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CLINICOPATHOLOGICAL AND BIOCHEMICAL CORRELATES OF CARBAPENEM-RESISTANT ENTEROBACTERIACEAE INFECTIONS AND THEIR ASSOCIATION WITH ORAL MICROBIOTA DYSBIOSIS AND SLEEP DISORDERS IN HOSPITALIZED PATIENTS

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ABSTRACT

Background: Carbapenem-resistant Enterobacteriaceae (CRE) have emerged as a major public health concern due to their extensive drug resistance and association with prolonged hospital stays and increased mortality. Recent evidence suggests that systemic infections and microbial dysbiosis may influence both host immunity and sleep regulation, yet the interplay between CRE infections, oral microbiota alterations, and sleep disorders remains poorly understood.

Objective: This study aims to explore the clinicopathological and biochemical characteristics of hospitalized patients with CRE infections and to examine their association with oral microbiota dysbiosis and sleep disturbances.

Methods: A cross-sectional analytical study was conducted among hospitalized patients with laboratory-confirmed CRE infections. Clinical and biochemical profiles were obtained through medical records and laboratory investigations. Oral swabs were analyzed using culture and molecular methods to assess microbiota composition. Sleep quality was evaluated through standardized questionnaires and clinical assessment. Correlation analyses were performed to identify associations between infection severity, biochemical markers, microbiota alterations, and sleep parameters.

Results: Patients with CRE infections exhibited marked systemic inflammation, reflected by elevated C-reactive protein and altered liver enzyme levels. Significant shifts in oral microbial diversity were observed, with an increased abundance of opportunistic pathogens. Sleep disturbances were common among CRE-infected patients and showed positive correlations with inflammatory markers and oral dysbiosis indices. Multivariate analysis indicated that biochemical abnormalities and microbial imbalance were independent predictors of poor sleep quality.

Conclusion: CRE infections are associated with distinct clinicopathological and biochemical profiles, accompanied by significant alterations in oral microbiota and increased prevalence of sleep disorders. These findings highlight the potential bidirectional link between systemic infection, microbial ecology, and sleep regulation, underscoring the need for integrated management strategies in hospitalized patients.

Keywords: Carbapenem-resistant Enterobacteriaceae, oral microbiota, sleep disorders, biochemical markers, hospitalized patients, dysbiosis, infection.

INTRODUCTION

In recent years, hospital-acquired infections due to highly resistant organisms have emerged as compelling challenges for clinical practice and infection control. Among these, Enterobacteriaceae resistant to the carbapenem antibiotic class commonly termed carbapenem-resistant Enterobacteriaceae (CRE) have drawn special attention due to their potential for widespread dissemination, limited treatment options, high morbidity and mortality, and health-care cost implications. The family Enterobacteriaceae comprises a large group of Gram-negative bacilli, which are common inhabitants of human intestinal flora but also cause a variety of community-acquired and health-care–associated infections (1). Carbapenems (such as imipenem, meropenem, ertapenem, and doripenem) have long served as drugs of last resort for multidrug-resistant Gram-negative infections, yet the emergence of CRE underscores the critical crisis in antimicrobial resistance (AMR) (2).

Mechanistically, CRE may resist carbapenems through several distinct yet sometimes overlapping pathways: carbapenemase enzyme production (e.g., KPC, NDM, OXA-48-like), efflux pump activation, porin channel alterations, and other intrinsic and acquired mechanisms (3). These mechanisms enable CRE to survive exposure to carbapenems, which severely restricts therapeutic options. Clinically, CRE infections most often present in vulnerable hospitalized patients—especially those in intensive care units, patients with invasive devices (e.g., central vascular catheters, urinary catheters), prior broad-spectrum antibiotic exposure, or prolonged hospitalization. For example, meta-analyses have shown that use of medical devices was associated with increased odds of CRE acquisition (OR ~5.09) and prior carbapenem use likewise raised the odds (OR ~4.71) (4).

Globally, the spread of CRE has been documented across multiple continents. A scoping review found that although CRE were initially largely confined to healthcare settings, community-onset CRE cases (0.04 % to 29.5 % of isolates) have also been reported, signaling potential transition beyond the hospital niche (5). In the United States, CRE infections were rarely reported before 2000 but have since gained a foothold in acute-care hospitals (6). The clinical outcomes of CRE infections are sobering mortality rates have been reported in the range of 40–50 % for certain bloodstream infections (7).

While the microbiological and epidemiological dimensions of CRE are well described, less attention has been accorded to the broader physiological, biochemical and systemic correlates in infected patients, and still less to interactions with other physiological domains, such as sleep regulation and microbial ecology of niches beyond the intestinal tract (8). This gap is increasingly relevant in the light of emerging research on the microbiome–host axis and the impact of sleep disorders on health and microbial ecosystems.

Sleep disorders ranging from insomnia and poor sleep quality to sleep-related breathing disorders such as Obstructive Sleep Apnea (OSA) are highly prevalent among hospitalized and medically ill populations, and are increasingly recognized as contributing to systemic inflammation, immune dysfunction, metabolic disturbance and altered microbiota profiles (9). For instance, studies have demonstrated that sleep disruption is associated with altered gut microbiota composition, increased systemic inflammatory markers and altered metabolic phenotypes (10). Although the bulk of research in this domain has focused on gut microbiota, there is growing recognition of changes in the oral microbiota in relation to sleep disorders: a systematic review found that patients with OSA showed significant differences in oral microbiota compared with controls (11).

Furthermore, the oral microbiota itself is increasingly recognized not just for local periodontal or dental implications but also for systemic interactions: microbial dysbiosis in the oral cavity has been implicated in systemic inflammatory states, cardiovascular disease, and potentially in modulating host susceptibility to other infections (11). For example, a review of OSAHS (Obstructive Sleep Apnea-Hypopnea Syndrome) highlighted that altered oral microbiota may contribute to immune, inflammatory and oxidative-stress pathways that link sleep disorder to cardiovascular disease (12). Hence, few studies have integrated these domains clinicopathological and biochemical correlates of

resistant-organism infection, oral microbiota alterations, and sleep disorders in a single analytic framework.

Accordingly, the present study is designed to investigate hospitalized patients with confirmed CRE infections in terms of clinicopathological and biochemical profiles, alterations in the oral microbiota, and the presence and severity of sleep disorders, and to examine the associations among these domains. By adopting a multidisciplinary approach, this research aims to explain the relationship between resistant-organism infection, microbial ecology of the oral cavity and sleep disruption, ultimately to contribute to broader understanding of patient vulnerability, prognosis and potential adjunctive therapeutic pathways.

METHODOLOGY

This analytical cross-sectional study was conducted between March and September 2024 in three tertiary care hospitals located in Karachi and Lahore, Pakistan. Ethical approval was obtained from the respective Institutional Review Boards prior to data collection. Informed written consent was obtained from all participants or their legal guardians before enrolment. A total of 120 hospitalized patients aged between 18 and 75 years with culture-confirmed carbapenem-

resistant Enterobacteriaceae (CRE) infection were included through purposive sampling. Exclusion criteria comprised patients receiving antifungal therapy, those with known psychiatric illness other than sleep disorders, and those who had received probiotic supplementation within the preceding four weeks. Clinical data were retrieved from hospital records, including demographic characteristics, comorbid conditions, duration of hospitalization, antibiotic exposure, and infection site. Blood samples were obtained to determine biochemical and hematological parameters such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), liver and renal function tests, fasting glucose, and lipid profile. These investigations were performed using standard hospital laboratory protocols, with strict adherence to quality control procedures. For microbiological confirmation, samples (blood, urine, sputum, or wound swabs) were cultured on MacConkey and blood agar plates. CRE isolates were identified using VITEK-2 Compact system (bioMérieux, France) and confirmed through modified Hodge test and carbapenemase gene detection by PCR (targeting blaNDM, blaKPC, blaOXA-48). Antimicrobial susceptibility testing was performed according to CLSI 2023 guidelines. Oral microbiota samples were obtained by sterile cotton swabs from the buccal mucosa and tongue dorsum early in the morning, prior to oral hygiene or food intake. DNA extraction was performed using the Qiagen QIAamp DNA Mini Kit (Germany). 16S rRNA gene sequencing (V3–V4 regions) was carried out using Illumina MiSeq platform. Microbial diversity indices (Shannon, Simpson) and relative abundance at genus level were computed using QIIME2 software. Dysbiosis Index was calculated based on deviation from the mean microbial composition of healthy reference data. Sleep quality was assessed using the Pittsburgh Sleep Quality Index (PSQI) and the Epworth Sleepiness Scale (ESS), both validated instruments for clinical research. Scores above 5 on PSQI and 10 on ESS were categorized as poor sleep quality and excessive daytime sleepiness, respectively. Each participant also underwent a brief clinical evaluation by a psychiatrist to exclude primary psychiatric disorders influencing sleep.Data analysis was performed using SPSS version 26.0 (IBM Corp.). Continuous variables were summarized as mean ± standard deviation, while categorical variables were expressed as frequencies and percentages. Pearson's correlation and multiple linear regression analyses were used to explore associations among biochemical parameters, oral dysbiosis index, and sleep quality scores. A p-value <0.05 was considered statistically significant.

RESULTS

A total of 120 patients with confirmed CRE infection were included, of whom 65 (54.2%) were male and 55 (45.8%) were female. The mean age was 49.6 ± 13.4 years. Most infections originated from urinary tract (36.7%) and bloodstream (30%), followed by respiratory tract (23.3%) and surgical wounds (10%). The overall mean hospital stay was 15.8 ± 6.2 days as shown in table 1.

Table 1. Baseline Characteristics of Study Participants (n = 120)

Variable	Frequency (%) / Mean ± SD
Age (years)	49.6 ± 13.4
Gender (Male/Female)	65 / 55
Duration of hospital stay (days)	15.8 ± 6.2
Diabetes mellitus	48 (40%)
Hypertension	51 (42.5%)
Chronic kidney disease	19 (15.8%)
ICU admission	37 (30.8%)
Prior broad-spectrum antibiotic use	93 (77.5%)

Most patients exhibited elevated inflammatory markers (CRP, ESR), while nearly half showed mild hepatic enzyme derangement, suggestive of systemic inflammatory stress due to CRE infection as shown in table 2.

Table 2. Biochemical and Inflammatory Parameters among CRE Patients

Parameter	Mean ± SD	Reference Range	% Above Normal
C-Reactive Protein (mg/L)	42.8 ± 18.7	<10	88%
ESR (mm/hr)	58.2 ± 21.3	<20	82%
ALT (U/L)	54.6 ± 22.5	<40	46%
Serum Creatinine (mg/dL)	1.9 ± 0.8	0.6–1.3	38%
Total Cholesterol (mg/dL)	179.5 ± 39.6	<200	–
Fasting Glucose (mg/dL)	118.4 ± 27.3	70–110	33%

CRE-infected patients showed significantly reduced microbial diversity and increased abundance of opportunistic Gram-

negative species in the oral cavity, reflecting marked oral dysbiosis as shown in table 3.

Table 3. Oral Microbiota Diversity and Dysbiosis Index

Metric	Mean ± SD	Control Mean*	p-value
Shannon Diversity Index	2.45 ± 0.61	3.18 ± 0.48	<0.001
Dysbiosis Index	4.2 ± 1.1	1.0 ± 0.5	<0.001
Dominant genera (↑ increased)	*Klebsiella, Enterococcus, Veillonella*	–	–
Dominant genera (↓ decreased)	*Streptococcus, Neisseria, Rothia*	–	–

Poor sleep quality (mean PSQI > 8) and excessive daytime sleepiness were prevalent among participants. Positive correlations between CRP, oral dysbiosis index, and PSQI/ESS scores suggest a bidirectional relationship between systemic inflammation, microbial imbalance, and sleep disturbance as shown in table 4.

Table 4. Sleep Quality and Correlation with Biochemical and Microbiota Indices

Variable	Mean ± SD	Correlation with CRP (r)	Correlation with Dysbiosis Index (r)	p-value
PSQI Score	8.9 ± 3.1	0.46	0.42	<0.01
ESS Score	11.2 ± 2.8	0.39	0.41	<0.01

Both high inflammatory burden (CRP) and oral dysbiosis independently predicted poor sleep quality, even after adjusting for age and ICU admission. These findings support a multifactorial link among infection, inflammation, and sleep disruption as shown in table 5.

Table 5. Multivariate Regression Model Predicting Poor Sleep Quality (PSQI >5)

Predictor Variable	β Coefficient	95% CI	p-value
Elevated CRP (>20 mg/L)	0.31	0.12–0.48	0.003
Dysbiosis Index (>3)	0.27	0.09–0.44	0.005
ICU stay	0.22	0.04–0.39	0.018
Age	0.11	−0.06–0.28	0.21 (NS)

DISCUSSION

In this study hospitalized patients with confirmed carbapenem-resistant Enterobacteriaceae (CRE) infections and their clinicopathological and biochemical profiles, oral microbiota dysbiosis and sleep disturbances were evaluated. Our key findings illustrate a complex interplay among severe antimicrobial-resistant infection, microbial ecology of the oral cavity and sleep dysfunction. These findings warrant integrated clinical attention and further mechanistic research. The clinicopathological and biochemical findings of elevated inflammatory markers (e.g., C-reactive protein, ESR) and evidence of hepatic or renal functional impact align with previous literature on CRE infections. For example, in a tertiary care center in Córdoba, Argentina, patients with CRE bacteremia exhibited higher rates of ICU stays, prior antibiotic use and worse outcomes compared to carbapenem-susceptible counterparts (13). In Pakistan, studies documented the molecular characterization of CRE isolated from intensive care units, confirming high prevalence of carbapenemase genes among ICU isolates (14). Our results reinforce that CRE infections represent not only a microbiological challenge but also a systemic inflammatory burden manifesting in altered biochemical markers. This systemic stress may predispose to or worsen sleep disturbances, as will be discussed further. The oral microbiota findings are of particular interest. We found significantly reduced diversity indices alongside increased abundance of opportunistic or pathogenic genera in the oral cavity of CRE patients. Although literature on oral microbiota in the context of CRE infections is scant, analogous findings emerge from sleep-disorder research. For instance, a systematic review of oral microbiota in obstructive sleep apnea (OSA) found significant differences in microbial composition in OSA patients compared to controls (15). Moreover, an analysis of U.S. adults from NHANES found associations between lower oral microbial α-diversity and sleep disorder reports (16). These findings suggest that oral microbial dysbiosis is plausibly linked to sleep disturbance and systemic health stressors. In the context of CRE infection, the disturbed systemic milieu (inflammation, antibiotic exposure, hospitalization) may create an environment conducive to oral dysbiosis. Such dysbiosis may reflect compromised mucosal immunity or altered microbial-host interactions.

Sleep quality in our cohort was notably poor, with elevated PSQI and ESS scores correlating with inflammation and oral dysbiosis metrics. This supports the hypothesis that sleep disturbance in hospitalized patients may not merely be the result of environmental factors (noise, interventions) but is also biologically embedded in systemic infection and

microbial-host interactions. Prior work on sleep and microbiota underscores this link: for example, research on insomnia disorder found altered gut and oral microbiota and changed serum metabolites in patients versus controls (17). Furthermore, a recent study demonstrated that sleep deprivation in animal models altered the gut microbiome and that melatonin mediated neuro-protective effects via microbial-derived metabolite (18). From a mechanistic standpoint, the observed associations may reflect several plausible pathways. First, systemic infection and inflammation can disrupt circadian regulation and sleep architecture via cytokine release (e.g., IL-6, TNF-α) and activation of the hypothalamic-pituitary-adrenal axis. Second, oral microbial dysbiosis may contribute to local inflammatory signaling (e.g., periodontal pathogens triggering IL-1β) or even translocation of microbial products into the bloodstream, thus further propagating systemic inflammation and sleep disruption. Third, sleep disruption itself may be feedback to microbiota: studies of oral biofilms show temporal changes in microbial composition pre- and post-sleep, with increases in certain genera (e.g., Prevotella, Corynebacterium) on awakening (19). Clinically, these results have several implications.

Hospitalized patients with CRE infections should be monitored not only for antimicrobial therapy and organ-system function, but also for sleep quality and oral hygiene/microbiota status. Sleep assessment (e.g., via PSQI) might identify patients at higher risk of poor recovery or extended hospitalization. Oral hygiene interventions and perhaps microbiota-preserving strategies (e.g., probiotic rinses or targeted periodontal care) may ameliorate oral dysbiosis and indirectly benefit sleep and systemic recovery. Moreover, in infection control and stewardship programs, recognizing that antibiotic exposure and hospitalization may affect microbiota and sleep suggests opportunities for adjunctive interventions (controlled antibiotic use, minimizing unnecessary invasive procedures, facilitating sleep hygiene). Our study does have limitations. The cross-sectional design precludes causal inference; we cannot definitively state whether oral dysbiosis caused sleep disturbance or whether both are consequences of CRE infection and hospitalization. Additionally, the study was conducted at tertiary care hospitals in one country, limiting generalizability. Oral microbiota was assessed at a single time-point, whereas dynamic changes (pre-hospitalization baseline, during hospital stay, post-discharge) would yield richer insight. We also did not measure detailed cytokine profiles or circadian hormone levels which may further clarify mechanistic pathways. Future work should include longitudinal designs, larger multi-center cohorts, measurement of host immune and circadian mediators, and interventions aiming to restore microbiota or improve sleep.

CONCLUSION

In conclusion, this study highlights that patients hospitalized with CRE infections manifest not only antimicrobial-resistant pathogen burden and systemic inflammation, but also significant oral microbiota dysbiosis and sleep disturbance. These inter-linked phenomena suggest that management of CRE infections should extend beyond antimicrobial therapy, including monitoring of sleep and microbial ecology and potentially targeted interventions. Integrative clinical pathways addressing infection, microbiota and sleep hold promise for improving outcomes in this high-risk population.

REFERENCES

1- Woodworth KR. Vital signs: containment of novel multidrug-resistant organisms and resistance mechanisms—United States, 2006–2017. MMWR. Morbidity and mortality weekly report. 2018;67. http://doi:10.15585/mmwr.mm6713e1. PMID: 29621209; PMCID: PMC5889247.
2- Lutgring JD. Carbapenem-resistant Enterobacteriaceae: an emerging bacterial threat. InSeminars in diagnostic pathology 2019 May 1 (Vol. 36, No. 3, pp. 182-186). WB Saunders. http://doi:10.1053/j.semdp.2019.04.011. Epub 2019 Apr 17. PMID: 31056277.
3- Suay-García B, Pérez-Gracia MT. Present and future of carbapenem-resistant Enterobacteriaceae infections. Advances in clinical immunology, medical microbiology, COVID-19, and big data. 2021 Dec 22:435-56. http://doi:10.3390/antibiotics8030122. PMID: 31430964; PMCID: PMC6784177.
4- Van Loon K, Voor in ‘t holt AF, Vos MC. A systematic review and meta-analyses of the clinical epidemiology of carbapenem-resistant Enterobacteriaceae. Antimicrobial agents and chemotherapy. 2018 Jan;62(1):10-128. http://doi:10.1128/AAC.01730-17. PMID: 29038269; PMCID: PMC5740327.
5- Kelly AM, Mathema B, Larson EL. Carbapenem-resistant Enterobacteriaceae in the community: a scoping review. International journal of antimicrobial agents. 2017 Aug 1;50(2):127-34. http://doi:10.1016/j.ijantimicag.2017.03.012. Epub 2017 Jun 21. PMID: 28647532; PMCID: PMC5726257.
6- Friedman ND, Carmeli Y, Walton AL, Schwaber MJ. Carbapenem-resistant Enterobacteriaceae: a strategic roadmap for infection control. infection control & hospital epidemiology. 2017 May;38(5):580-94. http://doi:10.1017/ice.2017.141. PMID: 28294079.

7- Ahn JY, Ahn SM, Kim JH, Jeong SJ, Ku NS, Choi JY, Yeom JS, Song JE. Clinical characteristics and associated factors for mortality in patients with carbapenem-resistant Enterobacteriaceae bloodstream infection. Microorganisms. 2023 Apr 25;11(5):1121. http://doi:10.3390/microorganisms11051121. PMID: 37317095; PMCID: PMC10220897.
8- Xiao Y, Duan J, Tan C, Zou J, Chen S, Liu T, Zhang L, Chen X, Xu Y, Li Y, Wu A. Correlation between intestinal CRE colonization and consequent systemic infection in hospitalized patients in China. Scientific Reports. 2024 Oct 29;14(1):26017. http://doi:10.1038/s41598-025-90543-w. PMID: 39472675; PMCID: PMC11522463.
9- Kulpatcharapong S, Chewcharat P, Ruxrungtham K, Gonlachanvit S, Patcharatrakul T, Chaitusaney B, Muntham D, Reutrakul S, Chirakalwasan N. Sleep quality of hospitalized patients, contributing factors, and prevalence of associated disorders. Sleep disorders. 2020;2020(1):8518396. http://doi:10.1155/2020/8518396. PMID: 32308998; PMCID: PMC7157800.
10- Morwani-Mangnani J, Giannos P, Belzer C, Beekman M, Eline Slagboom P, Prokopidis K. Gut microbiome changes due to sleep disruption in older and younger individuals: a case for sarcopenia?. Sleep. 2022 Dec 1;45(12):zsac239. http://doi:10.1093/sleep/zsac239. PMID: 36183306; PMCID: PMC9742900.
11- Bianchi G, de'Angelis N, Gavriilidis P, Sobhani I, de'Angelis GL, Carra MC. Oral microbiota in obstructive sleep apnea patients: a systematic review. Sleep and Breathing. 2023 Aug;27(4):1203-16. http://doi:10.1007/s11325-022-02718-8. Epub 2022 Oct 7. PMID: 36207622.
12- Zeng YM, Hu AK, Su HZ, Ko CY. A review of the association between oral bacterial flora and obstructive sleep apnea–hypopnea syndrome comorbid with cardiovascular disease. Sleep and Breathing. 2020 Dec;24(4):1261-6. http://doi:10.1007/s11325-019-01962-9. Epub 2019 Nov 22. PMID: 31758435.
13- Lipari FG, Hernández D, Vilaro M, Caeiro JP, Saka HA. Clinical, epidemiological and microbiological characterization of bacteremia produced by carbapenem-resistant enterobacteria in a university hospital in Córdoba, Argentina. Revista Chilena de Infectologia: Organo Oficial de la Sociedad Chilena de Infectologia. 2020 Aug 1;37(4):362-70.b http://doi:10.29271/jcpsp.2019.09.878. PMID: 31455486.
14- Fatima A, Kamran R, Rashid H, Shafique M. Molecular characterisation of carbapenem-resistant enterobacteriaceae from intensive care units. J Coll Physicians Surg Pak. 2019 Sep 1;29(9):878-81. http://doi:10.29271/jcpsp.2019.09.878. PMID: 31455486.
15- Li J, Gao J, Ma Y, Li W, Chen X, Li Z, Zhang X. Alterations of the salivary microbiome in obstructive sleep apnea and their association with periodontitis. Frontiers in Cellular and Infection Microbiology. 2025 Sep 9;15:1642766. http://doi:10.3389/fcimb.2025.1642766. PMID: 40995218; PMCID: PMC12454391.
16- Hao G, Wu Y, Mo X, Zhao X, Hou L, Xie T. Association between oral microbiome and sleep disorders in US adults: analysis of NHANES database 2009–2012. BMC Oral Health. 2025 Apr 1;25(1):469. http://doi:10.1186/s12903-025-05794-w. PMID: 40170173; PMCID: PMC11959752.
17- Lin W, Yang Y, Zhu Y, Pan R, Liu C, Pan J. Linking Gut Microbiota, Oral Microbiota, and Serum Metabolites in Insomnia Disorder: A Preliminary Study. Nature and Science of Sleep. 2024 Dec 31:1959-72. http://doi:10.2147/NSS.S472675. PMID: 39664229; PMCID: PMC11633293.
18- Wang X, Wang Z, Cao J, Dong Y, Chen Y. Gut microbiota-derived metabolites mediate the neuroprotective effect of melatonin in cognitive impairment induced by sleep deprivation. Microbiome. 2023 Jan 31;11(1):17. http://doi:10.1186/s40168-022-01452-3. PMID: 36721179; PMCID: PMC9887785.
19- Sotozono M, Kuriki N, Asahi Y, Noiri Y, Hayashi M, Motooka D, Nakamura S, Yamaguchi M, Iida T, Ebisu S. Impact of sleep on the microbiome of oral biofilms. PLoS One. 2021 Dec 9;16(12):e0259850. http**:**//doi:10.1371/journal.pone.0259850. PMID: 34882696; PMCID: PMC8659294.