VOLUME - 14, ISSUE - 08, AUGUST - 2025 • PRINT ISSN No. 2277 - 8160 • DOI : 10.36106/gjra

Original Research Paper

Microbiology

TRENDS IN CITROBACTER CLINICAL INFECTIONS AND RISING ANTIMICROBIAL RESISTANCE: A STUDY FROM A TERTIARY CARE CENTRE IN NORTH INDIA.

Ivneet Kour	MBBS, MD Dept Of Microbiology GMCH-32 Chandigarh
Parakriti Gupta	MD, DNB Department Of Microbiology GMCH-32 Chandigarh
Varsha Gupta	MD, MAMS, FAMS Department Of Microbiology GMCH 32 Chandigarh
Pratibhaa Chaliha	MBBS, MD Microbiology GMCH 32,Chandigarh
Navreet Kaur	MBBS, MD Department Of Microbiology GMCH 32 Chandigarh
Muskan Kalia	MBBS, MD Microbiology GMCH 32,Chandigarh
Lipika Singhal*	MD, MAMS Department Of Microbiology, GMCH 32 Chandigarh *Corresponding Author

ABSTRACT

Background: Citrobacter is one of the substantial members of order Enterobacterales, family Entrobacteriaceae, which has retained its position even after recent taxonomic changes. Infections caused by Citrobacter typically affects people with underlying illnesses. Recently, it has been observed that there is an increasing trend of resistance esp emergence of multidrug resistance among Citrobacter species. **Aims:** The purpose of this study was to look into the clinical infections and antimicrobial resistance profile of Citrobacter spieces. **Methods And Material:** This was a retrospective study conducted over a period of 4.5 years (2019 to August 2023) in Department of Microbiology, at our tertiary care centre (data was unavailable for 2021). All the Citrobacter spp isolated during the study period were included in the study and the updated trend of their antimicrobial susceptibility pattern was studied. **Statistical Analysis Used:** SPSS software version 28 was used to conduct the statistical comparisons. **Results:** Increased isolation of Citrobacter is worrisome owing to their resistance pattern to varied classes of current antimicrobials. Species differentiation was noted in pus samples with more C. koseri than C. freundii, while urine and blood samples had almost same distribution of both species. Yearly trend divulged overall increase in isolation of Citrobacter spp. Susceptibility profile revealed maximum susceptibility of C. koseri to gentamicin (74.5%), followed by minocycline (70.6%) and imipenem (70%). C. freundii was reported to be more susceptible than C. koseri in pus samples during 2019 and 2020. Moreover, C. koseri was noted to be more susceptible to all antimicrobials, except cefepime and cefotaxime.

KEYWORDS : Citrobacter spp., antimicrobial resistance, emerging threat, North India.

INTRODUCTION:

Citrobacter spp. is one of the substantial members of order Enterobacterales, family Entrobacteriaceae, which has retained its position after recent taxonomic changes.[1] Citrobacter genus encompasses Gram-negative facultative anaerobes with environmental niche in water, soil and gastrointestinal tract of animals and humans.[2,3] The members of genus were considered environmental contaminants decades ago, however, have established themselves as major etiological agents in nosocomial infections, with a propensity to cause outbreaks.[4] These bacteria are implicated in a wide array of infections, varying from soft tissue infection to infection of central nervous system. Infections are commonly reported among immunocompromised individuals and neonates[2] Citrobacter genus encompasses ~11 species, of which C. koseri and C. freundii are frequently implicated in human infections. Increased isolation of Citrobacter is worrisome owing to their resistance pattern to varied classes of antimicrobials[5] Emergence of multi-drug resistant (MDR) Citrobacter has been associated with high mortality rate.[6] MDR Citrobacter has been reported to be beta-lactamase or carbapenemase producers, conferring resistance to commonly used beta-lactams and carbapenems.[7] Despite the escalating isolation and resistance, data pertaining antimicrobial susceptibility pattern is scarce in India, and is limited to urinary tract infections or sepsis. Thereby, the present study was conducted to investigate the susceptibility pattern of various species of Citrobacter isolated from varied samples.

MATERIALS AND METHODS:

This was a retrospective study conducted over a period of 4.5 years (2019 to August 2023) in Department of Microbiology, at our tertiary care centre (data was unavailable for 2021). All the Citrobacter isolates reported in Bacteriology section during the study period were included in the study. Samples obtained in routine microbiology laboratory, including blood, pus and urine, were processed as per the standard operating procedures, under aseptic conditions, Gram stain and culture was done on blood, MacConkey agar and brain-heart infusion broth. The culture plates were noted for any growth the next day, and identification Citrobacter was achieved using battery of standard biochemical tests. Antimicrobial susceptibility (AST) was performed using Kirby-Bauer method of disk diffusion, for antibiotics: amikacin, ampicillin, ampicillin/sulbactam, amoxicillin/clavulanic acid, cefepime, cefotaxime, cefoxitin, ceftazidime, ciprofloxacin, gentamicin, imipenem, meropenem, minocycline, piperacillin/tazobactam, tetracycline, tobramycin and trimethoprim/sulfamethoxazole along with quality controls of ATCC E. coli and S. aureus. AST was interpreted as per the recommendations of Clinical and Laboratory Standards Institute.[8]

RESULTS:

A total of 401 isolates were noted as Citrobacter genus during the study period. Of these 294 isolates, 29.43% were C. koseri, 16.96% were C. freundii and 53.61% were identified as Citrobacter spp. Of all these isolates, majority were isolated from pus samples (76.3%; pus/tissue/wound swab), trailed by urine (59%) and blood (8.9%). The species-wise distribution in varied samples. C. koseri (25.53%) was noted to be more common than C. freundii (12.97%), though maximum isolates were reported as Citrobacter spp. (61.7%) in our study, owing to lack of automated identification systems. Species differentiation was noted in pus samples with more C. koseri than C. freundii, while urine and blood samples had almost same distribution of both species. Yearly trend divulged

overall increase in isolation of Citrobacter from pus samples, being highest in 2023. (Figure 1) We also noted increased isolation of C. freundii over the years, with C. freundii being more than C. koseri in 2022.

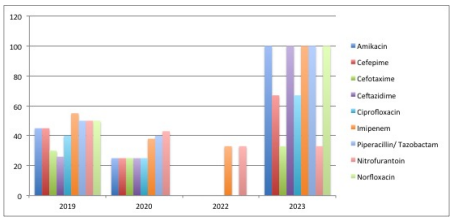

Figure 1- Yearly trend in Antimicrobial resistance in Citrobacter spp.

Susceptibility profile revealed maximum susceptibility of C. koseri to gentamicin (74.5%), followed by minocycline (70.6%) and imipenem (70%). On the contrary, least susceptibility was reported for ampicillin (22.7%), cefotaxime (31.1%) and amoxicillin-clavulanic acid (41.7%) and ciprofloxacin (42%). Of the beta lactam-beta lactamase inhibitors, maximum susceptibility was noted for ampicillin-sulbactam. C. freundii exhibited maximum susceptibility to imipenem (61.3%), followed by gentamicin (57.1%) and cefepime (52.1%), while least susceptibility was reported for ampicillin (21.6%), ciprofloxacin (31.9%) and minocycline (35.3%). Citrobacter spp. showed maximum susceptibility to minocycline (66.7%%), followed by imipenem (51.9%) and gentamicin (50%), with least susceptibility to ampicillin (18.2%), amoxicillin-clavulanic acid (20%) and cefotaxime (21.8%). (Table 1) C. freundii was reported to be more susceptible than C. koseri in pus samples during 2019 and 2020. Moreover, C. koseri was noted to be more susceptible to all antimicrobials, except cefepime and cefotaxime.

DISCUSSION:

The present study divulged significant isolation of Citrobacter spp. from extra-intestinal samples. Maximum isolation was reported from pus samples, followed by urine and blood, which is in contrast to the available literature. [2,4,9,10] Most of the studies have shown increased isolation of Citrobacter from urine samples, ranging from 46.2-56%. [2,4,9,10,11] Study conducted in Massachusetts, Missouri and New Delhi, India showed that Citrobacter was commonly isolated from urine, followed by respiratory tract. However, our findings are in concordance to Lipsky et al, who revealed tissue and wounds as most common sample yielding Citrobacter spp. [12] Citrobacter has been implicated in both deep-seated as well as superficial wound infections, both in community and hospitals.[13] Most of the infections reported in literature have beenreported as hospital-acquired.[14,15] Study by Mohanty et al showed 2.87% isolation from soft tissue infections, majority being hospital-acquired.[4] Few studies have shown Citrobacter as substantial agent in surgical site infections. [13] The source of infection in most of hospital-acquired cases has been traced back to hands or gastrointestinal colonization of health care workers.

Another significant finding of our study was implication of Citrobacter in bloodstream infections (8.9%). The findings are in congruence to study by Rao et al who stated Citrobacter as fourth most common causes of sepsis.[16] Christo et al also highlighted the significance of Citrobacter in patients with neonatal sepsis.[17] C. koseri was reported as more commonly isolated species than C. freundii, which is in congruence to the available literature.[24] On the contrary, few studies have reported C. freundii as the most common species implicated in human illness.[18,19]

Owing to the resistant nature of organism, isolation of Citrobacter is considered as a matter of concern. The present study also divulged resistance of Citrobacter to almost all classes of antibiotics. Carbapenem-resistant Citrobacter (24.2% in C. koseri and 33.3% in C. freundii) was also noted in the study, which comes under the major public health concerns globally.[20] The same has been conferred to the acquisition of New Delhi Metallo-b-lactamase, OXA-48, VIM and KPC-2 genes.[21] Higher level of resistance noted in our study is in concordance to the literature. Study by Mohanty et al reported 86.3% resistance to cefotaxime and 7.35 resistance to imipenem and meropenem. Ciprofloxacin was resistant in 81.95 isolates, while ceftazidime in 85.3% of isolates.[4]Similarly, 100%, 83.3%, 55.6%, 88.9% and 77.8% resistance was noted for ampicillin, cefazolin, gentamicin, nitrofurantion and norfloxacin, by Navaneeth et al in urinary isolates.[22]

Susceptibility patterns in the literature have revealed higher level of resistance in C. freundii than C. koseri,[23] though few studies have shown more resistance in C. koseri recently.[4] The same pattern of higher resistance in C. freundii was noted in our study for all antibiotics, except cefepime and cefotaxime. Though C. koseri was reported as more resistant species, pus isolates in 2019 and 2020 divulged the reverse scenario. The changing trend highlights the varying epidemiology among these species, in our region, which can be attributed to the indiscriminate usage of antibiotics or to the selection pressure, as ours is a tertiary care hospital and many patients are on empirical therapy.

Limitations Of The Study:

The present study has limitations, including the molecular work was not done on the strains, as it was retrospective study.

CONCLUSION:

The study highlights the increasing isolation along with escalated antimicrobial resistance among Citrobacter isolates over the years. There is an urgent need to adhere to stringent usage of targeted therapy after the susceptibility report and significance of hospital infection practices, to contain the growing resistance among these species.

Consent For Publication

The author reviewed and approved the final version and has agreed to be accountable for all aspects of the work,including any accuracy or integrity issues. The author declares that they do not have any financial involvement or affiliations with any organization, association, or entity directly or indirectly related to the subject matter or materials presented in this review paper. This includes honoraria, expert testimony, employment, ownership of stocks or options, patents, or grants received or pending royalties.

Data Availability

Information for this original paper is available only for research purpose only.

Authorship Contribution

All authors contributed significantly to the work, whether in the conception, design, utilization, collection, analysis, and interpretation of data or all these areas.They also participated in the paper's drafting, revision,or critical review, gave their final approval for the version that would be published, decided on the journal to which the article would be submitted, and made the responsible decision to be held accountable for all aspects of the work.

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