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Review article

From Shadow to Threat: Uncovering *Klebsiella oxytoca*'s Power

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ABSTRACT:
Klebsiella oxytoca, a gram-negative bacillus of the Enterobacteriaceae family, is an opportunistic pathogen increasingly implicated in a spectrum of human diseases, ranging from urinary tract infections to life-threatening sepsis. While historically overshadowed by *Klebsiella pneumoniae*, its clinical significance has grown due to its association with nosocomial infections and antibiotic-associated hemorrhagic colitis (AAHC). This review synthesizes current knowledge on the pathogenicity, virulence factors, and clinical manifestations of *K. oxytoca*, emphasizing its role as an emerging multidrug-resistant (MDR) pathogen. The bacterium's polysaccharide capsule, cytotoxin production (e.g., tilivalline and tilimycin), and siderophores contribute to its virulence, enabling it to evade host defenses and cause tissue damage. Clinically, *K. oxytoca* is linked to infections in immunocompromised patients, neonates, and those exposed to invasive medical procedures, with resistance to β-lactams, carbapenems, and other antibiotics complicating treatment. Genetic studies reveal a diverse array of resistance genes, underscoring the bacterium's adaptability. Epidemiologically, healthcare settings remain the primary reservoir, though community-acquired cases are emerging. Diagnosis relies on culture and molecular techniques, while treatment requires tailored antibiotic regimens based on susceptibility profiles. This review also explores future research directions, including genomic sequencing to uncover novel virulence mechanisms and the development of targeted therapies to combat MDR strains.

Keywords:
Klebsiella oxytoca, Multidrug resistance (MDR), Antibiotic-associated hemorrhagic colitis, Nosocomial infections, Virulence factors

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INTRODUCTION

Klebsiella oxytoca is a gram-negative, encapsulated, rod-shaped bacterium belonging to the Enterobacteriaceae family, closely related to *Klebsiella pneumoniae* but distinguished by its unique pathogenic traits and clinical relevance [1]. Long regarded as a less prominent pathogen compared to its notorious counterpart, *K. oxytoca* has gained recognition as an opportunistic organism capable of causing a diverse array of infections, particularly in healthcare settings [2]. It is ubiquitous in nature, thriving in environmental niches such as soil, water, and plant surfaces, while also colonizing human mucosal surfaces, including the gastrointestinal tract, nasopharynx, and skin, where it typically resides as a commensal [3]. However, under conditions such as immunosuppression, disruption of the normal microbiota by antibiotics, or breaches in host barriers due to medical interventions, *K. oxytoca* can shift from a benign colonizer to a significant pathogen, contributing to both nosocomial and, to a lesser extent, community-acquired infections [4].

The pathogenicity of *K. oxytoca* is driven by an array of virulence factors that enable it to evade immune responses and inflict damage on host tissues. Its polysaccharide capsule, a hallmark of the genus, forms a protective shield that prevents phagocytosis by neutrophils and macrophages and inhibits complement-mediated lysis, allowing the bacterium to persist in hostile environments such as the bloodstream or tissues [5]. Additionally, *K.*

oxytoca produces siderophores small, iron-chelating molecules that scavenge essential iron from host proteins like transferrin and lactoferrin, supporting bacterial proliferation during infection [6]. In contrast to K. pneumoniae, which is often associated with hypervirulent strains causing severe community-acquired diseases like necrotizing pneumonia and liver abscesses, *K. oxytoca* is more frequently linked to healthcare-associated infections and a distinctive syndrome known as antibiotic-associated hemorrhagic colitis (AAHC) [7]. This condition, triggered by the production of cytotoxins such as tilivalline and tilimycin, typically emerges following the use of β-lactam antibiotics, which disrupt gut flora and favor *K. oxytoca* overgrowth [8].

Clinically, *K. oxytoca* poses a significant threat to vulnerable populations, including neonates, the elderly, and immunocompromised individuals, such as those with cancer, diabetes, or HIV [9]. Nosocomial infections are common, encompassing urinary tract infections (UTIs), pneumonia, bacteremia, and wound infections, often associated with indwelling medical devices like catheters, ventilators, and surgical implants [10]. The bacterium's ability to form biofilms on these surfaces enhances its persistence, making eradication challenging and increasing the risk of chronic or recurrent infections [11]. Furthermore, the emergence of multidrug-resistant (MDR) strains has amplified its clinical importance, with resistance to a broad spectrum of antibiotics including β-lactams, carbapenems, fluoroquinolones, and aminoglycosides posing substantial therapeutic obstacles [12]. This resistance profile is mediated by both intrinsic mechanisms, such as the chromosomally encoded OXY β-lactamase, and acquired genetic elements, including plasmid-borne extended-spectrum β-lactamases (ESBLs) and carbapenemases like KPC and NDM [13].

Epidemiologically, *K. oxytoca* is predominantly a healthcare-associated pathogen, with key risk factors including prolonged hospitalization, invasive procedures, and prior antibiotic exposure, all of which create opportunities for colonization and infection [14]. Outbreaks, particularly in neonatal intensive care units (NICUs), have been documented, often linked to contaminated medical equipment, solutions, or healthcare worker transmission, highlighting its epidemic potential [15]. While community-acquired infections are less common, they are increasingly reported in individuals with underlying conditions such as diabetes, chronic alcoholism, or liver disease, suggesting that *K. oxytoca* may have a broader ecological and clinical footprint than previously recognized [16]. The global rise of MDR strains, especially in regions with high antibiotic consumption, underscores the need for enhanced surveillance and infection control measures [17].

The management of *K. oxytoca* infections is complicated by its resistance patterns, requiring precise diagnostic and therapeutic approaches. Diagnosis typically involves culture-based methods supplemented by biochemical tests and molecular techniques, such as PCR, to detect resistance genes, though rapid identification remains a priority for improving outcomes [18]. Treatment options vary from third-generation cephalosporins for susceptible strains to advanced regimens involving carbapenems, colistin, or newer agents like ceftazidime-avibactam for MDR isolates, often guided by susceptibility testing [19]. Genetic studies have provided critical insights into *K. oxytoca*'s adaptability, with whole-genome sequencing revealing a diverse array of virulence and resistance genes that reflect its evolutionary plasticity [20]. These findings emphasize the bacterium's ability to thrive under selective pressures, such as antibiotic use, and its potential to evolve new pathogenic traits.

This review aims to deliver a comprehensive analysis of *K. oxytoca*'s role in human diseases, synthesizing its pathogenicity, clinical manifestations, resistance mechanisms, epidemiology, and genetic characteristics. By exploring its virulence factors capsule protection, toxin production, iron acquisition, and biofilm formation—this article elucidates the mechanisms driving its emergence as a significant pathogen. The clinical and epidemiological implications are examined in detail, alongside diagnostic and therapeutic challenges. Additionally, the review looks forward to future research directions, including genomic approaches to uncover novel virulence determinants and the development of innovative interventions to mitigate its impact.

PATHOGENICITY AND VIRULENCE FACTORS

The pathogenicity of *Klebsiella oxytoca* is rooted in a multifaceted array of virulence factors that collectively enable it to colonize host tissues, evade immune defenses, and cause disease. At the core of its virulence is the polysaccharide capsule, a thick, carbohydrate-based structure surrounding the

bacterial cell, composed of K-antigens that vary across strains [5]. This capsule serves as a physical barrier, preventing phagocytosis by host immune cells such as neutrophils and macrophages and blocking complement-mediated killing, a trait critical for survival during systemic infections like bacteremia [21]. Research has shown that the capsule's antiphagocytic properties are essential for *K. oxytoca*'s persistence in the host, distinguishing it from other gram-negative pathogens with less robust encapsulation [22].

Iron acquisition is another pivotal virulence mechanism, mediated by siderophores—small, high-affinity iron-chelating compounds like enterobactin—that extract ferric iron from host proteins such as transferrin and hemoglobin [6]. Iron is a limiting nutrient in the host environment, and *K. oxytoca*'s ability to scavenge it supports bacterial growth and proliferation, particularly in iron-restricted niches like abscesses or the bloodstream [23]. The regulation of siderophore production is tightly controlled by the Fur (ferric uptake regulator) system, which responds to environmental iron levels, enhancing the bacterium's adaptability across diverse conditions [24]. This iron piracy is a key factor in its competitiveness against host defenses and other microbiota.

A distinguishing feature of *K. oxytoca*'s pathogenicity is its production of cytotoxins, notably tilivalline and tilimycin, which are implicated in antibiotic-associated hemorrhagic colitis (AAHC) [8]. These nonribosomal peptide toxins, synthesized by specific biosynthetic gene clusters, target intestinal epithelial cells, disrupting tight junctions, inducing apoptosis, and causing mucosal damage [25]. This leads to inflammation, hemorrhage, and the characteristic bloody diarrhea observed in AAHC, particularly following penicillin-based antibiotic therapy, which selectively enriches *K. oxytoca* in the gut by eliminating competing flora [26]. Experimental studies using cell culture and animal models have confirmed that toxin-producing strains exhibit significantly greater virulence in the gastrointestinal tract compared to non-toxigenic isolates, underscoring the toxins' role in disease severity [27].

Adhesion to host surfaces is facilitated by adhesins and pili, including type 1 and type 3 fimbriae, which enable *K. oxytoca* to bind to mucosal epithelia and abiotic surfaces like catheters and ventilators [28]. This adhesion is a prerequisite for biofilm formation—a structured bacterial community encased in an extracellular matrix that enhances resistance to antibiotics, immune clearance, and environmental stresses [11]. Biofilms are particularly problematic in nosocomial infections, contributing to chronicity and device-related complications, with genomic analyses identifying fimbrial genes as key mediators of this process [29]. The ability to form biofilms distinguishes *K. oxytoca* as a tenacious pathogen in clinical settings, where it can persist despite aggressive interventions.

Lipopolysaccharide (LPS), a major component of the gram-negative outer membrane, further amplifies *K. oxytoca*'s virulence by eliciting a potent inflammatory response through Toll-like receptor 4 (TLR4) activation [30]. The lipid A portion of LPS acts as an endotoxin, triggering the release of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), which can exacerbate tissue damage and, in severe cases, precipitate septic shock [31]. While structurally similar to LPS in other Enterobacteriaceae, *K. oxytoca*'s specific O-antigen composition may modulate the intensity of the host immune response, potentially influencing infection outcomes [32]. This inflammatory cascade is a double-edged sword, aiding bacterial clearance in some contexts while worsening pathology in others.

The synergy among these virulence factors—capsule protection, iron acquisition, toxin production, adhesion, and LPS-mediated inflammation—enables *K. oxytoca* to exploit host vulnerabilities, particularly in immunocompromised or antibiotic-treated individuals [33]. Unlike K. pneumoniae, which often exhibits hypervirulence in healthy hosts, *K. oxytoca*'s opportunistic nature is tailored to specific clinical niches, such as the gut during AAHC or device surfaces in nosocomial

infections [7]. Its metabolic versatility, including the ability to ferment a wide range of sugars, further supports its survival across diverse environments, from the human body to external reservoirs [34]. Understanding the regulation of these virulence traits through transcriptomic or proteomic approaches could reveal novel therapeutic targets, offering hope for disarming this adaptable pathogen [35] [Table 1].

Table 1: The key virulence factors of *Klebsiella oxytoca* and their associated roles in pathogenicity:

Virulence Factor	Description	Role in Pathogenicity
Polysaccharide Capsule	A thick carbohydrate-based structure composed of K-antigens.	Prevents phagocytosis, blocks complement-mediated killing, essential for survival in systemic infections.
Iron Acquisition (Siderophores)	Small, high-affinity iron-chelating compounds like enterobactin.	Scavenges iron from host proteins, supporting bacterial growth, particularly in iron-limited environments.
Cytotoxins (Tilivalline, Tilimycin)	Nonribosomal peptide toxins synthesized by specific biosynthetic gene clusters.	Disrupts intestinal epithelial cells, causes mucosal damage, hemorrhage, and bloody diarrhea in AAHC.
Adhesins & Pili (Type 1, Type 3 Fimbriae)	Surface structures that enable attachment to host tissues and abiotic surfaces.	Facilitate adhesion to mucosal epithelia and biofilm formation, important for chronic and device-related infections.
Lipopolysaccharide (LPS)	A major component of the outer membrane that includes lipid A and O-antigen.	Triggers inflammatory responses, can lead to septic shock, amplifies virulence via TLR4 activation.
Biofilm Formation	A structured bacterial community encased in an extracellular matrix.	Enhances resistance to antibiotics and immune clearance, critical in nosocomial infections.

CLINICAL MANIFESTATIONS

Klebsiella oxytoca is implicated in a broad spectrum of clinical diseases, ranging from localized infections to systemic, life-threatening conditions, predominantly in healthcare settings [2]. Its role as an opportunistic pathogen is most pronounced in immunocompromised individuals, neonates, and patients with indwelling medical devices, where it exploits breaches in host defenses to establish infection [9]. Below, we detail the primary clinical manifestations associated with *K. oxytoca*, supported by clinical and microbiological evidence.

Urinary Tract Infections (UTIs): *K. oxytoca* is a significant cause of UTIs, particularly in catheterized patients or those with structural abnormalities of the urinary tract [36]. Its ability to adhere to uroepithelial cells and form biofilms on catheters enhances its persistence, leading to recurrent or chronic infections [11]. Symptoms typically include dysuria, frequency, and suprapubic pain, though in immunocompromised or elderly patients, UTIs may progress to pyelonephritis or bacteremia [37]. Studies estimate that *K. oxytoca* accounts for approximately 5-10% of nosocomial UTIs, with higher rates in long-term care facilities [38].

Pneumonia: Although less common than K. pneumoniae-induced pneumonia, *K. oxytoca* can cause severe, necrotizing lung infections, especially in mechanically ventilated patients in ICUs [39]. These infections are characterized by hemoptysis, fever, and rapid progression to lung abscesses or empyema, reflecting the bacterium's destructive potential [40]. Risk factors include prolonged ventilation, aspiration, and prior antibiotic exposure, which select for *K. oxytoca* over commensal flora [41]. The mortality rate for *K. oxytoca* pneumonia can exceed 50% in critically ill patients, underscoring its clinical severity [42].

Antibiotic-Associated Hemorrhagic Colitis (AAHC): One of the most distinctive syndromes linked to *K. oxytoca* is AAHC, a form of colitis that typically follows treatment with β-lactam antibiotics, such as amoxicillin [8]. The condition is driven by the bacterium's production of cytotoxins (tilivalline and tilimycin), which damage the colonic mucosa, leading to bloody diarrhea, abdominal pain, and mucosal hemorrhage [25].

Endoscopic findings often reveal segmental colitis with erythematous and ulcerative lesions, predominantly in the right colon [43]. AAHC is self-limiting upon cessation of the offending antibiotic, but severe cases may require supportive care or, rarely, surgical intervention [44].

Bacteremia and Sepsis: In immunocompromised patients, such as those with malignancy, diabetes, or neutropenia, *K. oxytoca* can invade the bloodstream, resulting in bacteremia and sepsis [45]. Sources of infection include the gastrointestinal tract, urinary tract, or indwelling devices, with the bacterium's capsule and LPS contributing to systemic dissemination and inflammatory cascades [5, 30]. Clinical features include fever, hypotension, and multi-organ dysfunction, with mortality rates approaching 30-40% in MDR cases [46]. Prompt identification and treatment are critical to improving outcomes [47].

Wound Infections and Abscesses: *K. oxytoca* is frequently isolated from surgical site infections, traumatic wounds, and soft tissue abscesses, often as part of a polymicrobial flora [48]. Its biofilm-forming capacity and resistance to host defenses enable it to persist in necrotic tissue, leading to delayed wound healing and chronic suppuration [11]. In neonates, *K. oxytoca* has been implicated in necrotizing enterocolitis (NEC), a devastating condition characterized by intestinal inflammation and necrosis, though its role remains secondary to other pathogens [49].

The clinical diversity of *K. oxytoca* infections poses diagnostic challenges, as symptoms may overlap with those caused by other pathogens [50]. For instance, distinguishing *K. oxytoca* pneumonia from that caused by K. pneumoniae requires microbiological confirmation, given their shared genus but differing virulence profiles [51]. Furthermore, the bacterium's role in polymicrobial infections complicates attribution of disease, necessitating advanced diagnostic tools like MALDI-TOF MS to ensure accurate identification [52]. Patient-specific factors, such as immune status and prior antibiotic exposure, significantly influence the clinical course, highlighting the need for personalized management strategies [53].

MECHANISMS OF ANTIBIOTIC RESISTANCE

The emergence of multidrug-resistant (MDR) *Klebsiella oxytoca* strains has significantly complicated its clinical management, rendering many standard antibiotic therapies ineffective [12]. The bacterium's resistance mechanisms are a combination of intrinsic chromosomal traits and acquired genetic elements, enabling it to withstand a broad range of antimicrobial agents [13]. Mechanisms explore in detail, supported by molecular and clinical studies shower in [Table 2].

Table 2: Mechanisms of Antibiotic Resistance in *Klebsiella oxytoca*

Resistance Mechanism	Description	Key Genes/Proteins	Clinical Impact
Intrinsic OXY β-Lactamases	Chromosomally encoded enzymes hydrolyzing penicillins and first-generation cephalosporins.	*blaOXY* (OXY-1 to OXY-6)	Reduces efficacy of ampicillin, piperacillin, and first-generation cephalosporins.
Extended-Spectrum β-Lactamases (ESBLs)	Plasmid-mediated enzymes that hydrolyze third- and fourth-generation cephalosporins.	*blaCTX-M, blaTEM, blaSHV*	Resistance to ceftazidime, cefepime; requires carbapenems for treatment.
Carbapenemases	Enzymes breaking down carbapenems and most β-lactams, leading to MDR	*KPC, NDM, OXA-48*	High resistance to carbapenems (imipenem, meropenem); limited

	strains.		treatment options.
Efflux Pumps	Actively expel antibiotics from the bacterial cell, reducing intracellular drug concentration.	*AcrAB-TolC*	Decreases susceptibility to fluoroquinolones, tetracyclines, and some β-lactams.
Porin Loss	Mutations/downregulation of outer membrane proteins limiting antibiotic entry.	*OmpK35, OmpK36*	Synergizes with β-lactamases to enhance carbapenem resistance.
Biofilm Formation	Protective bacterial communities that reduce antibiotic penetration and enhance gene transfer.	*Various biofilm-associated genes*	Increases persistence in chronic infections (e.g., catheter-associated UTIs, pneumonia).
Combination Resistance Mechanisms	Multiple mechanisms working together, compounding antibiotic resistance.	Various combinations	Requires combination therapies; complicates treatment strategies.

Intrinsic Resistance via OXY β-Lactamases: *K. oxytoca* naturally produces a chromosomally encoded β-lactamase, known as the OXY enzyme, which hydrolyzes penicillins and confers intrinsic resistance to drugs like ampicillin and piperacillin [54]. The OXY family includes multiple variants (e.g., OXY-1 to OXY-6), each with differing substrate specificities and expression levels, influenced by regulatory mutations in the blaOXY promoter region [55]. Overexpression of OXY enzymes can also reduce susceptibility to first-generation cephalosporins, posing challenges in empiric therapy [56].

Extended-Spectrum β-Lactamases (ESBLs): The acquisition of plasmid-mediated ESBLs has expanded *K. oxytoca*'s resistance to third- and fourth-generation cephalosporins, such as ceftazidime and cefepime [57]. Common ESBL genes include blaCTX-M, blaTEM, and blaSHV variants, which are often co-transferred with resistance determinants for aminoglycosides and fluoroquinolones [58]. ESBL-producing *K. oxytoca* strains are increasingly reported in nosocomial outbreaks, necessitating the use of carbapenems as a last resort [59].

Carbapenemases: The rise of carbapenem-resistant *K. oxytoca* is driven by the production of carbapenemases, such as KPC, NDM, and OXA-48-like enzymes [60]. These metallo- or serine-based enzymes hydrolyze carbapenems (e.g., imipenem, meropenem) and most other β-lactams, leaving few treatment options [61]. Plasmid-mediated spread of carbapenemase genes, often alongside ESBLs, amplifies the MDR phenotype, with global dissemination documented in healthcare settings [62].

Efflux Pumps and Porin Loss: Beyond enzymatic resistance, *K. oxytoca* employs efflux pumps, such as AcrAB-TolC, to expel fluoroquinolones, tetracyclines, and some β-lactams, reducing intracellular drug concentrations [63]. Mutations or downregulation of outer membrane porins (e.g., OmpK35 and OmpK36) further limit antibiotic entry, particularly for carbapenems, synergizing with β-lactamases to enhance resistance [64]. These non-enzymatic mechanisms are often underappreciated but critical in MDR strains [65].

Biofilm Formation: The ability to form biofilms on medical devices and mucosal surfaces provides a physical barrier against antibiotics, reducing their penetration and efficacy [11]. Biofilms also facilitate horizontal gene transfer, accelerating the spread of resistance plasmids among bacterial populations [66]. This phenomenon is particularly relevant in chronic infections, such as catheter-associated UTIs or ventilator-associated pneumonia [67].

The complexity of *K. oxytoca*'s resistance mechanisms requires a multifaceted approach to treatment. For instance, combination therapies targeting both enzymatic and non-enzymatic resistance (e.g., β-lactamase inhibitors with efflux pump inhibitors) are under investigation to restore antibiotic efficacy [68]. Additionally, the rapid evolution of resistance, driven by selective pressure from antibiotic overuse, underscores the need for stewardship programs to limit the emergence of MDR strains [69]. Surveillance of resistance patterns at local and global levels is essential to guide empirical therapy and predict therapeutic outcomes [70].

EPIDEMIOLOGY AND RISK FACTORS

Klebsiella oxytoca infections are predominantly healthcare-associated, reflecting its status as a nosocomial pathogen, though community-acquired cases are increasingly recognized [14]. Understanding its epidemiology and associated risk factors is crucial for prevention and control, particularly in high-risk settings. Below, we examine these aspects in detail, supported by epidemiological data.

Nosocomial Prevalence: *K. oxytoca* is a frequent colonizer of hospital environments, thriving in moist areas such as sinks, ventilators, and catheters [71]. It accounts for approximately 5-10% of gram-negative infections in ICUs and long-term care facilities, with higher incidence in neonates and the elderly [72]. Outbreaks are well-documented, particularly in neonatal ICUs, where contaminated solutions, equipment, or healthcare worker hands serve as transmission vectors [15]. A notable outbreak in a German hospital traced *K. oxytoca* to contaminated disinfectant, highlighting its environmental resilience [73].

Risk Factors: Key risk factors for *K. oxytoca* infection include prolonged hospitalization, invasive procedures (e.g., catheterization, mechanical ventilation), and prior antibiotic use, particularly β-lactams, which disrupt normal microbiota and select for resistant strains [74]. Immunocompromised states—such as malignancy, diabetes, or HIV—heighten susceptibility, as do extremes of age (neonates and the elderly) [9]. In AAHC, penicillin exposure is a specific trigger, enriching toxin-producing *K. oxytoca* in the gut [8].

Community-Acquired Infections: While less common, community-acquired *K. oxytoca* infections occur, typically in individuals with underlying conditions like chronic alcoholism, diabetes, or liver disease [16]. These cases often present as UTIs or bacteremia, with a lower prevalence of MDR strains compared to nosocomial isolates [75]. Environmental exposure (e.g., soil or water) may play a role, though human-to-human transmission is rare outside healthcare settings [3].

Geographic Variation: The prevalence of MDR *K. oxytoca* varies globally, with higher rates of ESBL and carbapenemase-producing strains in Asia, Southern Europe, and parts of North America, driven by antibiotic overuse and poor infection control [76]. Surveillance data indicate a rising trend, necessitating region-specific strategies [17].

Transmission Dynamics: In healthcare settings, *K. oxytoca* spreads via direct contact, contaminated surfaces, or aerosols from respiratory devices [77]. Its ability to persist in biofilms enhances its tenacity, making eradication challenging [11]. Community transmission, though less studied, may involve fecal-oral routes or environmental reservoirs, warranting further investigation to clarify its ecological niche [78]. Preventive measures, including hand hygiene, device sterilization, and isolation protocols, are critical to interrupt these pathways [79].

DIAGNOSIS AND TREATMENT

Accurate diagnosis and effective treatment of *K. oxytoca* infections are critical yet challenging due to its diverse clinical presentations and resistance profile [18]. Below, we outline current approaches, supported by clinical and laboratory evidence.

Diagnosis: Identification of *K. oxytoca* begins with culture-based methods, isolating the bacterium from clinical specimens (e.g., urine, blood, sputum) on selective media like MacConkey agar, where it appears as lactose-fermenting colonies [80]. Biochemical tests, such as indole positivity and citrate utilization, distinguish it from K.

pneumoniae [81]. Automated systems (e.g., VITEK) and MALDI-TOF MS provide rapid, accurate speciation [52]. Molecular techniques, including PCR targeting blaOXY or ESBL genes, are increasingly used to detect resistance determinants, particularly in MDR cases [82]. In AAHC, toxin detection via cell culture assays or PCR for biosynthetic genes (e.g., npsA/B) confirms *K. oxytoca*'s role [27].

Treatment: Therapy is guided by susceptibility testing due to widespread resistance [19]. For susceptible strains, third-generation cephalosporins (e.g., cefotaxime) or fluoroquinolones (e.g., ciprofloxacin) are effective, though OXY β-lactamases limit penicillin use [83]. ESBL-producing strains require carbapenems (e.g., meropenem), while carbapenemase producers may respond to colistin, tigecycline, or newer agents like ceftazidime-avibactam, often in combination [84]. AAHC typically resolves with antibiotic withdrawal, though severe cases may need supportive care [44]. Biofilm-associated infections often necessitate device removal alongside antibiotics [85].

Challenges and Innovations: Diagnostic delays due to slow culture methods and resistance complexity necessitate faster tools, such as next-generation sequencing for real-time resistome profiling [86]. Treatment failures in MDR cases highlight the need for novel agents, including β-lactamase inhibitors or phage therapy, currently in preclinical stages [87]. Patient-specific factors, like renal function or comorbidities, further complicate dosing and drug selection, emphasizing individualized care [88].

GENETIC STUDIES OF *KLEBSIELLA OXYTOCA*

Genomic analyses have illuminated the molecular basis of *K. oxytoca*'s pathogenicity and resistance, revealing a dynamic genetic landscape [20]. The complete genome sequence of *K. oxytoca* KCTC 1686 identified approximately 5.5 million base pairs encoding over 5,000 genes, including those for capsule biosynthesis, siderophore production, and toxin synthesis [89]. The polysaccharide capsule, a primary virulence factor, is regulated by the cps gene cluster, which exhibits variability across strains, influencing antigenic diversity and immune evasion [90].

The chromosomally encoded OXY β-lactamase gene family (blaOXY-1 to OXY-6) is a hallmark of *K. oxytoca*, with mutations in promoter regions driving overexpression and resistance to penicillins and cephalosporins [55]. Plasmid-mediated resistance genes, such as blaCTX-M, blaKPC, and blaNDM, are frequently detected in clinical isolates, often co-located with aminoglycoside and fluoroquinolone resistance determinants, reflecting extensive horizontal gene transfer [91]. The toxin genes npsA and npsB, responsible for tilivalline and tilimycin production, are plasmid-borne in some strains, linking toxinogenesis to mobile genetic elements [92].

Comparative genomics with K. pneumoniae highlights *K. oxytoca*'s distinct evolutionary path, with fewer hypervirulence genes but a robust capacity for environmental adaptation and biofilm formation [93]. Whole-genome sequencing of outbreak strains has traced transmission routes and resistance spread, aiding infection control [94]. Population genomics studies suggest that *K. oxytoca*'s genetic diversity is shaped by niche-specific selective pressures, with hospital-adapted clones emerging as dominant lineages [95]. These insights pave the way for precision medicine approaches targeting strain-specific vulnerabilities [96].

FUTURE STUDIES AND PERSPECTIVES

Future research on *K. oxytoca* should focus on large-scale genomic sequencing to uncover novel virulence and resistance genes, leveraging tools like next-generation sequencing and CRISPR-based editing to dissect pathogenicity mechanisms [97]. Developing rapid diagnostics, such as point-of-care PCR for blaOXY or toxin genes, could enhance early detection of MDR or toxigenic strains [98]. Therapeutic innovation is critical, with bacteriophage therapy, anti-toxin molecules, and biofilm-disrupting agents offering promise against resistant infections [99].

Vaccine development targeting capsule antigens or siderophores could prevent colonization in high-risk

groups [100], while synthetic biology approaches might engineer probiotics to outcompete *K. oxytoca* in the gut [101]. Enhanced global surveillance, integrating genomic and epidemiological data, is essential to track MDR clones and inform public health policies. Interdisciplinary collaboration—spanning microbiology, bioinformatics, and clinical research—will be key to translating these advances into practical solutions [102].

CONCLUSION

Klebsiella oxytoca is an opportunistic pathogen with a multifaceted role in human diseases, driven by its virulence factors, clinical diversity, and resistance mechanisms. Its genetic adaptability and epidemiological spread necessitate advanced diagnostics, tailored treatments, and forward-looking research to address this emerging threat. By integrating clinical, microbiological, and genetic perspectives, this review highlights the urgent need for enhanced surveillance and innovative strategies to mitigate the growing impact of *K. oxytoca* in modern medicine. Future efforts should prioritize rapid diagnostics, novel therapeutics, and preventive measures to curb the spread of MDR strains in both healthcare and community settings.

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