and environmental factors (56). This strain can carry the acquired AMR genes and plasmids and move between the ecological niches of the environment, human and animal hosts. The environment is the natural reservoir for bacteria. There are numerous bacteria in soil, water sources and surfaces of public facilities, which can serve as vectors for the spread of bacteria. The strain can invade human and animal hosts from the environment through contact, drinking contaminated water sources or consuming contaminated plant-based foods; it can also be transmitted between humans and animal hosts through contact and consumption of contaminated food; and it can also flow back to the environment from hosts through sewage and sewer discharges (Fig. 1) (65). Similarly, animals serve as important hosts for

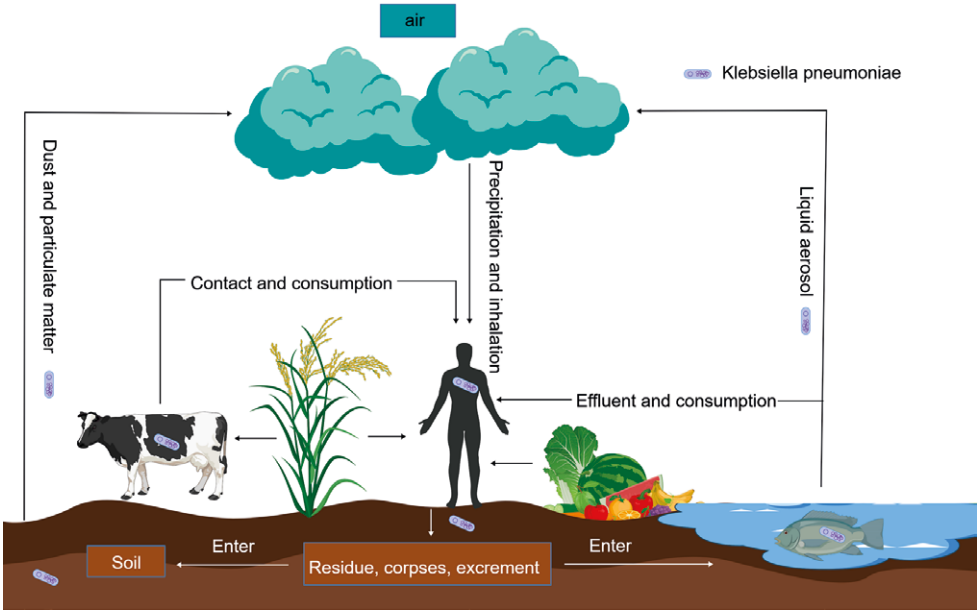

Fig. 1. The relationship of *Klebsiella pneumoniae* in terms of its transmission among humans, animals, food and the environment (Created with BioGDP.com (22))

bacteria; they can contaminate the surrounding environment through feces, fur, respiratory secretions, and wound exudates, and can also transmit bacteria to food during slaughter and processing. Humans can become infected through contact with contaminated animals, consumption of contaminated food, and exposure to contaminated environments, thereby threatening human health; meanwhile, human and animal excreta and secretions continuously release pathogens into the environment.

Consequently, humans, animals, food, and the environment act as sources of infection and transmission routes, creating a vicious cycle. Whole-genome analyses have shown that, in a longitudinal study of KP isolates collected simultaneously from urinary tract infections and retail meat (chicken, turkey, and pork), human and food borne isolates are phylogenetically closely related (11, 18). There is phylogenetic overlap between isolates from Thai hospitals and those from nearby waterways. Both clinical and environmental isolates exhibit closely related lineages (45). Certain populations, including those considered as global hospital pathogens, have demonstrated the ability to transition between different habitats and to reproduce in multiple environments, facilitating genetic interactions with various bacterial species (65). Only by blocking the transmission in each link, doing a good job in environmental disinfection, food safety management, animal epidemic prevention and control, and personal hygiene protection, can this cycle be broken and the public health safety risks be reduced.

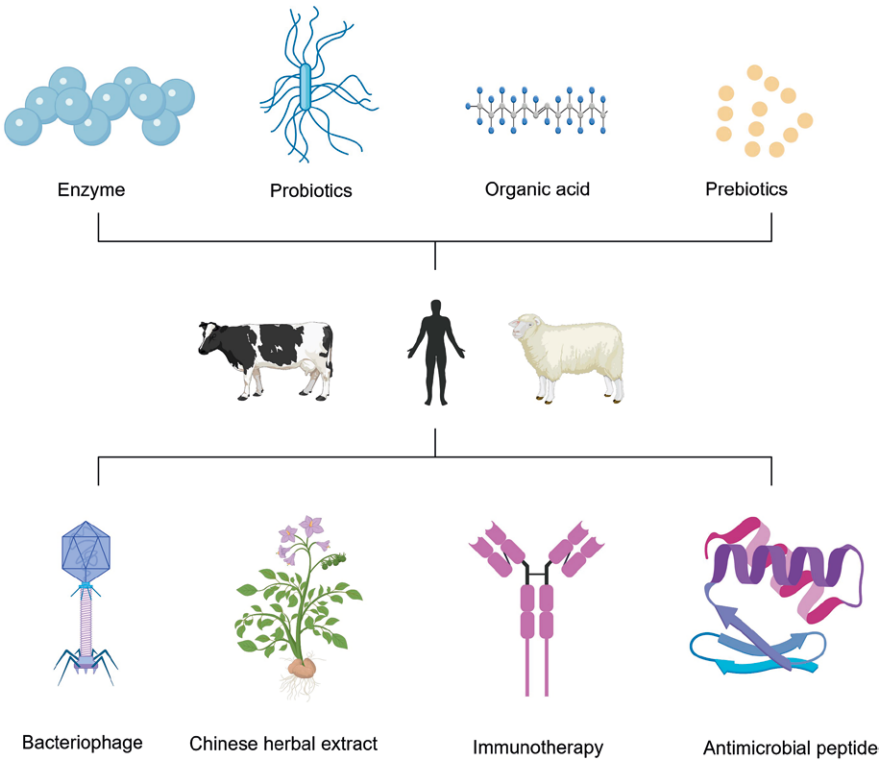

Fig. 2. Alternative antibacterial agents against *Klebsiella pneumoniae* (Created with BioGDP.com (22))

Prevention and control strategies for *Klebsiella pneumoniae*

Treatment of *Klebsiella pneumoniae*. Currently, the commonly used treatment drugs for KP are still antibiotics. However, due to the inappropriate use and abuse of antibiotics, the resistance of KP has increased, making it difficult to treat in clinical settings. It is an urgent matter to find alternatives to antibiotics and anti-resistance drugs. Common antibiotic substitutes include bacteriophages therapy, herbal extracts, antimicrobial peptides and immunotherapy, etc (Fig. 2) (10, 29). Bacteriophages are the natural enemies of pathogenic bacteria and are widely present in nature (52). Le Bris et al. utilized bacteriophages that targeted the surface receptors of KP, invaded the bacterial cells and bound to them, then released their genetic material, inducing the lysis of bacterial cells and releasing new bacteriophage particles. This process can effectively reduce the bacterial population, inhibit the growth and reproduction of bacteria (25). Rouse et al. used bacteriophage to treat a mouse model infected with the bioluminescent strain *AB5075 attTn7*, which reduced the expression levels of pro-inflammatory factors and restored the pneumonia in the mice (44). Hassan et al. evaluated the efficacy of ciprofloxacin and *Artemisia judaica* extract in treating pneumonia in rats infected with KP. The results showed that administration of these agents improved pathological damage, reduced levels of pro-inflammatory factors, and increased levels of anti-inflammatory factors (17). Paula-Ramos et al. evaluated the effects of extracts from *Pfaffia paniculata* K., *Juglans regia* L., and *Rosmarinus officinalis* L. on the planktonic form and biofilm of KP. The results showed that all the extracts had antimicrobial effects on the planktonic form of KP, but only *P. paniculata* K. and *R. officinalis* L. were effective against the biofilm (41). Li et al. investigated the mechanism of antibacterial activity of the antibacterial peptide Cecropin-4 (Cec4) against CRKP in both *in vitro* and *in vivo* studies and found that Cec4 exhibits rapid antibacterial activity even at low concentrations, with even better results when used in combination with antibiotics (28). Pan et al. discovered that the sea snake antimicrobial peptide Hydrostatin-AMP3 exhibited highly effective antibacterial activity against MDR KP strains. Moreover, Hydrostatin-AMP3 exerted its bactericidal effect through a unique dual mechanism, namely the disruption of the bacterial membrane and the targeting of DNA (40). Abhinand et al. reviewed the role of KP in host-directed therapy

(HDTs), including epigenetic and immunomodulatory interventions, which can replace antibiotic drugs (1). Iwanaga et al. used recombinant IL-22 for immunotherapy, which could improve the mouse lung infection model caused by KP. The study regarded host-directed immunotherapy as an adjunctive treatment method for new antibiotics (20).

Prevention and control measures for *Klebsiella pneumoniae*. KP is widely present in the natural environment and is prone to outbreaks in healthcare settings; therefore, we must implement effective prevention and control measures to reduce infections. The primary objectives of infection prevention and control measures are to control the source of infection, interrupt the routes of transmission, and protect susceptible humans and animals. In human transmission, medical staff should prioritize avoiding unnecessary invasive devices such as indwelling urinary catheters or intravenous infusion tubes. They should maintain strict hand hygiene practices, enhance barrier measures, and implement isolation protocols for patients who are settled or infected with carbapenemase-producing organisms. To address the main issues related to the cleaning of medical equipment and environmental colonization, it is necessary to conduct early rectal screening upon admission, implement strict environmental cleaning procedures, mark cases and trace contacts, and actively monitor KP carriers to effectively prevent the spread and outbreak of KP (5, 71). Similarly, in animal transmission, disinfect equipment used by animals and their housing environments, isolate the animals that are infected with KP, and carry out mosquito and rodent control measures. Finally, protect susceptible populations and animals. For humans, this involves strengthening physical health, treating underlying medical conditions, using antibiotics appropriately, and preventing nosocomial infections. For animals, it involves improving nutrition, enhancing living conditions, reducing stocking density, implementing scientific vaccination protocols and appropriate medication use, and boosting animal immunity. In addition, to ensure the long-term effectiveness of medications, efforts to strengthen the management of antimicrobial drugs should be intensified (59).

Conclusions and prospects

KP poses serious threats to humans, animals, food, and the environment, which can form a closed loop through various links, leading to increased transmissibility of KP. Therefore, treatment and preventive measures for KP are essential. However, treatment options for KP remain limited. When MDR and highly virulent KP coexist, there is no specific drug available for treatment; the case-fatality rate is far higher than that of ordinary drug-resistant strains, and it is prone to causing cross-infection with drug resistance, further complicating treatment (7, 68). Methods such as bacteriophages therapy, herbal extracts, antimicrobial peptides, and immunotherapy have shown potential in clinical applications but have not yet been widely adopted or applied in the market (10). For infections caused by MDR and highly virulent KP, future research could focus on developing novel dual-target drugs that combat both drug resistance and virulence. Concurrently, non-antibiotic therapies such as bacteriophages therapy, herbal extracts, and antimicrobial peptides should be promoted to reduce antibiotic resistance pressure. A zoonotic surveillance system should be established, and the use of antibiotics in animal husbandry should be strictly regulated to prevent the cross-host transmission of bacterial strains. The administration plan to increase the therapeutic effect after infection should be optimized. This will provide a reference for the treatment and prevention measures of KP in the future.

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