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:** A cross-sectional study of 585 clinical specimens were done from Jan 2023 to Sept 2023 with antibiotic susceptibility test performed and data 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 multicenter studies to develop targeted interventions against AMR in hospital settings.

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

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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	
Provendcia 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 September 2023 at Saidu showing Smack emergency clinic. A total of 585 different microbiological lab samples were gathered from various wards and utilized for research reason. Samples were gathered utilizing Standard Culture Vials (BACTEC) and investigated by clinic principles.

The anti-toxin opposition was resolved utilizing the Kirby-Bauer Plate Dispersion Technique and Stock Weakening Strategy. The antimicrobial powerlessness for GNB and Gram-positive microbes (GPB) was resolved 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).

RESULTS

A total of 585 positive culture specimens were collected from different departments and wards. The larger number of bacterial isolations was accompanied by blood specimens (399/585) ensued by urine (92/585) Table 2. *Salmonella typhi* was the most common organism isolated (199), ensued by E. coli ESBL (110). The most isolated organisms were from OPD (137) followed by PEADS (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

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 obstruction for carbapenem in *Acinetobacter*, *Burkholderia cepacia* and *Klebsiella* whereas opposition in *Pseudomonas aeruginosa* was seen as low (Fig. 1). Likewise, *E. coli* and *Klebsiella pneumoniae* kept on showing a high extent of ESBL (Fig. 2).

Among the WHO 'High need' microbes, Staph. Aureus kept on showing a high extent of carbapenem resistance while *Salmonella typhi* showed high resistance from Cephalosporins. Low methicillin-resistance was seen against vancomycin (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			
Acinetobacter Spp	49 (24/25) 49-51 %	Blood (39) Fluid (1) MSWA (1) Pus (4) Sputum (1) Urine (3)	Gynae (1) Medical (5) NICU (19) OPD (12) PEADS (7) PEADS OPD (2) Surgical (3)
Burkholderia Cepacia	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)
Citrobacter Spp	5 (2/3) 40-60%	Blood (5)	NICU (4) OPD (1)
Coliform	9 (7/2) 77.8-22.2%	Blood (2) Urine (7)	Medical (3) Nephrology (1) OPD (4) Urology (1)
E.Coli	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)
Enterobacter Spp	1 (1/0) 100%-0	Blood (1)	NICU (1)
Klebsiella Spp	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)
Protease Spp	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)
Provendcia Spp	1 (1/0) 100%-0	Urine (1)	Medical (1)
Pseudomonas aeruginosa	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 () PEADS (3) PEADS Surgery (2) Surgical (3)
Serratia Spp	2 (2/0) 100%-0	Blood (1) Pus (1)	OPD (1) Surgical (1)
High Priority Organism			
Enterococcus spp	4 (2/2) 50-50%	Blood (2) Urine (2)	PEADS (2) PEADS OPD (1) Surgical (1)
MRSA *Staph aureus*	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 *Staph aureus*	4 (3/1) 75-25%	Pus (2) Sputum (1) Urine (1)	Medical (1) OPD (2) PEADS (1)
Salmonella Typhi	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)
Staphylococcus	4 (1/3) 25-75%	Blood (1) Fluid (1) Pus (1) Sputum (1)	Medical (2) PEADS (1) PEADS OPD (1)
Medium Priority Organism			
Stenotrophomonas	1 (0/1) 0-100%	Blood (1)	PEADS (1)
Total	585 (300/285) 51.3-48.7%	Blood (399) Fluid (4) MSWA (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								
Acinetobacter Spp	48/67	72%	128/144	89%	-	-	40/68	59%
Burkholderia Cepacia	80/123	65%	64/125	51%	-	-	3/89	3%
Citrobacter Spp	5/7	71%	16/16	100%	-	-	4/7	57%
Coliform	3/9	33%	17/24	71%	-	-	10/15	67%
E.Coli	47/139	34%	245/314	78%	-	-	115/147	78%
Enterobacter Spp	0/2	0%	4/5	80%	-	-	0/1	0%
Klebsiella Spp	39/65	60%	146/159	92%	-	-	54/75	72%
Protease Spp	4/10	40%	16/19	84%	-	-	6/7	86%
Provendcia Spp	0/2	0%	1/2	50%	-	-	2/2	100%
Pseudomonas aeruginosa	15/31	48%	55/68	81%	-	-	24/35	69%
Serratia Spp	0/3	0%	3/4	75%	-	-	1/2	50%
High Priority Organisms								
Enterococcus spp	2/4	50%	8/8	100%	0/4	0%	3/3	100%
MRSA Staph aureus	4/4	100%	23/30	77%	8/41	20%	29/36	81%
MSSA Staph aureus	0/0	0%	0/2	0%	1/7	14%	10/12	83%
Staphylococcus	0/0	0%	1/3	33%	0/8	0%	6/7	86%
Salmonella Typhi	12/212	6%	651/704	92%	0/0	0%	351/379	93%
Medium Priority Organisms								
Stenotrophomonas	0/0	0%	2/3	67%	0/0	0%	0/1	0%

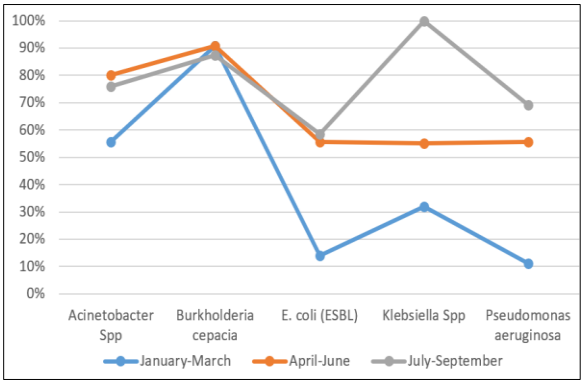

Figure-1: Carbapenem resistance patterns among selected WHO Critical Priority Pathogens

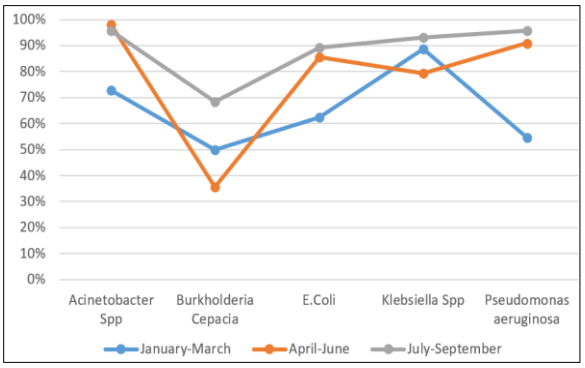

Figure-2: Third generation cephalosporin-resistant trends (due to extended-spectrum beta lactamases (ESBL) among selected WHO Critical Priority Pathogens.

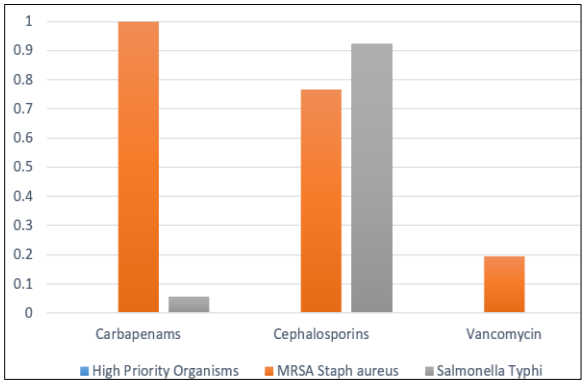

Figure-3: Resistance trends among selected WHO High Priority Pathogens

DISCUSSION

The findings of this study highlight the growing threat of antimicrobial resistance (AMR) among WHO priority pathogens in a tertiary care hospital. 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 extended-spectrum beta-lactamase (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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