**Journal of Communicable Diseases**
**Volume 58, Issue 2 - 2026, Pg. No. 143-151**
**Peer Reviewed & Open Access Journal**

**Review Article**

# Emerging Threats in *Citrobacter* Nosocomial Infections: Mechanisms of Virulence and Resistance

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**DOI:** https://doi.org/10.24321/0019.5138.202640

## INFO

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**How to cite this article:**
Ramadoss R, Moovarkumudalvan B, Lakshmanan D, Pradeep J, Bilal M I, Saravanan S K. Emerging Threats in Citrobacter Nosocomial Infections: Mechanisms of Virulence and Resistance. J Commun Dis. 2026;58(2):143-151.

Date of Submission: 2026-01-20
Date of Acceptance: 2026-02-26

## ABSTRACT

*Citrobacter* species, especially *Citrobacter* freundii, have emerged as important nosocomial pathogens over the past decade. Rising rates of multidrug resistance (including extended-spectrum β-lactamases (ESBLs) and carbapenemases) and documented hospital outbreaks have heightened clinical concern. This review consolidates recent literature on the aspects of epidemiology, clinical manifestations, virulence and resistance mechanisms in hospital-acquired Citrobacter infections. Most *Citrobacter* infections are nosocomial infections, with urinary tract, bloodstream, and intra-abdominal infections being predominant. *Citrobacter* species possess multiple virulence factors like adhesins, fimbriae, biofilm capability and Type VI secretion systems (T6SS), that facilitate colonisation, persistence and host interaction. Intrinsic chromosomal AmpC β-lactamases and increasing acquisition of plasmid-mediated ESBLs and carbapenemases along with tripartite efflux pumps drive the emergence of multidrug-resistant (MDR) phenotypes. Environmental reservoirs for *Citrobacter* species and mobile genetic elements increase nosocomial transmission. Therapeutic management is increasingly challenging with emergence of newer β-lactam/β-lactamase inhibitor combinations. Siderophore cephalosporins could be potential inhibitors for carbapenemase-producing isolates, though interpretation of susceptibility testing remains essential. Effective nosocomial infection prevention requires strict adherence to hand hygiene, intubation device-care, decontamination of hospital environment, and antimicrobial stewardship. Despite growing awareness, substantial knowledge gaps persist, particularly regarding molecular mechanisms behind virulence, optimal treatment pathways to reduce resistant infections, and cost-effective surveillance strategies. *Citrobacter* species is an emerging opportunistic pathogen with a dual challenge of virulence and resistance. This emphasizes the urgency to prioritize genomic surveillance, diagnostics and stewardship-informed therapies to address the clinical and public health impact.

**Keywords**: Nosocomial infections, Opportunistic pathogens, *Citrobacter*, Antimicrobial resistance, Carbapenemase

## Introduction

*Citrobacter* is a Gram-negative, non-spore-forming, rod-shaped, facultatively anaerobic bacteria within the family Enterobacteriaceae.[1] These bacteria were first identified by Werkman and Gillen in 1932 and were characterized by their ability to utilize citrate as a primary carbon source.[1] *Citrobacter* was historically considered as commensals, that inhabit diverse environments such as soil, sewage, water, food, and the intestinal tracts of animals and humans.[1] The *Citrobacter* species particularly, *Citrobacter freundii* and *Citrobacter* koseri were previously regarded as low-virulence organisms, but have now transformed by acquiring multiple antimicrobial resistance (AMR) and virulence traits (host tissue invasion, surface colonization, biofilm formation, and toxin production).[1,2] This evolution has shifted *Citrobacter* from a largely harmless commensal to a significant opportunistic nosocomial pathogen, which could cause significant hospital-acquired infections (HAIs) like urinary tract infections (UTIs), intra-abdominal infections, bacteremia and intubation device-associated infections.[1] Consequently, medical and public health strategies must adapt, treating Citrobacter not merely as a benign contaminant but as an emerging clinical challenge.

This review summarises the current understanding of the epidemiology, virulence mechanisms and antimicrobial resistance determinants of hospital-acquired Citrobacter infections, with emphasis on mechanisms that facilitate nosocomial spread, diagnostic challenges and contemporary therapeutic and infection prevention strategies.

## Emergence of Citrobacter as a Nosocomial Opportunistic Pathogen

Surveillance studies indicate that *Citrobacter* accounts for approximately 3–6% of hospital-acquired *Enterobacteriaceae* isolates, with a notable prevalence in intensive care units (ICUs) and surgical wards.[3,4] This increase correlates with widespread use of invasive procedures, prolonged hospitalization, and broad-spectrum antimicrobial exposure, conditions that facilitate colonization and infection.[5]

Neonates and elderly individuals are especially vulnerable where *C. koseri* is a cause of neonatal meningitis and brain abscesses, whereas in adults with malignancy, organ transplantation, or immunosuppressive therapy, it frequently causes bloodstream and urinary tract infections.[3,6] Device-associated infections, including ventilator-associated pneumonia and catheter-related bloodstream infections, represent a substantial share of nosocomial disease burden.[2] Resistance profile of these bacteria influence mortality rates and multidrug-resistant (MDR) strain associated infections are mostly associated with worse clinical outcomes.[3]

An alarming rise in MDR *Citrobacter* infections is observed among the global epidemiological data. For instance, Asia, Latin America, and Africa are increasingly reporting ESBL and carbapenemase-producing strains.[4,7] Carbapenem-resistant *Citrobacter* is now included within the World Health Organization's critical priority group of carbapenem-resistant Enterobacteriaceae.[9] Nosocomial transmission to contaminated sinks, surfaces, medical equipment, or healthcare workers is often investigated during and outbreak. Biofilm forming ability of *Citrobacter* enhances their persistence in hospital environments.[2,5] and perpetuates clonal spread. *Citrobacter* and other related *Enterobacteriaceae* acquire resistance genes by horizontal gene transfer.

## Virulence Mechanisms Underlying the Pathogenesis of Citrobacter Infections

Multiple pathogenic mechanisms have been deployed by *Citrobacter* to emerge as an opportunistic nosocomial pathogen and infect vulnerable host (Figure 1). These mechanisms include surface adherence and biofilm formation, molecular secretion systems that modulate the host environment, production of toxins, evasion of host immune defences, and efficient nutrient acquisition.[8,9]

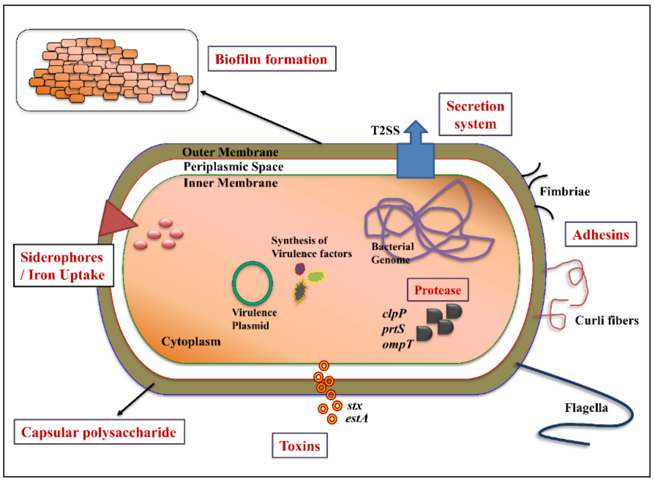

**Figure 1.Illustration of the virulence factors that facilitate infection by Citrobacter spp**

### Adhesins

*Citrobacter* spp., particularly *C. freundii* and *C. rodentium*, employ a range of adhesins (fimbriae, pili, and other surface proteins) to attach to host receptors such as carbohydrates and extracellular matrix proteins. These adhesins enable colonization and invasion.[10,11] For instance, the *Salmonella* fimbrial homologue in *C. freundii* aids invasion and traversal of the blood–brain barrier in neonatal rats.[12] *C. rodentium* uses the translocated intimin receptor (Tir) to form actin-rich pedestals on enterocytes for strong intestinal colonization.[10] Pili also contribute to biofilm formation which supports resistance to host defences and antibiotics.[13] Adhesins are central to *Citrobacter* virulence which drives attachment, invasion, and chronic infection.

### Biofilm Formation

*Citrobacter* persists in healthcare settings majorly due to the virulence trait of biofilm formation. Biofilms are structured bacterial communities, enclosed within a matrix of extracellular polymeric substances (EPS) consisting polysaccharides, proteins, and DNA. EPS protects the biofilm against immune clearance and antimicrobials.[14] Notably, *C. freundii* isolates derived from diarrheagenic cases were mainly biofilm producers.[9] Biofilm formation promotes chronic and device-associated infections by enhance multidrug resistance. This trait also creates diffusion barriers that hinder antibiotic penetration which contributes to treatment failure.[15]

### Secretion Systems

*Citrobacter* infection is mainly driven by active secretion systems, particularly Type II and Type III Secretion systems. The Type II Secretion System (T2SS) is known for exporting mucin degrading enzymes and for promoting adherence. Studies indicate that *C. rodentium* with T2SS mutation exhibit defective colonization and virulence.[16–19] Type III Secretion System (T3SS) is a syringe-like apparatus, which are well characterized in *E. coli* and *Salmonella*. T3SS aid in colonization and dissemination of Citrobacter by injecting effectors that disrupt host cytoskeleton, signalling, and immunity.[20,21]

### Other Key Virulence-Associated Factors

*Citrobacter* deploys additional virulence factors apart from biofilms and secretion systems (Table 1). Some *C. freundii* strains produce Shiga-like and heat-stable toxins. Capsular polysaccharides such as the Vi antigen produced by Citrobacter aid immune evasion by blocking complement proteins and phagocytosis by immune cells.[8,9,22] Iron acquisition via siderophore production further supports growth of *Citrobacter* even in nutrient-limited body sites like the bloodstream and urinary tract.[9,23] Together, these mechanisms enable *Citrobacter* to transform into an opportunistic pathogen from a commensal organism, particularly in immunocompromised hosts.

**Table 1.List of molecular mechanisms contributing for virulence in Citrobacter**

| Virulence Factor | Associated Genes/Proteins | Role in Pathogenesis |
|---|---|---|
| Adhesins | *fimA*, *fimH*, *sfmA*, *tir*, *afa/dra* family genes, *papG*, *papC* | Initiates colonization and host–pathogen interaction |
| Biofilm Formation | *bssR*, *bssS*, *csgA* (curli fimbriae) | Colonization and persistence; enhanced pathogenesis; protection from antibiotics |
| Type II Secretion System (T2SS) | *gspD* (T2SS), *escN* (T3SS ATPase, in C. rodentium) | Degradation of intestinal mucin for nutrient acquisition; promotion of attachment to host cells; mucosal colonization |
| Toxins | *stx* (Shiga-like toxin), *estA* (heat-stable toxin) | Inducing host inflammation and cell damage |
| Capsular Polysaccharide | *cps* gene clusters, *viaB* locus (Vi antigen) | Immune evasion; resistance to complement and phagocytosis |
| Siderophores / Iron Uptake | *iutA*, *entB*, *fepA* | Iron acquisition for bacterial growth and survival |
| Protease Production | *clpP*, *prtS*, *ompT* homologues | Breakdown of host proteins for nutrient acquisition |

## Mechanisms of Antimicrobial Resistance in Citrobacter

Molecular mechanisms that drive AMR have enabled *Citrobacter* to cause severe infections. AMR mechanisms deployed by *Citrobacter* includes enzymes like ESBLs, AmpC enzymes, and carbapenemases, alongside efflux pumps, porin loss, and plasmid-mediated genes (Figure 1).[24–27] These mechanisms lead to resistance against multiple drug classes which complicates antibacterial therapy and prolongs infection.[28] Multiple strategies like rapid diagnostics, antimicrobial stewardship, and novel therapeutics are required to combat AMR.[29]

### Chromosomal and Plasmid-Mediated Resistance

Worldwide, AMR in *Citrobacter* is caused by both intrinsic and acquired genetic elements.[26] These resistance determinants may be encoded on the chromosome or, carried on mobile genetic elements (MGEs) such as plasmids and integrons.[24] Plasmid-mediated AMR mechanisms are particularly concerning since it enables rapid horizontal transfer of resistance genes across bacterial species and accelerates the spread of multidrug resistance.

### β-Lactamase

Production of β-lactamases to counter AMR is one of the principal mechanisms of resistance in *Citrobacter*. These enzymes hydrolyze and inactivate β-lactam antibiotics. There are two types of β-lactamases, namely, inducible Chromosomal AmpC β-Lactamases and Extended-Spectrum β-Lactamases (ESBLs). Inducible Chromosomal AmpC β-Lactamases: *Citrobacter* possess an intrinsic, inducible chromosomal AmpC β-lactamase, which confers resistance to extended-spectrum cephalosporins.[25] The presence of these enzymes has been associated with increased mortality in patients with bloodstream infections.[28]

Extended-Spectrum β-Lactamases (ESBLs): A more alarming development is the widespread emergence of plasmid-mediated ESBLs, which extend resistance to third-generation cephalosporins.[24] Prevalence rates of ESBL-producing *Citrobacter* vary in reported studies. Some studies document rates as high as 62.2% and 30%.[28] while a systematic review estimated a pooled prevalence of 22%.[30]

### Carbapenemase

Carbapenemases are enzymes capable of hydrolyzing carbapenems. Given that carbapenems are one of the last line of drugs in antibiotic therapy against AMR infections, these enzymes pose the most critical threat.[27] This has led to a therapeutic impasse, with few viable empiric options remaining.[26] Regad et al., studied 803 carbapenemase-producing *Citrobacter* isolates in a genomic surveillance study conducted in France.[31] 15 distinct carbapenemases, including OXA-48, NDM-1, and OXA-181 were identified to be prevalent among these isolates.[31] Also, other studies have confirmed the occurrence of KPC-2 in *C. freundii*.[28] The plasmid-mediated dissemination of these carbapenemase genes represents a major global public health concern.[31]

### Efflux Pumps and Outer Membrane Modifications

Apart from enzymatic inactivation, *Citrobacter* employs additional adaptive mechanisms like efflux pumps and Outer Membrane (OM) Modifications to resist antimicrobial drugs (Table 2). Efflux Pumps such as AcrAB-TolC are tripartite resistance-nodulation-division (RND) efflux pumps. AcrAB-TolC could actively expel a broad spectrum of antibiotics and significantly contribute to multidrug resistance.[32,33]

Modifications in OM reduces its permeability and further enhances resistance, as hydrophilic antibiotics must pass through porin channels to enter the cell. *Citrobacter* are capable of decreasing porin expression or altering porin structure via mutations. This reduces antimicrobial drug influx.[34] The combination of carbapenemase production with porin loss is particularly concerning as it results in high-level carbapenem resistance.[28] This illustrates that AMR in *Citrobacter* is more harmful via synergistic mechanisms rather than additive mechanisms and probably the reason behind reduced efficacy of single-agent based anti-Citrobacter therapy.

**Table 2.List of key adaptive antimicrobial resistance Mechanisms inherent in Citrobacter spp**

| Drug class | Mechanism | Genes | Clinical relevance |
|---|---|---|---|
| β-lactams | Hydrolysis by β-lactamase | *AmpC*; plasmid-mediated ESBLs (e.g., TEM, SHV, CTX-M) | Intrinsic resistance |
| Cephalosporins | ESBL production | *bla*CTX-M | Resistance to 3rd-gen cephalosporins |
| Carbapenems | Hydrolysis by Carbapenemases | *bla*KPC, *bla*NDM, *bla*OXA-48, *bla*OXA-181 | Resistance to carbapenems |
| Fluoroquinolones | Target mutations/PMQR | *gyrA*, *qnr* | Reduced ciprofloxacin efficacy |
| Colistin | mcr genes, chromosomal changes | *mcr*-1 | Last-line drug resistance |
| Multiple Classes (e.g., β-lactams, quinolones) | Active efflux from the cell / Reduced permeability to the cell | RND efflux pumps (e.g., AcrAB-TolC) / Modifications or loss of outer membrane porins | Multi-drug resistance |

## Horizontal Gene Transfer and Co-localization drive Citrobacter Pathogenicity

Horizontal gene transfer (HGT) is a fundamental evolutionary mechanism in Citrobacter that has led to its alarming rise of multidrug-resistance. HGT enables the rapid acquisition of large genetic segments, including both virulence and resistance determinants, thereby transforming the bacterium's pathogenic potential (Figure 2).[35,36]

## The Role of Mobile Genetic Elements

HGT is majorly mediated by mobile genetic elements (MGEs) involved in fundamental evolutionary mechanisms, namely, plasmids, integrons, and transposons.[35] These MGEs assimilate and disseminate antibiotic resistance genes (ARGs) as gene cassettes, facilitating the rapid spread of resistance across different species.[37] Their high mobility potential is a central factor in the global AMR crisis.[29]

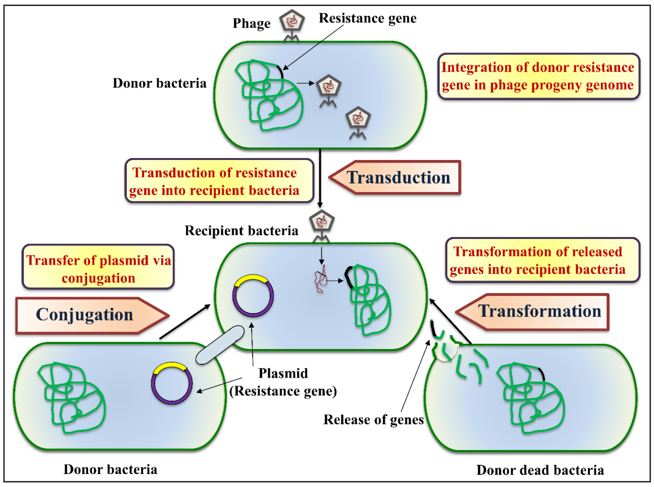

**Figure 2.Illustration of horizontal gene transfer (HGT) mechanism in Citrobacter that contributes for AMR phenotype development**

## Co-localization of Virulence and Resistance Genes

Instances where the virulence factors and ARGs co-localize on the same MGE is a highly concerning phenomenon. This confers a strong selective advantage to the bacterium. Here, exposure to a single antibiotic may inadvertently co-select for both resistance and virulence traits.[37,38] Consequently, a commensal bacterium can rapidly acquire both high-level drug resistance and enhanced pathogenicity in a single transfer event, rather than through gradual adaptive evolution. This acquisition of underlies the sudden emergence of *Citrobacter* as a formidable nosocomial pathogen and explains the difficulty in containing its spread.

## Case Studies of Multidrug-Resistant *Citrobacter* Outbreaks

Various outbreaks of multidrug-resistant *Citrobacter* have emphasized the clinical risk posed by these bacteria. For instance, there was a foodborne outbreak of carbapenemase-producing *C. freundii* that occurred at Jena University Hospital, Germany in 2016. The outbreak was traced to contaminated food items (pudding and vegetable salads) and a mixing machine that was used in preparation.[39] The *Citrobacter* clone responsible for the outbreak was a novel lineage of environmental origin. Hence indicating that even a reservoir outside of direct patient contact could also seed nosocomial outbreaks (Figure 3) in hospitals. Also, this emphasizes the importance of extending infection control strategies beyond patient-to-patient transmission to include hospital environments and supply chains.

Three high-risk clones—*C. freundii* ST8, ST22, and ST91—were implicated in nationwide dissemination. These high-risk clones show rapid evolution of *Citrobacter* into a global AMR threat.[31] The study by Regad et al. have further indicated that MDR *Citrobacter* presents a complex epidemiological scenario with widespread clonal expansion even in localized outbreaks.

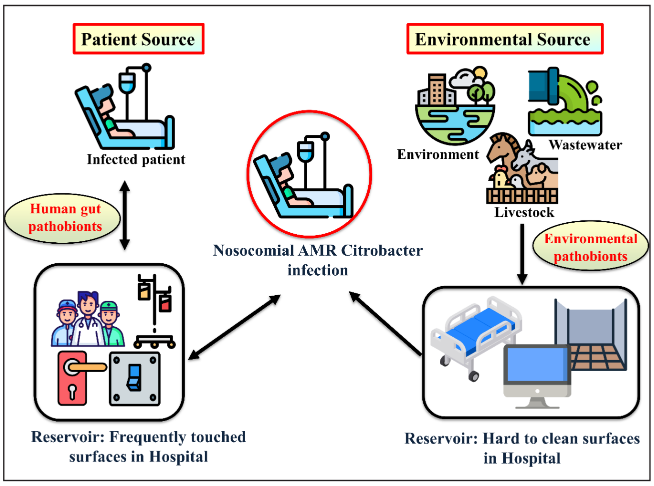

**Figure 3.Schematic representation of transmission dynamics of nosocomial AMR Citrobacter infections in hospital settings**

## Therapeutic and Public Health Strategies

*Citrobacter* poses a major therapeutic challenge due to its widespread resistance to β-lactams, carbapenems, and fluoroquinolones. Choice of the right therapeutic antibiotic or drug against the infection heavily relies on susceptibility testing.[24,25,27] It is concerning that ESBL-producing *Citrobacter* strains have become resistant to most drugs leaving only carbapenems as last-line therapeutics.[24] However, the rise of carbapenemase producing *Citrobacter* strains further complicates management.[27] On the other hand, new therapeutic agents such as gepotidacin and meropenem/vaborbactam have proven to be effective against urinary infections,[40] carbapenem-resistant strains,[41] respectively. These drugs further expand the treatment options against MDR *Citrobacter* strains.

### Therapeutic Guidance

Therapeutic management of a *Citrobacter* infection must be individualized, based on the infection site, severity of infection, host factors, and susceptibility data.[24,42] Listed below are some of the therapeutic guidance to manage different types of AMR *Citrobacter* infections.

- **AmpC producers**: Cefepime or carbapenems are reliable therapeutic agents against Citrobacter strains that could produce AmpC β-lactamases. piperacillin–tazobactam is less dependable in severe infections.[25,42]
- **ESBL producers**: For the ESBL producing strains, carbapenems are mainly effective. Even though cefepime or BL/BLI combinations have also been used in some non-severe infections where the source of infection is well-contained.[38,42,43]
- **Carbapenemase producers**: In cases of infection by carbapenemase producing *Citrobacter* strains, an expert consultation is required. Such that experts can decide the treatment strategy based on the enzyme type. For instance, KPC and OXA-48 enzyme producing strains respond to ceftazidime–avibactam, while NDM enzyme producers often require aztreonam–avibactam combinations or cefiderocol.[42,44,45]

Altogether, studies reveal that the crucial steps like source control, optimized dosing, and selective combination therapy are essential.[43] for controlling MDR infections by *Citrobacter* strains. Also, infection management should follow susceptibility results such that selective pressure on such MDR pathogens could be limited.[42]

## Alternative Therapies

Phage therapy is an emerging tool to combat MDR and biofilm-related infections. It can be combined with antibiotics to inhibit effectively, although the outcomes of such studies are variable.[46,47] CRISPR systems can be employed to target the resistance genes that are plasmid-mediated. This approach is specific and does not exert selective pressure.[48]

## Prevention & Control

Infection control in a hospital setting is important because of the limitations of treatment. Hand hygiene and contact precautions are the most important steps.[49,50] In addition, environmental disinfection of reservoirs such as sinks and drains.[51,52] is necessary. Early detection of any outbreak of hospital-acquired MDR *Citrobacter* could be made possible by rapid diagnostic tests (PCR, NGS). In this case, predictive modeling using AI further improves outbreak control and risk assessment.[53]

## Global Perspectives, Knowledge Gaps and Future Directions

The appearance of *Citrobacter* as a serious MDR nosocomial pathogen is a microcosm of the AMR crisis, rather than an isolated event. The AMR crisis is fueled by the same processes that cause it: HGT, environmental reservoirs, and global distribution.

The intercontinental transfer of resistant bacteria and their associated mobile genetic elements is facilitated, in large part, by international travel and global trade.[49] Environmental factors are increasingly recognized as catalysts of this crisis, in addition to human-mediated mobility. In particular, climate change is likely to exacerbate AMR. It has been shown that rising temperatures accelerate bacterial growth rates and facilitate horizontal gene transfer, which selects for the emergence and spread of resistant pathogens.[50]

To successfully combat *Citrobacter* infections and gain a deeper understanding of how this pathogen continues to evolve and develop novel disease-causing mechanisms, the following research priorities must be addressed. a) Standardization of surveillance: multicenter, standardized surveillance studies to quantify the burden, temporal trends, and geographical distribution of *Citrobacter* spp. resistance mechanisms; b) Virulence mechanism studies: target identification for anti-virulence strategies by functional characterization of adhesins, secretion systems (including T6SS), and biofilm regulators; c) Plasmid ecology: high-resolution genomic studies of plasmid transfer among patients, workers, and environmental reservoirs; d) Research on therapeutic outcomes: observational cohorts and pragmatic trials focused on the effectiveness of novel agents (ceftazidime-avibactam, cefiderocol, aztreonam-avibactam) specifically for *Citrobacter* infections; e) Environmental strategies: pragmatic studies evaluating the cost-effectiveness and effectiveness of point-of-use filters, plumbing modifications, and continuous environmental decontamination systems. The knowledge gap for targeted clinical and public health research will be improved by addressing these areas.

## Conclusion

*Citrobacter* has evolved into a highly resistant pathogen with relatively low virulence from a commensal bacterium. Horizontal gene transfer of various virulence and resistance genes, which have made many traditional antibiotics ineffective, has provided the basis for this evolution.[29] *Citrobacter* is a reminder to the global health community that it is a prime example of the larger AMR pandemic, requiring rapid, coordinated, and multidisciplinary responses.

A One Health framework is essential going forward, combining environmental, animal, and human health approaches to address the underlying causes of AMR.[54] This strategy needs to go beyond patient care to include supply chain management and environmental monitoring. The quick adoption of sophisticated diagnostics, the quick development and translation of new treatments, including those based on CRISPR and bacteriophage, and the strengthening of basic infection prevention measures are all equally important.[55] Without taking these all-encompassing, proactive steps, the world community runs the risk of experiencing a dangerous return to the pre-antibiotic era in the future, when infections brought on by *Citrobacter* and other resistant pathogens become incurable.

**Conflict of Interest**: None

**Source of Funding**: This research work was supported by the "Intramural Research Grant: SBV-Seed money (SBV/IRC/SEED MONEY/171/2023)", Sri Balaji Vidyapeeth, Pondicherry.

**Authors Contribution**: Conceptualization- RR, BM. Methodology- RR, BM. Data collection- RR, BM. Writing-original draft preparation- RR, BM. Writing-review and editing- RR, BM, DL, JP, BMI, SKS. All authors have read and agreed to the published version of the manuscript.

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