

ORIGINAL ARTICLE

THE GROWING THREAT OF CARBAPENEM AND CEPHALOSPORIN RESISTANCE: ANTIMICROBIAL RESISTANCE PATTERNS OF WHO PRIORITY PATHOGENS IN A TERTIARY CARE SETTING

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Background: Antimicrobial resistance is an increasing global health issue with increased resistance to carbapenems and cephalosporins among WHO priority pathogens, particularly in low- and middle-income countries like Pakistan. The current study aimed to analyze the prevalence and resistance patterns of selected WHO Priority Pathogens at Saidu Teaching Hospital, SWAT, Pakistan. **Methods:** This was a cross-sectional study that reviewed 585 clinical specimens collected between January and December 2023 with antibiotic susceptibility test performed. The data was analyzed using SPSS v23.0. **Results:** The findings showed a high prevalence of MDR organisms. Among gram negative organisms, *Acinetobacter* spp. exhibited 72% resistance to carbapenems and 89% to cephalosporins, while *Klebsiella* spp. showed 92% cephalosporin resistance. *Escherichia coli* and *Pseudomonas aeruginosa* also demonstrated significant resistance to fluoroquinolones and β -lactams. Among Gram-positive pathogens, methicillin-resistant *Staphylococcus aureus* (MRSA) displayed 100% resistance to carbapenems and 81% to fluoroquinolones. High levels of cephalosporin and fluoroquinolone resistance were also observed in *Salmonella* Typhi, raising concerns about treatment efficacy. These alarming resistance patterns emphasize the urgent need for antimicrobial stewardship programs, strict infection control measures, and continuous surveillance. **Conclusion:** The study underscores the necessity of localized antibiograms to guide empirical treatment and reduce inappropriate antibiotic use. Future research should focus on molecular characterization and multicentre studies to develop targeted interventions against AMR in hospital settings.

Keywords: Antimicrobial resistance; WHO priority pathogens; Carbapenem resistance; Cephalosporin resistance; Pakistan; Hospital surveillance

Citation: Ali I, Mufti S, Taj N, Ashfaq M, Sharif MJH, Khan Q, Abid SMA. The growing threat of carbapenem and cephalosporin resistance: antimicrobial resistance patterns of who priority pathogens in a tertiary care setting. J Ayub Med Coll Abbottabad 2025;37(1):92-97.

DOI: 10.55519/JAMC-14380

INTRODUCTION

Antimicrobial resistance (AMR) is progressively perceived as a significant general wellbeing concern.¹⁻⁴ The prevalence of AMR bacteria in various hospital wards has been rising at an alarming rate.^{5,6} According to a published study, approximately 700,000 deaths are attributed to AMR annually, and projections suggest that without effective preventive and control measures, AMR may emerge as a major cause of death for both hospitalized and non-hospitalized individuals in both advanced and developing nations.⁷ Ensuring the appropriate use and administration of antibiotics is critical for the effective treatment of infections.⁸

Antimicrobial resistance is a critical global challenge, particularly in low- and middle-income countries. With around 70% of antibiotic resistance in the region increasing, South Asia is regarded as a hotspot for antibiotic-resistant bacteria, posing dangers

on a regional and global scale.⁹ Pakistan, a developing country in South Asia, is notably affected by antibiotic resistance, which has occurred as a substantial concern at both regional and international levels.¹⁰ Both multi-drug-resistant (MDR) and extensively drug-resistant (XDR) bacteria have been discovered in Pakistan in recent years. For example, resistance to quinolones among Enterobacteriaceae has increased over the past decade.¹¹ In 2016, an outbreak of XDR *Salmonella* demonstrated complete resistance to fluoroquinolones.¹² Similarly, a study on bloodstream infections reported that 93.7% of isolates were tolerant to third-generation cephalosporins.¹³ Mismanagement of antibiotics and inappropriate prescribing significantly contribute to the emergence of AMR pathogens, limiting therapeutic options, prolonging hospitalization, increasing treatment costs, and ultimately leading to higher mortality rates.^{14,15} The World Health Organization's global action plan on AMR give emphasis to the importance of

raising awareness through monitoring and research initiatives across different regions.¹⁶⁻¹⁸ Checking AMR is fundamental, offering a few advantages, including: 1) offering data on bacterial resistance rates, 2) guiding the selection of appropriate antibiotics to reduce AMR, 3) decreasing hospitalization rates and associated costs, and 4) reducing mortality rates.¹⁹

To support the Global Action Plan on Antimicrobial Resistance (AMR), the World Health Organization (WHO) has established a Priority Pathogens List (PPL) through a comprehensive consultative process. This ranking framework utilized a multi-criteria decision analysis (MCDA) approach to assess various factors, including disease mortality, transmissibility, treatment options, healthcare burden, and the potential for prevention in both healthcare and community settings.¹⁷ The PPL categorizes twelve families of drug-resistant bacteria into critical, high, and medium priority groups based on their resistance to selected antimicrobials. This classification aims to guide research and development efforts towards the creation of novel antimicrobials to address the most critical threats. Nonetheless, the PPL additionally underlines the pivotal job of disease avoidance and control measures and the wise utilization of anti-microbials.²⁰ This study investigates the patterns of AMR susceptibility for WHO-priority pathogens found in clinical isolates taken from patients admitted to Saidu Teaching Hospital in Swat, Khyber-Pakhtunkhwa, Pakistan, in 2023. In order to understand local priorities that can be applied to local policies and practices, this investigation compares AMR patterns in WHO priority pathogens found in a tertiary healthcare facility.

Table-1: Organisms included according to WHO PPL list

Critical Priority Organism	
Acinetobacter Spp	Carbapenem resistance
Burkholderia Cepacia	Cephalosporins resistance
Citrobacter Spp	
Coliform	
E.Coli	
Enterobacter Spp	
Klebsiella Spp	
Protease Spp	
Providencia Spp	
Pseudomonas aeruginosa	
Serratia Spp	
High Priority Organism	
Enterococcus spp	Fluoroquinolone resistance
MRSA Staph aureus	Vancomycin resistance
MSSA Staph aureus	
Salmonella Typhi	
Staphylococcus	
Medium Priority Organism	
Stenotrophomonas	Fluoroquinolone resistance

MATERIAL AND METHODS

A cross-sectional study was conducted on patients' clinical samples gathered between January 2023 and December 2023 at Saidu Teaching Hospital. A total of 585 different microbiological lab samples were gathered from various wards and were included in this study after obtaining ethical approval and hospital permission. Blood samples were collected utilizing Standard Culture Vials (BACTEC) while other samples were collected in sterile containers using standard microbiological procedures. The anti-microbial sensitivity was determined utilizing the Kirby-Bauer Plate Dispersion Technique and Stock Weakening Strategy. The antimicrobial susceptibility for gram negative bacilli (GNB) and gram positive bacilli (GPB) was assessed utilizing the accompanying anti-microbial plates: Trimethoprim/sulfamethoxazole (SXT); Meropenem (MEM); Ampicillin (AMP); Cefoperazone-sulbactam (SCF); Colistin (CT); Chloramphenicol (C); Azithromycin (AZM); Cefixime (CXM); Ciprofloxacin (CIP); Cefotaxime (CTX); Ceftriaxone (CRO); Nalidixic Acid (NA); Imipenem (IPM); Cefuroxime (CFX); Levofloxacin (LEV); Linezolid (LZD); Vancomycin(VA); Teicoplanin (TEC); Amikacin (AK); Gentamicin (CN); Cefoxitin (FOX); Nitrofurantoin (F); Fosfomycin (FOS); TZP Piperacillin-Tazobactam (TZP); Doxycycline (DO); Tobramycin (TOB); Norfloxacin (NOR); Cefepime (FEP); Amoxicillin-clavulanic acid (AMC); Ceftazidime (CAZ); Fucidic acid (FD); Penicillin (P); Aztreonam (ATM) and Moxifloxacin (MXF). The aftereffects of the exploration were archived as either susceptible (S), resistant (R) or intermediate (I). Patient data, including gender, age, specimen type, hospitalized ward, and antibiotic susceptibility profiles, were analyzed using SPSS software version 23.0 (SPSS Inc., Chicago, IL, USA). Data confidentiality was ensured.

RESULTS

A total of 585 positive culture specimens were collected from different departments and wards. The highest number of bacterial isolates was obtained from blood specimens (399/585) followed by urine samples (92/585) Table 2. *Salmonella typhi* was the most common organism isolated (199), followed by Extended-Spectrum β -Lactamases (ESBL) producing *E. coli* (110). The greatest number of organisms were isolated from OPD samples (137) followed by samples from Paediatrics (134) and NICU (118) departments.

Among the main WHO PPL organisms identified, *Acinetobacter* demonstrated high resistance across carbapenems (72%) and cephalosporins (89%). *E. coli* displayed moderate resistance to carbapenems (34%) but high resistance to cephalosporins and fluoroquinolones (both 78%). *Klebsiella spp* was

notably resistant to cephalosporins (92%) and fluoroquinolones (72%), with carbapenem resistance recorded at 60%. *Pseudomonas aeruginosa* exhibited moderate carbapenem resistance (48%) and high resistance to cephalosporins (81%) and fluoroquinolones (69%). *Enterococcus* spp showed complete resistance to cephalosporins (100%) and fluoroquinolones (100%). MRSA exhibited total resistance to carbapenems (100%), high resistance to cephalosporins (77%) and fluoroquinolones (81%), but relatively low vancomycin resistance (20%). *Salmonella* Typhi demonstrated extremely high resistance to cephalosporins (92%) and fluoroquinolones (93%), while resistance to carbapenems remained low (6%) Table 3. Time pattern examination of chosen WHO 'Basic need' microorganisms over the course of the year showed a high extent of resistance for carbapenem in *Acinetobacter*, *Burkholderia cepacia* and *Klebsiella*

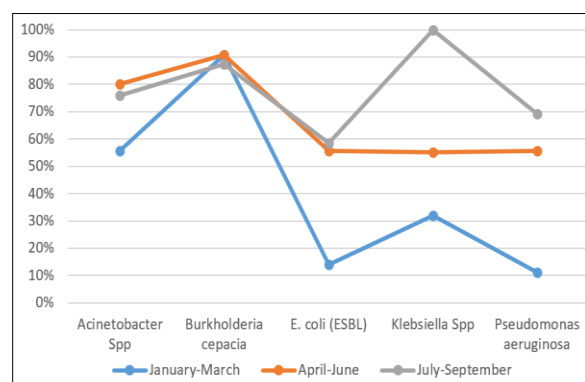
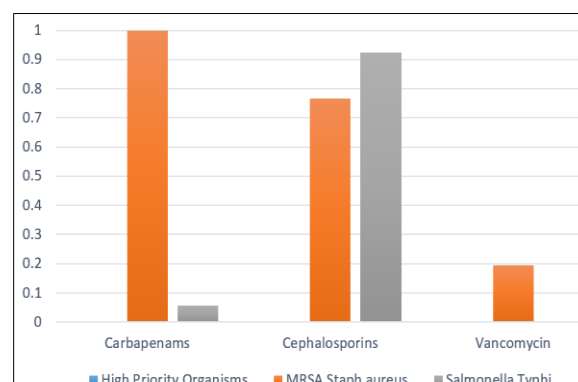
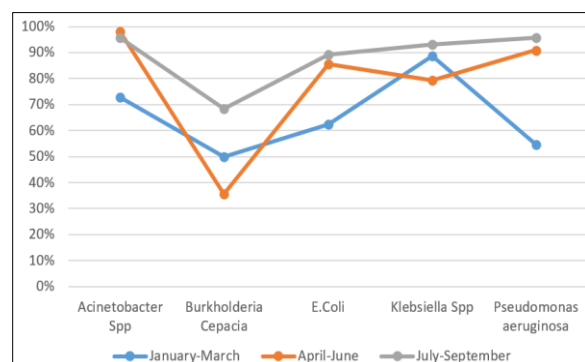
whereas, resistance in *Pseudomonas aeruginosa* was seen as low (Fig. 1). Likewise, *E. coli* and *Klebsiella pneumoniae* continued to exhibit a high extent of ESBL production (Fig. 2). Among the WHO 'High need' microbes, *Staphylococcus aureus* kept on showing a high degree of carbapenem resistance while *Salmonella* Typhi showed high resistance to Cephalosporins. Vancomycin resistance among methicillin-resistance isolates was found to be low (Fig. 3). Three of the WHO's "High priority" microbes *Campylobacter* spp. (resistant to fluoroquinolones), *Helicobacter pylori* (resistant to clarithromycin), and *Neisseria gonorrhoeae* (resistant to cephalosporins and fluoroquinolones) were not found, and antimicrobial sensitivity data was not available. *Haemophilus influenzae* (WHO's Medium Priority Organism), was not identified in this examination and its antimicrobial sensitivity data was additionally inaccessible.

Table-2: The WHO Pathogen Priority List organisms segregated in the study site by sampling type and ward from January 2023 to September 2023.

Organism	N (Female/Male) Percentage	Clinical Samples (N)	Ward Wise distribution (N)
Critical Priority Organism			
<i>Acinetobacter Spp</i>	49 (24/25) 49-51 %	Blood (39) Fluid (1) MSA (1) Pus (4) Sputum (1) Urine (3)	Gynae (1) Medical (5) NICU (19) OPD (12) PEADS (7) PEADS OPD (2) Surgical (3)
<i>Burkholderia Cepacia</i>	89 (48/41) 53.9-46.1%	Blood (88) Pus (1)	Medical (2) NICU (65) OPD (5) PEADS (14) PEADS OPD (1) PEADS Surgery (1) Surgical (1)
<i>Citrobacter Spp</i>	5 (2/3) 40-60%	Blood (5)	NICU (4) OPD (1)
<i>Coliform</i>	9 (7/2) 77.8-22.2%	Blood (2) Urine (7)	Medical (3) Nephrology (1) OPD (4) Urology (1)
<i>E.Coli</i>	110 (76/34) 69.1-30.9%	Blood (16) Pus (28) Urine (66)	Casualty (1) Gastro (1) Gynae (1) Medical (24) Nephrology (2) NICU (2) OPD (36) PEADS (14) PEADS OPD (3) PEADS Surgery (3) Surgical (20) Urology (3)
<i>Enterobacter Spp</i>	1 (1/0) 100%-0	Blood (1)	NICU (1)
<i>Klebsiella Spp</i>	56 (31/25) 55.4-44.6%	Blood (30) Pus (21) Urine (5)	Gastro (1) Gynae (1) Medical (5) NICU (19) OPD (9) PEADS (5) PEADS Surgery (2) Surgical (11) Urology (3)
<i>Protease Spp</i>	6 (4/2) 66.7-33.3%	Blood (1) Tissue (1) Urine (4)	Medical (1) Nephrology (1) OPD (1) PEADS (1) PEADS Surgery (1) Urology (1)
<i>Providencia Spp</i>	1 (1/0) 100%-0	Urine (1)	Medical (1)
<i>Pseudomonas aeruginosa</i>	24 (11/13) 45.8-54.2%	Blood (13) Pus (8) Urine (3)	Cardiology (1) Casualty (1) Ent (3) Medical (3) NICU (6) OPD (2) Orthopedic (1) PEADS (3) PEADS Surgery (2) Surgical (3)
<i>Serratia Spp</i>	2 (2/0) 100%-0	Blood (1) Pus (1)	OPD (1) Surgical (1)
High Priority Organism			
<i>Enterococcus spp</i>	4 (2/2) 50-50%	Blood (2) Urine (2)	PEADS (2) PEADS OPD (1) Surgical (1)
MRSA <i>Staph aureus</i>	21 (10/11) 47.6-52.4%	Fluid (2) Pus (17) Pus Ear (2)	Ent (4) Medical (3) OPD (5) PEADS (2) PEADS OPD (1) PEADS Surgery (3) Surgical (3)
MSSA <i>Staph aureus</i>	4 (3/1) 75-25%	Pus (2) Sputum (1) Urine (1)	Medical (1) OPD (2) PEADS (1)
<i>Salmonella Typhi</i>	199 (77/122) 38.7-61.3%	Blood (199)	Casualty (1) Medical (38) NICU (2) OPD (59) Orthopedic (1) PEADS (83) PEADS OPD (13) PEADS Surgery (1) Urology (1)
<i>Staphylococcus</i>	4 (1/3) 25-75%	Blood (1) Fluid (1) Pus (1) Sputum (1)	Medical (2) PEADS (1) PEADS OPD (1)
Medium Priority Organism			
<i>Stenotrophomonas</i>	1 (0/1) 0-100%	Blood (1)	PEADS (1)
Total	585 (300/285) 51.3-48.7%	Blood (399) Fluid (4) MSA (1) Pus (83) Pus Ear (2) Sputum (3) Tissue (1) Urine (92)	Cardiology (1) Casualty (3) Ent (7) Gastro (2) Gynae (3) Medical (88) Nephrology (4) NICU (118) OPD (137) Orthopedic (1) PEADS (134) PEADS OPD (22) PEADS Surgery (13) Surgical (43) Urology (9)

Table-3: Selected AMR organisms isolated according to WHO PPL (Jan 2023 - Dec 2023).

	Carbapenems		Cephalosporins		Vancomycin		Fluoroquinolones	
	Resistant/ Tested (n)	Resistant (%)	Resistant/ Tested (n)	Resistant (%)	Resistant/ Tested (n)	Resistant (%)	Resistant/ Tested (n)	Resistant (%)
Critical Priority Organisms								
<i>Acinetobacter Spp</i>	48/67	72%	128/144	89%	-	-	40/68	59%
<i>Burkholderia Cepacia</i>	80/123	65%	64/125	51%	-	-	3/89	3%
<i>Citrobacter Spp</i>	5/7	71%	16/16	100%	-	-	4/7	57%
<i>Coliform</i>	3/9	33%	17/24	71%	-	-	10/15	67%
<i>E. Coli</i>	47/139	34%	245/314	78%	-	-	115/147	78%
<i>Enterobacter Spp</i>	0/2	0%	4/5	80%	-	-	0/1	0%
<i>Klebsiella Spp</i>	39/65	60%	146/159	92%	-	-	54/75	72%
<i>Protease Spp</i>	4/10	40%	16/19	84%	-	-	6/7	86%
<i>Providencia Spp</i>	0/2	0%	1/2	50%	-	-	2/2	100%
<i>Pseudomonas aeruginosa</i>	15/31	48%	55/68	81%	-	-	24/35	69%
<i>Serratia Spp</i>	0/3	0%	3/4	75%	-	-	1/2	50%
High Priority Organisms								
<i>Enterococcus spp</i>	2/4	50%	8/8	100%	0/4	0%	3/3	100%
<i>MRSA Staph aureus</i>	4/4	100%	23/30	77%	8/41	20%	29/36	81%
<i>MSSA Staph aureus</i>	0/0	0%	0/2	0%	1/7	14%	10/12	83%
<i>Staphylococcus</i>	0/0	0%	1/3	33%	0/8	0%	6/7	86%
<i>Salmonella Typhi</i>	12/212	6%	651/704	92%	0/0	0%	351/379	93%
Medium Priority Organisms								
<i>Stenotrophomonas</i>	0/0	0%	2/3	67%	0/0	0%	0/1	0%

**Figure-1: Carbapenem resistance patterns among selected WHO Critical Priority Pathogens****Figure-3: Resistance trends among selected WHO High Priority Pathogens****Figure-2: Third generation cephalosporin-resistant trends (due to extended-spectrum beta lactamases (ESBL)) among selected WHO Critical Priority Pathogens.**

DISCUSSION

The findings of this study highlight the growing threat of antimicrobial resistance (AMR) among WHO priority pathogens in a tertiary care hospitals. The high resistance rates observed among Gram-negative and Gram-positive bacteria underscore the urgent need for enhanced infection control measures, antimicrobial stewardship programs, and continuous surveillance to mitigate the risk of treatment failures.

The resistance profile of *Escherichia coli* and *Klebsiella pneumoniae* in this study aligns with global trends, particularly the high resistance to third-generation cephalosporins and carbapenems.²¹ This suggests an increasing prevalence of ESBL and carbapenemase-producing strains, limiting therapeutic options. The widespread resistance to fluoroquinolones further complicates empirical therapy choices, necessitating the need for localized

antibiograms to guide appropriate prescribing practices.²²

The emergence of carbapenem-resistant *Acinetobacter baumannii* is particularly concerning, as it is associated with high morbidity and mortality rates.²³ The findings corroborate prior research that reports *A. baumannii* as a predominant cause of healthcare-associated infections (HAIs), resistant to multiple antibiotic classes, including polymyxins, which are often considered the last resort.²⁴ The increasing resistance observed in *Pseudomonas aeruginosa* also warrants attention, particularly resistance to aminoglycosides and cephalosporins, further narrowing available treatment options.²⁵

Among Gram-positive pathogens, the prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) remains a significant challenge. Our study observed high resistance rates to beta-lactams and fluoroquinolones, consistent with reports from similar healthcare settings.²⁶ The resistance of *Enterococcus faecium* to vancomycin, a critical concern globally, was also noted in our study, reflecting the ongoing rise in vancomycin-resistant enterococci (VRE) infections.²⁷

The study emphasizes the need for stringent antimicrobial stewardship initiatives to optimize antibiotic use, minimize selective pressure, and reduce the emergence of resistant strains. Implementing infection prevention strategies such as hand hygiene, patient isolation, and decontamination protocols can significantly curb the transmission of multidrug-resistant organisms (MDROs) in hospital settings.¹⁸ Furthermore, periodic resistance surveillance is essential to monitor evolving resistance patterns and adapt empirical treatment guidelines accordingly.²⁸

Despite the strength of this study in providing current AMR trends within a tertiary care hospital, limitations include its single-center design, which may not be generalized to other healthcare settings. Additionally, molecular characterization of resistance mechanisms was not performed, which could have provided deeper insights into the genetic basis of observed resistance patterns. Future research should focus on large-scale multicenter studies and genomic analyses to better understand AMR dynamics and inform public health interventions.

CONCLUSION

The findings of this study underscore the alarming rise of antimicrobial resistance (AMR) among WHO priority pathogens, posing a significant threat to effective treatment in a tertiary care hospital setting. The high prevalence of resistance among both Gram-negative and Gram-positive bacteria, particularly in *E. coli*, *K. pneumoniae*, *A. baumannii*, *P. aeruginosa*,

MRSA, and VRE, highlights the urgent need for comprehensive antimicrobial stewardship programs, robust infection control measures, and continuous surveillance. The growing resistance to critical antibiotic classes, including carbapenems, cephalosporins, and fluoroquinolones, reinforces the necessity for localized antibiograms to guide empirical therapy and reduce inappropriate antibiotic use. While this study provides valuable insights into current resistance trends, its single-center design limits broader applicability, and the absence of molecular characterization leaves gaps in understanding the genetic drivers of resistance. Future research should focus on multicenter studies and genomic analyses to better characterize resistance mechanisms and inform targeted public health strategies. Strengthening hospital-based infection control policies and integrating AMR surveillance into national healthcare frameworks remain crucial steps in mitigating the spread of multidrug-resistant organisms and preserving the efficacy of existing antimicrobials.

AUTHORS' CONTRIBUTION

IA, SM, NT: Concept, literature search, write-up, proof reading. MA, MJHS, QK, SMAA: Data collection data analysis, data interpretation, review.

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Submitted: September 11, 2024

Revised: November 22, 2024

Accepted: December 27, 2024

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