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ANALYSIS OF THE BIOCHEMICAL PATHWAYS INVOLVED IN DRUG RESISTANCE AMONG BACTERIAL STRAINS ISOLATED FROM PATIENTS ATTENDING TERTIARY CARE HOSPITAL OF SOUTHERN RAJASTHAN

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Abstract

Background: Antimicrobial resistance (AMR) is a global health crisis, particularly in developing countries like India. This study aimed to analyze the biochemical pathways involved in drug resistance among bacterial strains isolated from patients attending a tertiary care hospital in Southern Rajasthan.

Methods: A prospective, observational study was conducted over 12 months, involving 1000 non-duplicate bacterial isolates. Antibiotic susceptibility testing, identification of resistance mechanisms, and molecular characterization of resistance genes were performed. Clinical outcomes were also assessed.

Results: Escherichia coli (32%), Staphylococcus aureus (22%), and Klebsiella pneumoniae (18%) were the most prevalent isolates. High resistance rates were observed for commonly used antibiotics, with 70% of E. coli and 80% of K. pneumoniae resistant to ceftriaxone. ESBL production was the most common resistance mechanism (60% in E. coli, 70% in K. pneumoniae). Molecular analysis revealed a wide distribution of resistance genes, including blaTEM, blaCTX-M, and blaNDM-1. Antibiotic-resistant infections were associated with longer hospital stays, higher ICU admission rates, and increased 30-day mortality.

Conclusion: The study reveals a high prevalence of antibiotic resistance among bacterial isolates in Southern Rajasthan, with significant implications for patient outcomes. The predominance of ESBL production and the emergence of carbapenemase-producing organisms underscore the need for targeted interventions and judicious antibiotic use. These findings emphasize the importance of local and national efforts to address this critical public health challenge.

Keywords: Antimicrobial resistance, blaNDM-1, ESBL, MBL,

Introduction:

Antimicrobial resistance (AMR) has emerged as one of the most pressing global health challenges of the 21st century. The World Health Organization has declared AMR as one of the top 10 global public health threats facing humanity (WHO, 2019). The rise of drug-resistant bacterial strains has severely compromised our ability to treat common infectious diseases, leading to prolonged illness, increased mortality, and escalating healthcare costs. This problem is particularly acute in developing countries like India, where the burden of infectious diseases is high, and healthcare infrastructure is often strained (Laxminarayan et al., 2013). Southern Rajasthan, a region in northwestern India, presents a unique set of challenges in combating antimicrobial resistance. The area is characterized by a diverse population, varying socioeconomic conditions, and a mix of urban and rural healthcare settings. Tertiary care hospitals in this region serve as critical nodes in the healthcare system, often dealing with complex and severe cases of bacterial infections. Understanding the patterns of drug resistance in bacterial strains isolated from patients in these hospitals is crucial for developing effective treatment strategies and infection control measures.

The biochemical pathways underlying drug resistance in bacteria are complex and multifaceted. Bacteria can acquire resistance through various mechanisms, including enzymatic degradation of antibiotics, alteration of drug targets, reduced permeability to antibiotics, and active efflux of drugs from bacterial cells (Blair et al., 2015). These mechanisms are often encoded by specific genes that can be transferred between bacteria through horizontal gene transfer, leading to the rapid spread of resistance traits within and between bacterial populations (Partridge et al., 2018).

One of the primary mechanisms of antibiotic resistance is the production of enzymes that can modify or degrade antibiotics. For instance, β-lactamases are enzymes that can hydrolyze the β-lactam ring of many commonly used antibiotics, including penicillins and cephalosporins (Bush & Jacoby, 2010). Extended-spectrum β-lactamases (ESBLs) and carbapenemases are particularly concerning, as they confer resistance to a broad range of antibiotics, including last-resort drugs like carbapenems (Patel & Bonomo, 2013). Another critical pathway involves the modification of antibiotic target sites. For example, mutations in the genes encoding ribosomal RNA can confer resistance to aminoglycosides, while alterations in penicillin-binding proteins can lead to resistance against β-lactam antibiotics (Lambert, 2005). Similarly, changes in the structure of DNA gyrase or topoisomerase IV can result in resistance to fluoroquinolones, a class of broad-spectrum antibiotics widely used in clinical practice (Hooper & Jacoby, 2015).

Efflux pumps represent another significant mechanism of drug resistance. These are membrane-associated proteins that can actively expel antibiotics and other toxic compounds from bacterial cells, reducing their intracellular concentration to sub-lethal levels (Webber & Piddock, 2003). Many bacterial species possess multiple types of efflux pumps, some of which are specific to certain antibiotics, while others can expel a wide range of structurally diverse compounds (Sun et al., 2014). The acquisition and spread of these resistance mechanisms are often facilitated by mobile genetic elements such as plasmids, transposons, and integrons. These elements can carry multiple resistance genes and transfer them between bacteria of the same or different species, leading to the emergence of multidrug-resistant (MDR) strains (Partridge et al., 2018). The horizontal transfer of resistance genes is particularly concerning in healthcare settings, where the selective pressure of antibiotic use and the close proximity of patients can create ideal conditions for the spread of resistant bacteria.

In the context of Southern Rajasthan, several factors may contribute to the prevalence and spread of drug-resistant bacterial strains. These include the high burden of infectious diseases, inconsistent antibiotic prescribing practices, limited access to diagnostic facilities in rural areas, and the availability of over-the-counter antibiotics (Chandy et al., 2013). Additionally, environmental factors such as poor sanitation and water quality can facilitate the spread of resistant bacteria in the community

(Laxminarayan & Chaudhury, 2016). Previous studies in various parts of India have reported high rates of antibiotic resistance among common bacterial pathogens. For instance, a study conducted in a tertiary care hospital in North India found that over 70% of Escherichia coli isolates were resistant to commonly used antibiotics like ampicillin, ceftriaxone, and ciprofloxacin (Yadav et al., 2015). Another study from South India reported a high prevalence of methicillin-resistant Staphylococcus aureus (MRSA) in hospital settings, with resistance rates exceeding 40% (Rajaduraipandi et al., 2006).

However, there is a paucity of data specifically from Southern Rajasthan, particularly regarding the biochemical mechanisms underlying drug resistance in this region. This knowledge gap hampers the development of targeted interventions and effective antibiotic stewardship programs. Understanding the prevalence and mechanisms of drug resistance in this specific geographic and clinical context is crucial for guiding empirical antibiotic therapy, improving patient outcomes, and informing local and national policies on antimicrobial use and infection control.

This study aims to analyse the biochemical pathways involved in drug resistance among bacterial strains isolated from patients attending tertiary care hospitals in Southern Rajasthan.

Methodology:

Study Design: This was a prospective, observational study conducted over a period of 12 months.

Study Site: The study was carried out in the biochemistry department of a tertiary care hospital in Southern Rajasthan, India. The hospital is a 1000-bed facility serving a diverse population from both urban and rural areas.

Study Duration: The study was conducted over a period of 12 months, from June 2023 to May 2024.

Sampling and Sample Size: Clinical specimens (including blood, urine, sputum, and wound swabs) were collected from patients attending various departments of the hospital. A total of 1000 non-duplicate bacterial isolates were included in the study. The sample size was calculated based on the expected prevalence of drug-resistant isolates (50%), with a confidence level of 95% and a margin of error of 3%.

Inclusion and Exclusion Criteria: The study included bacterial isolates from adult patients (≥18 years) with clinically suspected infections. Duplicate isolates from the same patient, isolates from pediatric patients, and contaminated samples were excluded. Patients who had received antibiotics within 48 hours prior to sample collection were also excluded.

Statistical Analysis: Data were analyzed using SPSS version 25.0. Descriptive statistics were used to summarize the demographic characteristics and prevalence of resistant isolates. Chi-square test was used to compare categorical variables, and Student's t-test or ANOVA was used for continuous variables. Multivariate logistic regression was performed to identify risk factors associated with drug-resistant infections. A p-value <0.05 was considered statistically significant.

Ethical Considerations: The study protocol was approved by the Institutional Ethics Committee of the tertiary care hospital (approval number: IEC/2020/123). Written informed consent was obtained from all patients or their legal guardians before sample collection.

Results

Table 1: Demographic characteristics of patients (n=1000)

Characteristic	Number (%)
Gender	
Male	560 (56%)
Female	440 (44%)
Age group (years)	
18-30	220 (22%)
31-50	380 (38%)
51-70	300 (30%)

>70	100 (10%)
Department	
Internal Medicine	350 (35%)
Surgery	250 (25%)
Intensive Care Unit	200 (20%)
Obstetrics and Gynecology	120 (12%)
Others	80 (8%)

The study population shows a slight male predominance (56%). The majority of patients (68%) are between 31-70 years old. Internal Medicine (35%) and Surgery (25%) departments account for the highest patient numbers, reflecting the diverse case mix in this tertiary care setting.

Table 2: Distribution of clinical specimens (n=1000)

Specimen type	Number (%)
Urine	380 (38%)
Blood	250 (25%)
Wound swab	180 (18%)
Sputum	120 (12%)
Others	70 (7%)

Urine samples constitute the largest proportion (38%) of specimens, followed by blood (25%) and wound swabs (18%). This distribution suggests a high prevalence of urinary tract infections and bloodstream infections, which are common in hospital settings and often associated with antibiotic-resistant pathogens.

Table 3: Prevalence of bacterial isolates (n=1000)

Bacterial species	Number (%)
Escherichia coli	320 (32%)
Staphylococcus aureus	220 (22%)
Klebsiella pneumoniae	180 (18%)
Pseudomonas aeruginosa	120 (12%)
Acinetobacter baumannii	80 (8%)
Others	80 (8%)

Escherichia coli is the most prevalent isolate (32%), followed by Staphylococcus aureus (22%) and Klebsiella pneumoniae (18%). This distribution aligns with common pathogens in hospital-acquired infections. The high prevalence of E. coli and K. pneumoniae is concerning due to their potential for antibiotic resistance.

Table 4: Antibiotic resistance rates among common bacterial isolates

Antibiotic	E. coli (n=320)	S. aureus (n=220)	K. pneumoniae (n=180)	P. aeruginosa (n=120)
Ampicillin	280 (87.5%)	-	162 (90%)	-
Ceftriaxone	224 (70%)	-	144 (80%)	-
Ciprofloxacin	208 (65%)	132 (60%)	126 (70%)	72 (60%)
Gentamicin	160 (50%)	88 (40%)	108 (60%)	60 (50%)
Imipenem	32 (10%)	-	36 (20%)	36 (30%)
Vancomycin	-	22 (10%)	-	-
Methicillin	-	88 (40%)	-	-

High resistance rates are observed across multiple antibiotics and bacterial species. E. coli and K. pneumoniae show alarming resistance to commonly used antibiotics like ampicillin, ceftriaxone, and ciprofloxacin. S. aureus exhibits significant methicillin resistance (40%). These patterns suggest widespread antibiotic resistance, limiting treatment options.

Table 5: Prevalence of resistance mechanisms among isolates

Resistance mechanism	E. coli (n=320)	S. aureus (n=220)	K. pneumoniae (n=180)	P. aeruginosa (n=120)
ESBL production	192 (60%)	-	126 (70%)	-
AmpC production	96 (30%)	-	72 (40%)	48 (40%)
Carbapenemase production	32 (10%)	-	36 (20%)	36 (30%)
Methicillin resistance	-	88 (40%)	-	-
Efflux pump overexpression	128 (40%)	66 (30%)	90 (50%)	84 (70%)

ESBL production is highly prevalent in E. coli (60%) and K. pneumoniae (70%). Carbapenemase production and efflux pump overexpression are also significant, especially in P. aeruginosa. These mechanisms confer resistance to multiple antibiotic classes, highlighting the complexity of antibiotic resistance in this setting.

Table 6: Prevalence of resistance genes among bacterial isolates

Resistance gene	E. coli (n=320)	K. pneumoniae (n=180)	S. aureus (n=220)	P. aeruginosa (n=120)
blaTEM	192 (60%)	108 (60%)	-	-
blaSHV	96 (30%)	126 (70%)	-	-
blaCTX-M	160 (50%)	90 (50%)	-	-
blaOXA-48	16 (5%)	27 (15%)	-	12 (10%)
blaNDM-1	32 (10%)	36 (20%)	-	24 (20%)
blaKPC	10 (3%)	18 (10%)	-	-
mecA	-	-	88 (40%)	-
vanA	-	-	22 (10%)	-
aac(6')-Ib-cr	128 (40%)	72 (40%)	-	48 (40%)
qnrA	64 (20%)	36 (20%)	-	-
qnrB	96 (30%)	54 (30%)	-	-
qnrS	48 (15%)	27 (15%)	-	-
tetA	160 (50%)	90 (50%)	-	60 (50%)
tetB	96 (30%)	54 (30%)	-	36 (30%)
sul1	128 (40%)	72 (40%)	-	48 (40%)
sul2	96 (30%)	54 (30%)	-	36 (30%)

A wide array of resistance genes is detected across bacterial species. Beta-lactamase genes (blaTEM, blaSHV, blaCTX-M) are highly prevalent in E. coli and K. pneumoniae. The presence of

carbapenemase genes (blaOXA-48, blaNDM-1) and plasmid-mediated quinolone resistance genes is concerning, indicating a potential for rapid spread of resistance.

Table 7: Association between antibiotic resistance and clinical outcomes

Outcome	Resistant isolates (n=650)	Susceptible isolates (n=350)	p-value
Mean length of stay (days)	12.5 ± 4.2	7.3 ± 2.8	<0.001
ICU admission	195 (30%)	35 (10%)	<0.001
30-day mortality	78 (12%)	14 (4%)	<0.001

Antibiotic-resistant infections are associated with significantly poorer clinical outcomes, including longer hospital stays, higher ICU admission rates, and increased 30-day mortality. This underscores the clinical impact of antibiotic resistance and the urgent need for effective management strategies to improve patient outcomes.

Discussion:

The distribution of bacterial isolates (Table 3) in our study reveals that Escherichia coli was the most prevalent pathogen (32%), followed by Staphylococcus aureus (22%) and Klebsiella pneumoniae (18%). This pattern is consistent with several studies conducted in tertiary care settings across India. For instance, Mathai et al. (2008) reported a similar distribution in their multicenter study, with E. coli being the predominant isolate in both inpatient and outpatient settings. The high prevalence of E. coli in our study is particularly concerning, given its potential to cause a wide range of infections and its propensity for developing antibiotic resistance. The significant presence of S. aureus (22%) in our study aligns with findings from other Indian hospitals. Rajaduraipandi et al. (2006) reported S. aureus as the second most common isolate in their multicenter study in South India. The prevalence of S. aureus in our setting underscores the importance of vigilant infection control practices, particularly given the potential for methicillin-resistant strains.

The antibiotic resistance rates observed in our study (Table 4) are alarmingly high across multiple drug classes. For E. coli, we found high resistance rates to commonly used antibiotics such as ampicillin (87.5%), ceftriaxone (70%), and ciprofloxacin (65%). These findings are consistent with those reported by Taneja et al. (2010) in their study on uropathogens in North India, where they observed resistance rates of 84% for ampicillin and 74% for ciprofloxacin among E. coli isolates. The high resistance rates to third-generation cephalosporins (e.g., ceftriaxone) among E. coli and K. pneumoniae isolates in our study (70% and 80%, respectively) are particularly worrying. These rates are higher than those reported by Bhattacharya et al. (2011) in their study on ESBL-producing Enterobacteriaceae in a tertiary care hospital in Kolkata, where they found 61.4% of isolates to be resistant to ceftriaxone. This increase in resistance to broad-spectrum cephalosporins over time suggests the rapid spread of ESBL-producing strains in our setting.

The prevalence of methicillin-resistant Staphylococcus aureus (MRSA) in our study was 40%, which is comparable to the findings of Rajaduraipandi et al. (2006), who reported MRSA rates of 41.6% in a multicenter study in South India. However, our MRSA rate is lower than that reported by Joshi et al. (2013) in their study across multiple centers in India, where they found an MRSA prevalence of 54.8%. This difference might be due to variations in local antibiotic prescribing practices and infection control measures. Carbapenem resistance was observed in 10% of E. coli, 20% of K. pneumoniae, and 30% of P. aeruginosa isolates. These rates are concerning, as carbapenems are often considered last-resort antibiotics. Our findings are consistent with the growing trend of carbapenem resistance reported in

various studies across India. For instance, Datta et al. (2012) reported carbapenem resistance rates of 14.9% in Enterobacteriaceae isolates from a tertiary care center in North India.

The analysis of resistance mechanisms (Table 5) provides insight into the biochemical pathways underlying the observed resistance patterns. ESBL production was the most common mechanism among E. coli (60%) and K. pneumoniae (70%) isolates. These rates are higher than those reported by Nasa et al. (2012) in their study on nosocomial infections in an intensive care unit in North India, where they found ESBL production in 55% of Gram-negative isolates. The high prevalence of ESBL-producing strains in our study is a significant concern, as it limits treatment options and is associated with poorer clinical outcomes. Livermore et al. (2007) highlighted the global spread of ESBL-producing Enterobacteriaceae and emphasized the need for improved detection methods and antibiotic stewardship programs to combat this threat.

Carbapenemase production was observed in 10% of E. coli, 20% of K. pneumoniae, and 30% of P. aeruginosa isolates. These rates are consistent with the increasing trend of carbapenemase-producing organisms in India. Gupta et al. (2011) reported the emergence of NDM-1 producing Enterobacteriaceae in North India, underscoring the rapid spread of this resistance mechanism. The high prevalence of efflux pump overexpression, particularly in P. aeruginosa (70%) and K. pneumoniae (50%), is noteworthy. Efflux pumps contribute to multidrug resistance by actively expelling antibiotics from bacterial cells. Poole et al. (2005) reviewed the role of efflux pumps in antibiotic resistance and highlighted their significance in P. aeruginosa, which aligns with our findings.

The molecular characterization of resistance genes (Table 6) provides a comprehensive picture of the genetic determinants underlying the observed resistance phenotypes. Among the β-lactamase genes, blaTEM was highly prevalent in both E. coli (60%) and K. pneumoniae (60%), followed by blaCTX-M (50% in both species). These findings are consistent with the study by Ensor et al. (2009), who reported a high prevalence of blaTEM and blaCTX-M genes among ESBL-producing Enterobacteriaceae in India. The presence of carbapenemase genes, particularly blaNDM-1 in 10% of E. coli and 20% of K. pneumoniae isolates, is alarming. Kumarasamy et al. (2010) first reported the emergence of NDM-1 producing Enterobacteriaceae in India and highlighted its potential for rapid spread. Our findings suggest that this resistance mechanism has become established in our setting.

The detection of plasmid-mediated quinolone resistance genes (qnrA, qnrB, qnrS) in a significant proportion of E. coli and K. pneumoniae isolates is concerning. Robicsek et al. (2006) described the emergence of these genes and their role in conferring low-level quinolone resistance, which can facilitate the selection of high-level resistance mutations. The presence of mecA in 40% of S. aureus isolates corresponds with the phenotypic MRSA rates observed in our study. This gene, encoding a modified penicillin-binding protein (PBP2a), is the primary determinant of methicillin resistance in S. aureus. Our findings are in line with those of Nadig et al. (2012), who reported similar mecA prevalence rates among MRSA isolates in a tertiary care hospital in South India.

The association between antibiotic resistance and clinical outcomes (Table 7) demonstrates the significant impact of resistant infections on patient care. Patients with resistant isolates had a longer mean length of stay (12.5 days vs. 7.3 days), higher rates of ICU admission (30% vs. 10%), and increased 30-day mortality (12% vs. 4%) compared to those with susceptible isolates. These findings are consistent with previous studies that have linked antibiotic resistance to poorer clinical outcomes. For instance, Schwaber et al. (2006) conducted a meta-analysis on the clinical and economic impact of antimicrobial resistance and found that infections caused by ESBL-producing bacteria were associated with increased mortality, longer hospital stays, and higher healthcare costs. Similarly, de Kraker et al. (2011) reported increased mortality and prolonged hospital stays associated with

methicillin-resistant S. aureus and third-generation cephalosporin-resistant E. coli bloodstream infections in Europe.

The increased length of stay and higher ICU admission rates observed in our study for patients with resistant infections have significant implications for healthcare costs and resource utilization. Cosgrove et al. (2005) demonstrated that MRSA infections were associated with nearly twice the length of hospital stay and cost compared to methicillin-susceptible S. aureus infections. The higher mortality rate observed in patients with resistant infections (12% vs. 4%) underscores the critical need for effective antibiotic therapies and infection control measures. This finding aligns with the study by Kumar et al. (2006), who reported that inappropriate initial antimicrobial therapy was associated with a fivefold higher 28-day mortality in patients with septic shock.

The high prevalence of antibiotic resistance observed in our study highlights the urgent need for comprehensive antibiotic stewardship programs in tertiary care settings. Such programs should focus on: Optimizing antibiotic prescribing practices through the implementation of evidence-based guidelines and regular audits. Enhancing diagnostic capabilities to ensure rapid and accurate identification of pathogens and their resistance profiles. Promoting the judicious use of broad-spectrum antibiotics and encouraging de-escalation of therapy when appropriate. Implementing effective infection control measures to prevent the spread of resistant organisms within healthcare facilities. Friedman et al. (2008) demonstrated that implementation of an antibiotic stewardship program in a university hospital led to a significant reduction in antibiotic use and resistance rates over a three-year period. Similarly, Carling et al. (2003) showed that a multifaceted intervention program could effectively reduce the incidence of antibiotic-resistant infections in intensive care units.

Conclusion:

Our study reveals a high prevalence of antibiotic resistance among bacterial isolates in a tertiary care hospital in Southern Rajasthan, with significant implications for patient outcomes. The predominance of ESBL production and the emergence of carbapenemase-producing organisms underscore the need for targeted interventions and judicious use of antibiotics. The genetic characterization of resistance determinants provides valuable insights into the molecular epidemiology of resistant strains in our setting. These findings contribute to the growing body of evidence on antibiotic resistance in India and emphasize the importance of local and national efforts to address this critical public health challenge. Future studies should focus on longitudinal surveillance of resistance trends, assessment of the impact of intervention strategies, and exploration of novel therapeutic approaches to combat multidrug-resistant infections.

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