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ANTIBIOTIC PRESCRIBING PRACTICES IN PEDIATRIC INTENSIVE CARE UNITS: A CROSS-SECTIONAL STUDY FROM ABBOTTABAD, PAKISTAN

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Abstract
The misuse of antibiotics is a global concern, with potential consequences including illness, death, and increased healthcare costs. Ensuring appropriate antibiotic use is crucial and should be integrated into pharmaceutical care plans. This study evaluated the prescribing trends of inappropriate antibiotic use among children under 12 years old in both public and private hospitals in District Abbottabad, Pakistan. The study conducted a prospective clinical assessment of antimicrobial drug utilization patterns using Patient Bedside Files (PBF) and Culture Sensitivity Test (CST) reports. Two key indicators were used to assess antibiotic prescribing: prescribed dose and indication for use. Antibiotic resistance was assessed for 25 selected antibiotics. Findings showed that in the private sector hospital, 75% of neonates, 14.5% of infants, and 10% of children in the ICU received antibiotics, but only 57% of neonates, 62% of infants, and 55.9% of children had valid indications. Additionally, 27% of neonates, 19% of infants, and 22.1% of children received under-dosed antibiotics, potentially contributing to antimicrobial resistance and increased hospitalization costs. Rational dosing was observed in only 29% of neonates, 30% of infants, and 36.8% of children. In public sector hospitals, antibiotics were administered to 65.6% of neonates, 19.4% of infants, and 15% of children, with valid indications found in 35% of neonates, 41% of infants, and 35% of children. The irrational use of antibiotics was high (over 50%) in the public sector hospital across all age groups, while in the private sector hospital, it was closer to 50%. The prescription rates of certain antibiotics exceeded 80% in both hospitals, with Amoxicillin, Penicillin, Erythromycin, and Cephalexin showing a higher resistance rate of 49.2%.

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INTRODUCTION

The increasing threat of antimicrobial resistance (AMR) poses a significant challenge to global health, food security, and economic development, despite notable advancements in medical science [1, 2]. In 2019, AMR was responsible for a substantial 4.95 million deaths worldwide, with 1.27 million of these deaths directly attributed to AMR [3, 4]. The burden of AMR-related mortality was disproportionately high in sub-Saharan Africa and South Asia [5]. In countries like Pakistan, the excessive use of antibiotics is a pressing concern that needs to be addressed urgently [6].

Neonates and pediatric populations are extremely susceptible to bacterial infections due to their immature physiological systems, heightened exposure to pathogens, and nascent immune responses [7, 8]. The escalating prevalence of antimicrobial resistance (AMR) in these vulnerable populations in Pakistan is a pressing concern [9, 10]. Studies have consistently reported high rates of antibiotic prescription in children, ranging from 50% to 85%, contributing to the alarming rise in AMR-related mortality, particularly among newborns [10-12]. The drivers of this phenomenon include the inappropriate and excessive use of antimicrobials, perpetuated by unnecessary prescriptions in healthcare settings, especially in low- and middle-income countries (LMICs) [13]. Despite significant advances in antimicrobial development, infectious diseases remain a major contributor to global morbidity and mortality, underscoring the need for judicious antibiotic stewardship and evidence-based treatment strategies [2, 14, 15].

Annually, the global community witnesses a substantial number of neonatal fatalities, with over 3 million deaths occurring within the early neonatal period, as reported by the World Health Organization (WHO) [16]. This alarming trend has spurred concerted efforts by the WHO, in conjunction with the International Network for the Rational Use of Drugs, to devise and implement strategies aimed at optimizing antibiotic utilization and mitigating the risks associated with antimicrobial resistance [17, 18]. These initiatives are crucial in addressing the pressing need to improve neonatal outcomes and reduce the burden of infectious diseases in this vulnerable population [19].

In 2018, the World Health Organization (WHO) launched a novel antimicrobial point prevalence survey (PPS) instrument designed to assess antimicrobial utilization patterns, with a focus on low- and middle-income countries (LMICs) [20]. Research employing point prevalence survey (PPS) methodologies has consistently demonstrated the reliability and efficacy of this approach in gathering baseline data on antibiotic prescribing practices among hospitalized patients within defined time intervals. These data can subsequently inform the development of targeted quality improvement initiatives aimed at optimizing antimicrobial stewardship [21, 22].

This investigation primarily sought to assess the prevalence and characteristics of inappropriate antibiotic prescribing practices among pediatric patients (≤12 years) in both public and private sector hospitals in Abbottabad, Pakistan, with a specific focus on critical care settings within tertiary care facilities. The study aimed to evaluate the prescribing patterns and determinants of irrational antibiotic use in this vulnerable population, in order to inform evidence-based interventions and optimize antimicrobial stewardship.

1. Material and methods

2.1 Research Design and Context

This prospective observational study was conducted at one private and one public sector hospital in District Abbottabad, Pakistan, over a six-month period (October 2023 to April 2024). The research employed a retrospective chart review methodology, whereby Patient Bedside Files (PBFs) of hospitalized patients were audited to assess antimicrobial drug utilization patterns. Furthermore, Culture Sensitivity Test (CST) reports were analyzed to determine the resistance profiles of a pre-defined list of commonly prescribed antibiotics, providing valuable insights into antimicrobial resistance trends in this setting.

1.3 Ethical approval

After receiving approval from the Ethics Review Committee (ERC) at Abbottabad University of Science and Technology, authorization was requested from the Medical Superintendents (MS) of both chosen hospitals to review Patient Bedside Files (PBF)

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and conduct In-depth Interviews (IDIs) with pertinent Physicians/Consultants concerning patients' antimicrobial therapy.

1.4 Data collection

The dataset collected for evaluating antibiotic prescription patterns encompassed a range of variables, including demographic characteristics, clinical diagnoses, and antibiotic prescription details. Furthermore, specific aspects of antibiotic use were documented, such as the class of antibiotic, route of administration, and duration of treatment. This comprehensive dataset enabled a thorough assessment of antibiotic prescribing practices and related factors.

2.5 Dose

Following a thorough evaluation, the antibiotic dosages were assessed and categorized into one of three groups: sub-therapeutic (underdose), appropriate (rational dose), or excessive (higher dose). This categorization was based on a comprehensive review of the literature, specifically referencing the Drug Index 2015, to ensure accuracy and consistency in dosage evaluation.

2.6 Indication

The appropriateness of antibiotic prescribing was evaluated by matching the antibiotics with the corresponding diagnosed infections. Prescriptions aligning with evidence-based guidelines, where the antibiotic was prescribed for the correct indication, were classified as "appropriate" or "valid". Conversely, prescriptions that did not align with guidelines, where the antibiotic was prescribed for an incorrect indication, were classified as "inappropriate" or "invalid". This assessment enabled the evaluation of antibiotic prescribing practices and their adherence to established standards.

2.7 Culture Sensitivity Test (CST)

The Culture Sensitivity Test (CST) reports were procured from the hospital's Pathology Laboratory. In instances where the test was not initially ordered or was financially inaccessible to the patient, the principal investigator facilitated arrangements for the CST to be conducted. This involved liaising with the relevant Physicians/Consultants to elucidate the rationale behind the initial omission of the test, followed by a request for the CST and notification of the Pathological Laboratory regarding the ongoing antibiotic therapy that the patient had already initiated. A total of 1206 CST reports from enrolled cases were subsequently reviewed, and the frequency and percentage of antibiotic resistance among the most commonly prescribed antibiotics in the recruited cases were systematically tabulated and analyzed.

2.8 Statistical analysis

Data was analyzed using SPSS version 20. Descriptive statistical tests were performed.

2. Result

This study enrolled 982 patients admitted to the Pediatric Intensive Care Unit (PICU) and Neonatal Intensive Care Unit (NICU) across both private and public sector hospitals. In the private hospital, 378 patients were recruited, with a breakdown of 75% neonates (n=283), 14.5% infants (n=55), and 10% children (n=40). Conversely, in the public hospital, 604 patients were enrolled, comprising 65.6% neonates (n=396), 19.4% infants (n=117), and 15% children (n=91), as depicted in Table 2. This demographic distribution highlights the diverse population under investigation.

The analysis revealed significant discrepancies in antibiotic dosing across different age groups in both private and public hospitals. In the private hospital, a substantial proportion of patients received higher-than-recommended doses, with 44% of neonates, 51% of infants, and 41% of children receiving excessive antibiotic doses. In contrast, the public hospital showed a different trend, with 27% of neonates, 19% of infants, and 22.1% of children receiving higher doses, while 33.3% of neonates, 26.6% of infants, and 28.7% of children received sub therapeutic doses (Table 3). These findings highlight the need for improved antibiotic stewardship across both healthcare settings.

The analysis revealed a notable disparity in antibiotic prescription patterns between public and private sector hospitals. In the public hospital, a significantly higher proportion of inappropriate antibiotic prescriptions were observed, with 65.0% of neonates, 64.4% of infants, and 60.2% of children admitted to

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the PICU/NICU receiving invalid prescriptions. In contrast, only 35.0% of neonates, 35.0% of infants, and 40.0% of children received antibiotics for valid indications. Conversely, in the private hospital, the prevalence of irrational prescribing was highest among children (44.1%), followed by neonates (42.7%) and infants (38%). However, a majority of patients in the private hospital received appropriate antibiotic prescriptions, with 57.3% of neonates, 62% of infants, and 55.9% of children receiving antibiotics for valid indications (Table 4). These findings highlight the need for improved antibiotic stewardship in both healthcare settings.

The antibiotic resistance profile revealed a noteworthy trend, with four antibiotics exhibiting elevated resistance rates. Specifically, Amoxicillin, Penicillin, Erythromycin, and Cephalexin demonstrated a high resistance prevalence of 49.2% (Table 5), indicating a reduced efficacy of these agents against bacterial infections. These finding warrants attention and necessitates the reconsideration of empirical antibiotic therapy in clinical practice.

This investigation revealed a high prescribing frequency for nine antibiotics in both hospitals, exceeding 80% (Table 6). The antibiotics with high utilization rates were Amikacin, Cefixime, Cefotaxime, Meropenem, Amoxicillin, Vancomycin, Azithromycin, Levofloxacin, and Clarithromycin. This finding suggests a widespread use of these antibiotics in clinical practice, highlighting the need for antibiotic stewardship initiatives to optimize their use and mitigate the risk of antimicrobial resistance.

3. Discussion

This study uncovered a concerning trend in antibiotic prescribing practices, with a higher prevalence of irrational dosing and invalid prescriptions in the public hospital compared to the private hospital (Tables 3 and 4). This disparity may be attributed to the overwhelmed healthcare workforce and diminished attention to proper prescribing practices in the public sector. Alarmingly, only 16% of antibiotic prescriptions for admitted children in public hospital ICUs adhered to rational dosing guidelines, whereas private hospitals demonstrated a higher adherence rate of 36.8% (Table 3) [23] . The excessive use of higher antibiotic doses may lead to adverse effects and unnecessary medication costs [24], while under dosing or irrational prescribing may contribute to the emergence of antimicrobial resistance [24, 25]. These findings underscore the urgent need for improved antibiotic stewardship and rigorous prescribing practices in both healthcare settings [26].

The aminoglycoside class of antibiotics, comprising erythromycin, Vancomycin, and Amikacin, was extensively utilized in both public and private hospitals, exceeding 80% usage [27, 28]. The World Health Organization (WHO) recommends aminoglycosides as empirical treatment for community-acquired neonatal sepsis [29, 30]. However, notable resistance patterns emerged, with erythromycin exhibiting 49.2% resistance, compared to Amikacin (5.6%) and Vancomycin (4.2%) [23, 31]. A concerning trend of increasing erythromycin resistance was reported in Taiwan, which subsequently decreased following reduced antibiotic usage [32]. The resistance rate to erythromycin significantly decreased from 53.1% (1998-2000) to 14.6% (2002-2004) and further to 10.7% (2006-2010) [33]. Moreover, the highest prevalence of erythromycin-resistant *Streptococcus pyogenes* was observed among children [34]. These findings underscore the need for judicious antibiotic use and continuous monitoring of resistance patterns to ensure effective treatment outcomes [17].

A strikingly high resistance rate of 49.2% was observed against penicillin, while Ampicillin, a semi-synthetic penicillin derivative with an additional amino acid modification [35], exhibited a median resistance of 15.5% . Notably, both antibiotics were frequently used in both hospitals, with a usage rate ranging from 40% to 60%. The elevated resistance to penicillin and moderate resistance to Ampicillin highlight the need for prudent antibiotic use and continuous monitoring of resistance patterns to ensure effective treatment outcomes [36, 37].

The cephalosporin class of antibiotics was prominently represented in pediatric prescriptions in both hospitals, accounting for over 80% of prescribed antibiotics (Table 6). Cephalosporins are widely recommended as first-line agents for various community-acquired infections [38, 39]. Notably, Cefixime, a third-generation cephalosporin, exhibited a relatively lower resistance rate of 12.7%, compared to Cephalexin, a first-generation cephalosporin,

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which showed a significantly higher resistance rate of 49.2% (Table 5 and 6). These findings suggest a potential shift in susceptibility patterns among cephalosporins, emphasizing the need for ongoing monitoring and rational antibiotic use in pediatric populations [40, 41].

Amoxicillin, a widely prescribed antibiotic, exhibited a notable resistance rate of 49.2% in both hospitals [42, 43]. The prescribing pattern of amoxicillin varied by age group and hospital. In Private hospitals, more than 80% of infants and 60-80% of neonates and children received amoxicillin, whereas in public hospital, over 80% of children were prescribed amoxicillin (Table 5 and 6). These findings highlight the extensive use of amoxicillin across different age groups and healthcare settings, which may contribute to the observed high resistance rates [44, 45].

Meropenem, a carbapenem antibiotic, exhibited an alarming resistance rate of 19.7%, indicating a concerning trend towards reduced susceptibility [46]. Notably, meropenem was extensively prescribed in both hospital sectors, with over 80% of children receiving this antibiotic [47, 48]. The widespread use of meropenem, coupled with the emergence of resistance, highlights the need for vigilant monitoring and rational use of this critical antibiotic to mitigate the risk of further resistance development [49, 50].

In Pakistan, a significant proportion of the population (over 58.7 million individuals) lives below the poverty line, with a daily income of less than $1.25 [51, 52]. This socio-economic context renders the additional expense of unnecessary medications a substantial supplementary burden on the healthcare system, exacerbating the economic hardship faced by the Pakistani population [53, 54]. The financial implications of inappropriate medication use are particularly concerning in resource-constrained settings, highlighting the need for prudent prescribing practices and effective drug use strategies [55, 56].

Globally, approximately nine million children under the age of five succumb to mortality annually, with pneumonia, diarrhea, and other prevalent diseases being prominent contributors [57]. While these conditions can be effectively managed with appropriate antibiotics, the irrational use of these lifesaving drugs has led to a surge in adverse drug reactions and the emergence of drug-resistant pathogens, rendering treatment challenging [58, 59]. Therefore, it is imperative to promote judicious antibiotic use, particularly in pediatric populations, to ensure safe and effective drug utilization and mitigate the risk of drug resistance [60].

Conclusion

This study of 982 patients in pediatric intensive care units across private and public hospitals in Pakistan revealed significant disparities in antibiotic dosing and prescription patterns, highlighting the need for improved antibiotic stewardship in both healthcare settings. Suboptimal dosing and inappropriate antibiotic prescriptions were prevalent, with a higher proportion of patients receiving excessive doses in private hospitals and sub-therapeutic doses in public hospitals. Furthermore, a notable disparity in antibiotic prescription patterns was observed between public and private sector hospitals, with a significantly higher proportion of inappropriate antibiotic prescriptions in public hospitals. The analysis also revealed a high resistance prevalence of 49.2% for four antibiotics (Amoxicillin, Penicillin, Erythromycin, and Cephalexin), indicating reduced efficacy against bacterial infections. The widespread use of antibiotics in clinical practice, exceeding 80% for nine antibiotics, emphasizes the need for antibiotic stewardship initiatives to optimize their use and mitigate the risk of antimicrobial resistance. Overall, the study's findings emphasize the importance of promoting judicious antibiotic use, particularly in pediatric populations, to ensure safe and effective drug utilization and reduce the risk of drug resistance.

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Table 1: Demographic Characteristic of Recruited Patients

Hospitals	Neonates		Infants		Child		
	Count	Percentage	Count	Percentage	Count	Percentage	Total
Private	285	75%	55	14.5%	38	10%	378
Public	395	65.6%	117	20%	93	15.4%	604

Table 2: Prescribing Doses of Antibiotic

Hospitals	Neonates			Infants			Child		
	U-Dose N (%)	H-Dose N (%)	R-Dose N (%)	U-Dose N (%)	H-Dose N (%)	R-Dose N (%)	U-Dose N(%)	H-Dose N (%)	R-Dose N (%)
Private	83(27.0%)	128(44%)	85(29.0%)	9(19.0%)	24(51.0%)	15(30.0%)	8(22.1%)	14(41.0%)	13(36.8%)
Public	132(33.3%)	201(51.0%)	62(16.0%)	30 (26%)	69(59.0%)	17(14.7%)	23(29.0%)	48(56.2%)	15(16.0%)

Alphabets; U, H, and R stand for Under, Higher, and Rational respectively.

Table 3: Assessment of Antibiotic Prescribing practice

Hospitals	Neonates		Infants		Child	
	Valid N%	Invalid N%	Valid N%	Invalid N%	Valid N%	Invalid N%
Private	165 (57%)	125 (42.7%)	31(62.0%)	19(38.0%)	18(55.9%)	15(44.1%)

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Public	139(35.0%)	254(65.0%)	41(35.0%)	125(64.4%)	35(40.0%)	53(60.2%)

Number of participants (%)

Table 4: Frequency of resistant antibiotics among Culture sensitivity test report of In-Patients

Antibiotic	n	%	Antibiotic	n	%	Antibiotic	n	%	Antibiotic	n	%
Amikacin	24	5.6	Ceftazidine	24	5.6	Cloxacillin	180	42.2	Levofloxacin	138	32.4
Amoxicillin	210	49.2	Ceftriaxone	54	12.7	Co-Amoxiclave	138	32.4	Linezolid	18	4.2
Ampicillin	66	15.5	Cefuroxime	30	7.0	Co-Trimaxazole	144	33.8	Meropenem	84	19.7
Azithromycin	54	12.7	Cephalexin	210	49.2	Erythromycin	210	49.2	Ciprofloxacin	138	32.4
Cefixime	54	12.7	Cephradine	24	5.6	Gentamicin	138	32.4	Ofloxacin	174	40.8
Cefotaxime	42	9.8	Clarithromycin	102	23.9	Kanamycin	53	18.3	Penicillin	210	49.2

Table 5: Comparison of 25 Most Commonly Prescribed Antibiotics in Tertiary Care Teaching Hospitals

	Private Hospital					**Public Hospital**				
Age Group	Class I	Class II	Class III	Class IV	Class V	Class I	Class II	Class III	Class IV	Class V
Neonate	AMK CFX CFT MRP VAN CFN	AMX AZM CTX CFZ CFR CLT CLC ERT	AMP CPR GTM LVF PEN	LNZ CPL CAC	KMY OFL CIP	AMK AMX AZM CFX CFT CLT CTX MRP	CFR CPL CAC ERT OFL VAN CIP CFN	AMP CPR PEN	CFZ KMY GTM	CLC LNZ
Infant	AMX AMK CFX CFT MRP VAN	AZM CFZ CFR CPL CLT CLC	AMP CPR LVF PEN CTX LNZ	OFL CIP GTM	KMY	AMK AMX AZM CFX CFT CLT LVF	CFR CPL CAC ERT VAN CTX	AMP CPR PEN OFL CIP	CFZ KMY GTM	CLC LNZ

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	CFN	CAC					CFN			
Class-I	Antibiotics Being Prescribed in more than 80 % of Prescriptions									
Class-II	Antibiotics Being Prescribed in 60-80 % of Prescriptions									
Class-III	Antibiotics Being Prescribed in 40-60 % of Prescriptions									
Class-IV	Antibiotics Being Prescribed in 20-40 % of Prescriptions									
Class-V	Antibiotics Being Prescribed in less than 20 % of Prescriptions									