

Antimicrobial Resistance Pattern Amongst In-patients in a Tertiary Health Care Facility in Northern Nigeria

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ABSTRACT

Background: Antimicrobial resistance is one of the top 10 global health threats facing humanity. It causes an estimated annual death rate of 10 million, more than what is caused by cancer. Ascertaining the quality of drugs and ensuring rational prescribing can mitigate antimicrobial resistance and improve treatment outcomes in patients.

Objective: To establish the antimicrobial resistance pattern among in-patient at a tertiary health care institution in northern Nigeria and to determine the role of drug quality in combating antimicrobial resistance.

Method: Microbial culture sensitivity (MCS) results, drug quality control test results and drug stock availability data were collected using structured proforma from the department of microbiology, and pharmaceutical services (pharmacy bulk stores/chemistry and microbiology laboratories) respectively. The designed questionnaire was used to collect data on the antimicrobial prescribing habits of physicians.

Result: An analysis of the antimicrobial resistance pattern of 496 isolates showed the most resistance to ceftazidime, amoxicillin, ciprofloxacin and ceftriazone, with the least resistance to imipenem, amikacin, chloramphenicol and cefotaxime. The trend of resistance was organism dependent with the most resistant organisms being *Staphylococcus spp*, *Klebsiella spp*, and *Escherichia coli*. A total of 92.86% of antimicrobials passed the quality control tests. We observed a possible association between antimicrobial availability and development of resistance. There is no statistically significant association ($P>0.05$) between rank of physicians and their compliance with rational antimicrobial selection. A total of 74.5% of the physicians cited availability of antibiotics as a limiting factor for prescribing and 97.1% expressed willingness to prescribe antibiotics in line with MCS results if available. Most expressed quality and cost as factors considered in making a decision.

Conclusion: The quality and availability of antimicrobials may be predictive of the antimicrobial resistance pattern observed. Rational prescribing was largely influenced by the affordability and perceived quality of some brands of antimicrobials.

Key Words: Antimicrobial Resistance, Microbial Culture and Sensitivity, Quality tests, rational prescribing

INTRODUCTION

Antimicrobial resistance is considered a public health threats globally causing approximately 4.95 million deaths annually¹, with an estimated increase to 10 million deaths by 2050². According to the World Health Organization (WHO), antimicrobial resistance (AMR) is the ability of microorganisms to inhibit antimicrobials from working against them up to the point that the antimicrobials are no longer effective in inhibiting their growth or completely eradicating them³. The drugs normally effective in treating antimicrobial infections become less effective or completely ineffective, cumulating to the persistence and spread of antimicrobial resistant strains causing infections⁴.

There are different mechanisms by which microorganisms develop this resistance to antimicrobials, however, five main biochemical mechanisms have been elucidated⁵. These include enzymatic modification or destruction of the antibiotic; modification of the antibiotic target site; mimicking the antibiotic target with similar biochemical functions or overproduction of the antibiotic target; decreasing the antibiotic penetration; and elimination of the antibiotic from the cell by efflux pumps⁵.

Elsewhere, AMR is a growing cause of concern particularly with the limited array of antimicrobials available for the treatment of infections. The resistance of microorganisms can differ depending on the location of concern. Predominantly, in hospitals where the influx and use of antimicrobials is high and the infections being treated vary, the resistance pattern in this location is often diverse. In Tanzania a large number of gram-negative organisms isolated within a hospital facility are resistant to third generation cephalosporins⁶. This necessitates the need to constantly survey the resistance on a location-based approach in order to facilitate proper planning of antimicrobial purchase, prescribing, dispensing and utilization. The knowledge of the resistance pattern particularly in places where multidrug resistant isolates are known to be high like hospitals can further reduce the morbidity and mortality rates found in that region. According to a study conducted in Tanzania⁶, increased morbidity and mortality rates have been linked to multidrug resistant isolates.

Antibiotic susceptibility testing (AST) remains the standard diagnostic method for detecting bacterial resistance and guides clinicians in the appropriate and timely treatment of bacterial infections⁷. AST results are crucial for surveillance studies to generate epidemiological data on bacterial pathogens and associated AMR. According to WHO, AMR is one of the top 10 global health threats facing humanity⁸. By 2050, AMR is predicted to cause an estimated global cost of \$100 trillion and an annual death rate of 10 million, more than what can be caused by cancer². In Nigeria, this problem is aggravated by the substandard, counterfeit and fake antimicrobials which are below the stipulated official standard being peddled across the country⁹.

Sub-Saharan Africa has the highest rate of deaths attributed to AMR¹⁰. Furthermore, there are no known antibiotic use policies particularly in this facility and there is a huge vacuum in communication between all health practitioners involved in the management of infectious diseases, thus worsening the inability to properly manage infections. The pharmacist role in ensuring that only antimicrobials of certified quality are dispensed to patients can help minimize resistance and provide an edge in the war against antimicrobial resistance. Antibiotic resistance can be more prevalent where antibiotic consumption is found to be high such as this facility. Drug quality such as suboptimal dosing can greatly affect microbial resistance.

This study aims to evaluate the antimicrobial resistance pattern in ABUTH, Zaria and determine the role of drug quality and availability in combating antimicrobial resistance.

METHODS

Study Design and Instrument

A retrospective cross-sectional study using structured questionnaires was carried out at a tertiary health care institution in northern Nigeria. The data collection was for a period of six months. The antimicrobial resistance and sensitivity patterns of patients' microbial culture and sensitivity (MCS) tests were obtained from the record files available in the medical microbiology department over a period of six months. A total of 496 MCS data of organisms isolated from the

urine, blood and urogenital samples were specifically obtained. Antibiotics tested were amoxicillin, ceftriaxone, ceftazidime, azithromycin, meropenem, amikacin among others. Organisms used include *Pseudomonas spp*, *Staphylococcus aureus*, *Streptococcus aureus*, *E.coli*, *Klebsiella*, *Proteus spp* among others. The results were coded R for resistance and S for sensitivity.

The qualitative control data collection files available at the quality control unit of the pharmacy department were used. The pharmacopoeia standard and in-house analysis techniques were the metric used for analyzing the compliance of the drug samples to standard. The disintegration time, dissolution rate, pH, content uniformity, hardness and friability values were collected to ascertain the quality of a pharmaceutical product.

The stock history for six months of purchase of antibiotics was obtained from the monitoring section of the Pharmacy Bulk Store of the Department of pharmaceutical services.

Structured questionnaires were used to assess compliance by respondents on antibiotics selection and prescription. The respondents were recruited from nine clinical departments. The aim of the study was explained to the participants and verbal consent was obtained before the questionnaires were filled.

Ethical Consideration

Ethical approval was obtained from the Institutions Scientific and Health Research Ethics Committee before commencement of this study. The study was approved on the 17th October, 2022 by the Health Research Ethics Committee under the D-U-N-S Number 954524802. Verbal consent was obtained from each department and participant before the data collection was done.

Data Analysis

Statistical model was used to determine the associations between the respondent's demographic data and level of compliance to rational prescribing based on the MCS results. Compliance was considered significant at a level $p < 0.05$. Results are expressed as frequencies and presented as tables and charts.

RESULTS

The distribution of the samples collected from the microbiology laboratory for MCS from urogenital sample followed by urine and blood samples respectively (Figure 1). Similarly, the resistant strains across the various specimen showed dominance in urogenital samples, followed by urine samples and least was seen in blood samples. However, this was influenced by samples per specimen (Figure 2).

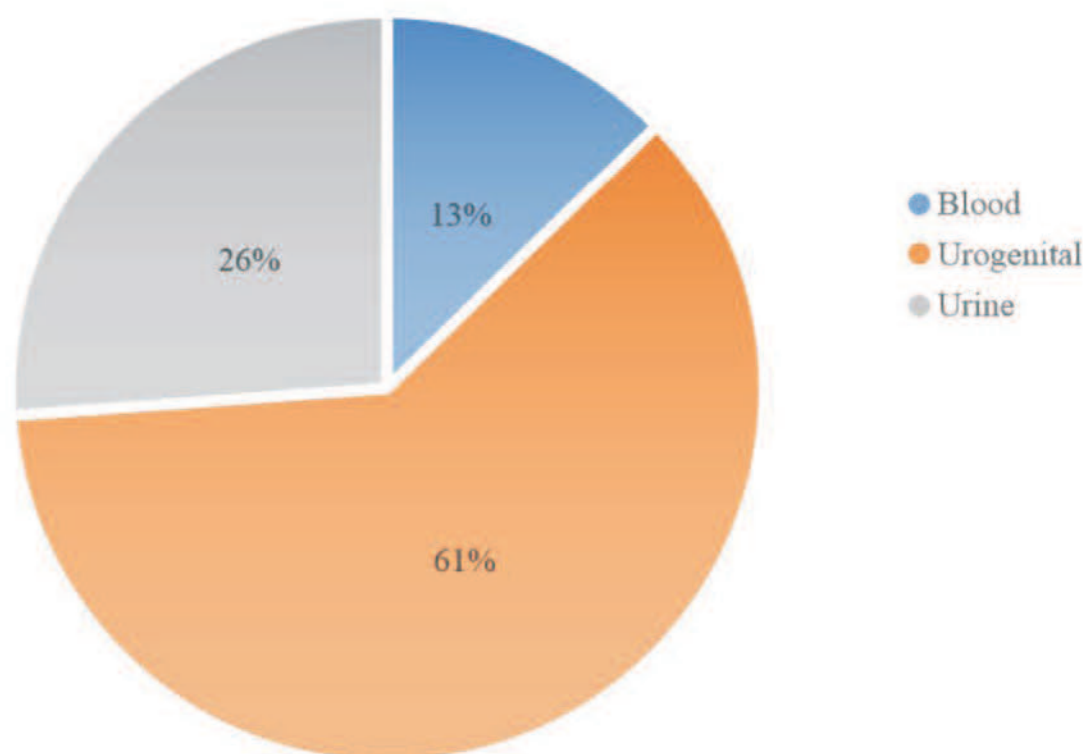


Figure 1. Sample Distribution of Specimens

Antimicrobial resistance pattern

The antimicrobial resistance patterns across all the samples showed organism related resistance to commonly used first line antimicrobials such as ceftazidime followed by ciprofloxacin and amoxicillin (Figure 3). The organisms were most

sensitive to nitrofurantoin, ampicillin, cefotaxime, chloramphenicol and amikacin. The most resistant organisms were *Staphylococcus spp*, *Escherichia coli*, *Klebsiela* and *Streptococcus.spp* (Table 2).

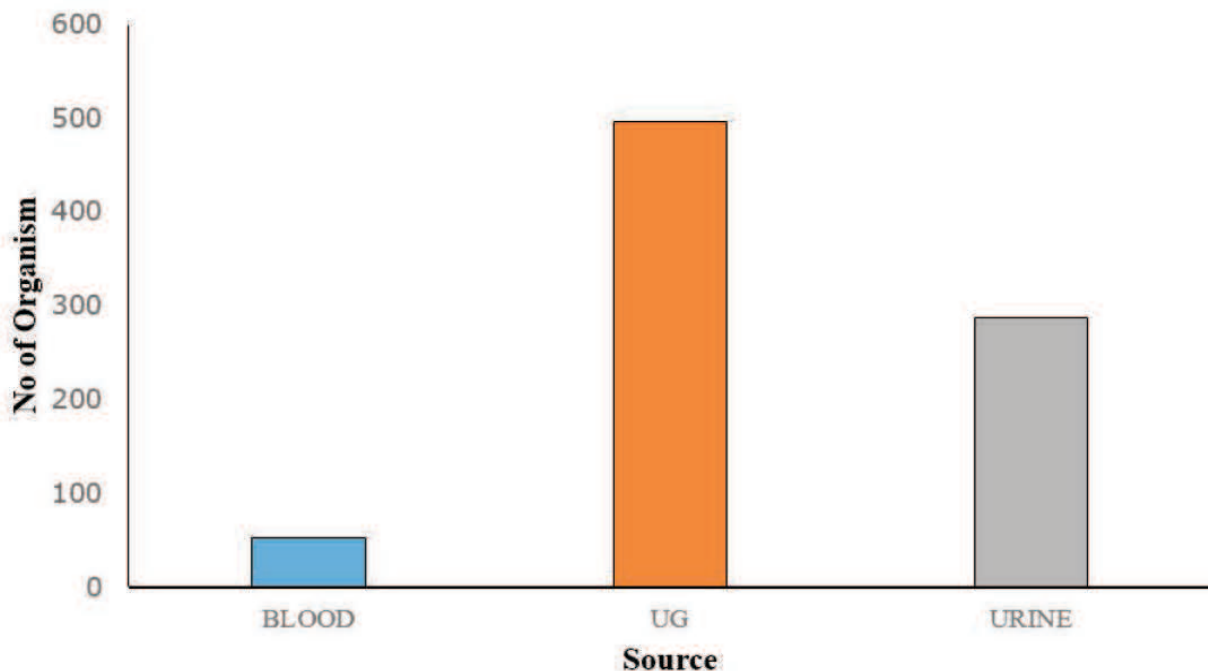


Figure 2: Number of Organisms Showing Resistance Based on Source

Key: UG (Urogenital)

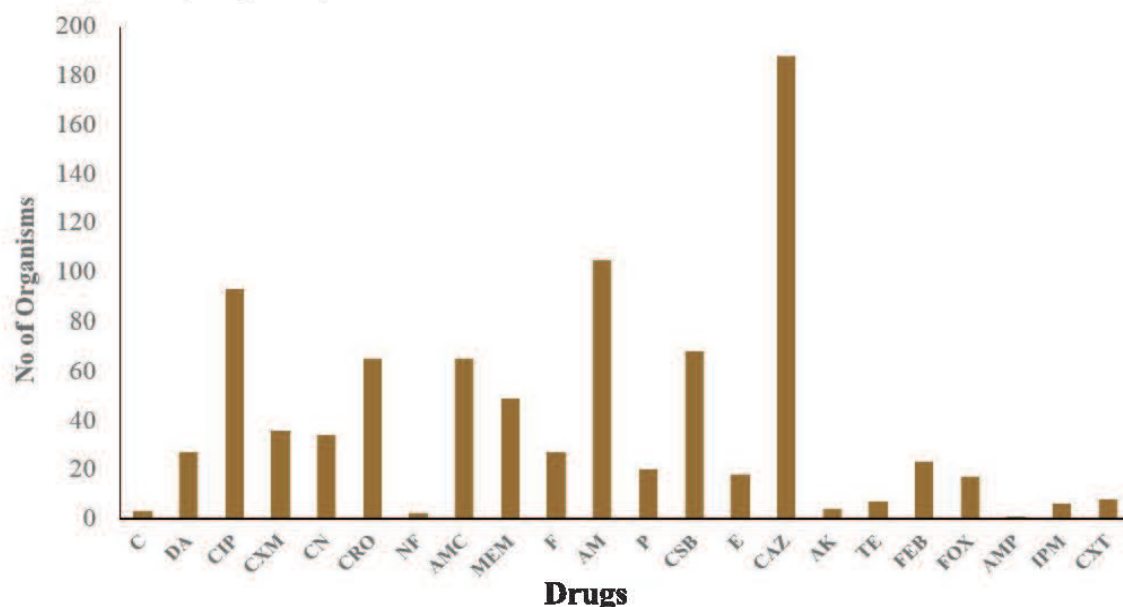


Figure 3: Resistance Pattern to Antimicrobials

KEY:

C	Chloramphenicol	NF	(Ornidazole /ofloxacin)	CAZ	Ceftazidime
DA	Clindamycin	AMC	Amoxicillin clavulanic	AK	Amikacin
CIP	Ciprofloxacin	MEM	Meropenem	TE	Tetracycline
CXM	Cefuroxime	F	Nitrofurantoin	FEP	Cefepime
CN	Cefalexin	AM	Amoxicillin	FOX	Cefoxitin
CRO	Ceftriaxone	IPM	Imipenem	AMP	Ampicillin
		CXT	Cefotaxime		

Table 1: Distribution of Isolated Organisms Among Various Samples

Organism	Blood	Urogenital	Urine	Total
<i>Aspergillus spp</i>	0	2	0	2
<i>Acinobacter spp</i>	0	5	0	5
<i>Aeromonas spp</i>	1	0	0	1
<i>Alcaligene spp</i>	1	4	0	5
<i>Citrobacter spp</i>	1	1	1	3
<i>E. coli</i>	6	33	37	76
<i>Enterobacter spp</i>	1	1	1	3
<i>Gardia spp</i>	0	6	0	6
<i>Kleb. Spp</i>	24	43	51	118
<i>Proteus spp</i>	0	1	1	2
<i>Pseudomonas spp</i>	2	3	1	6
<i>Staph. Spp</i>	25	135	38	198
<i>Strep. Spp</i>	2	69	0	71
Total	63	303	130	496

Key: *E.coli*: *Escherichia coli*, *S. spp*: *Staphylococcus specie*, *Kleb. Spp*: *Klebselia specie*, *Strep. Spp*: *Streptococcus specie*

Drug quality

The quality control tests carried out on the metronidazole infusion and cefuroxime tablet different samples revealed a greater percentage of which failed percentage content uniformity, pH samples passing the test except some brands of and hardness tests respectively (Table 2).

Table 2: Physicochemical Properties of Tested Drugs

Drug/Brand	Disintegration	Dissolution	pH	%Content	Hardness (N)	Friability
Tab Ciprofloxacin 500mg (A)	18m, 42s (NMT 30m)	0	NA	101.00 (95-105)	158.87 (20-200N)	0.081 (NMT 1.0%)
B	2m, 51s	0	NA	85.35	91.35	3.65
C	3m, 30s	0	0	98.14	162.47	0.04
Inj Ceftriaxone (A)	NA	0	6.55 (6.0 - 8.0)	80.40 (90.0 - 110.0)	0	0
B	NA	NA	6.81	90.67	0	0
C	NA	NA	6.42	78.45	0	0
Cap Azithromycin (A)	19.53 (NMT 30mins)	0	NA	0	108.21 (20N - 200N)	0.063 (NMT 1.0%)
B	4.3	0	NA	0	101	0.048
C	5.15	0	NA	0	182.03	0
Tab Amoxicillin (A)	8M, 38sec	0	NA	96.47 (90.0-110.0)	305.3 (20N-200N)	0.003
B	33 sec	0	NA	95.63	39.8	0.61
Eye drop Chloramph	NA	NA	6.85 (7.0-7.5)	107.2 (90.0-110.0)		
Tab Metronidazole	2m, 24s	0	NA	95.77 (95.0 - 105.0)	51.93 (20-200N)	0.324 (NMT 1.0%)
Metronidazole infusion (A)	NA	NA	5.85 (4.5 - 6.0)	97.0 (95.0-105.0)	-	-
B	NA	NA	6.45	101.03	-	-
Tab Cefuroxime	1m, 30s	0	NA	103.90 (90.0-110.0)	242.72 (20N - 200N)	0.031 (NMT 1.0%)
Ciprofloxacin infusion	NA	NA	4.41 (3.9 - 4.5)	101.1 (95.0 - 105.0)	-	-

Response rate and demographics of respondents

A total number of 100 Medical Doctors were issued the printed questionnaires and 70 completed and returned them. This gave a total response rate of 70%. The frequency distribution of the respondents who completed the survey, were male 47 (67.1%), and female 23 [32.9%] respectively. The frequency distribution based on designation (rank) categorization indicated that, 37.1% were house officers, 24.3% were medical

officers, 30.0% resident doctors and 8.6% were consultants. A total 34.3% had below 1 year of experience, 25.7% had 1-3 years of experience, no respondent in the category of 4-6, 12.9% in the category of 6-10 years of experience, while 7.1% had over 10 years of working experience. The frequency distribution based on department shows that internal medicine had the highest participants (60.0%) followed by pediatrics (20.0%). Others are represented in the table below (Table 3).

Table 3: Demographics of Respondents

Variables		Frequency (n)	Percentage (%)
Gender	Male	47	67.1
	Female	23	32.9
Designation	HO	26	37.1
	MO	17	24.3
	RD	21	30
	C	6	8.6
	<1	24	34.3
Years of Experience	1–3	18	25.7
	4–6	14	20.0
	7–10	9	12.9
	>10	5	7.1
	Anest.	1	1.4
Department	CM	1	1.4
	IM	42	60.0
	O&G	7	10.0
	Orth	1	1.4
	Paed	14	20.0
	Surg.	2	2.9
	FM	2	2.9

HO = House officer, MO = Medical officer, RD = Resident Doctor, C = Consultant, CM = Community medicine, IM = Internal Medicine, O&G = Obstetrics & gynecology

Level of prescription compliance in line with MCS results

There was a high level of compliance by respondents on antibiotics selection and prescription. However, low and average

compliance were also observed. No statistically significant association ($P>0.05$) between the rank of physicians and their compliance to rational antimicrobial selection. (Table 4).

Table 4: Respondents' Level of Prescription Compliance in Line with MCS Results

Variable	HO	MO	RD	Consultant	P value	%TR
Are MCS results available when the prescribing decisions are made? (yes)	6/26 23.1%	4/17 23.5%	3/21 14.3%	1/6 16.7%	0.166	19.4%
Are there limiting factors that hinders your decision when prescribing some antibiotics in compliance with MCS result? (yes)	21/26 80.8%	14/17 82.4%	17/21 81.0%	6/6 100.0%	0.801	86.1%
Does availability of some of these antibiotics within this facility influence your prescribing options despite being sensitive on a patient's MCS result? (yes)	21/26 80.8%	9/17 52.9%	17/21 81.0%	5/6 83.3%	0.367	74.5%
Will you be willing to prescribe these antibiotics if they are made available within this facility? (yes)	26/26 100.0%	15/17 88.2%	21/21 100.0%	6/6 100.0%	0.093	97.1%

Key: HO=House Officer, MO=Medical Officer, RD=Resident Officer, TR=Total Response

DISCUSSION

Our study revealed that the organisms from urogenital samples showed more resistance, followed by urine samples and the least resistance from blood samples. However, this was influenced by the number of samples per specimen. *Staphylococcus spp.* was the most commonly isolated (a total of 198 out of 496 isolates (40%) and highly resistant organism similar to a study conducted in Delta state". Highest resistance by *Staphylococcus spp.* was noted against ceftazidime followed by ceftriaxone, amoxicillin, ciprofloxacin and amoxicillin/clavulanate. This pattern of resistance has been shown in other studies such as that conducted by Kumar et al. Least resistance was however noted against ornidazole/ofloxacin, amikacin and cefotaxime.

The next most common organism isolated was *Klebsiella spp.* (23.7%). The Organism is

observed to be resistant to drugs such as Amoxicillin, Ceftazidime, Ceftriaxone and Ciprofloxacin. This is supported by a study conducted in 2013¹². Least resistance was exhibited to penicillin G, amikacin, ampicillin and tetracycline.

Escherichia Coli was isolated in 15% of the sample, it showed the highest resistance against amoxicillin/clavulanate, amoxicillin, ciprofloxacin, ceftriaxone/sulbactam and cefuroxime. This pattern of resistance has been shown by a community-based surveillance done by WHO. The organism showed least resistance against amikacin, imipenem, meropenem, ornidazole/ofloxacin and chloramphenicol. This is partly not in line with similar studies which showed more susceptibility to gentamicin and nitrofurantoin. However, the least resistance to amikacin was noted which is in line with those studies.

The next most commonly isolated organism was *Streptococcus spp* (14%). Highest resistance was noted against ceftazidime, clindamycin, ciprofloxacin, and ceftriaxone/sulbactam, while least resistance was noted against chloramphenicol, cefalexin, ornidazole/ofloxacin, meropenem and tetracycline.

In summary, the highest resistance by organisms was shown against ceftazidime, amoxicillin, ciprofloxacin, ceftriaxone, amoxicillin/clavulanate and ceftriaxone/sulbactam. This may be due to the inactivation by enzymes, over prescribing, frequent usage and ease of access. On the other hand, least resistance was noted against amikacin, ampicillin, imipinem, cefotaxime, ornidazole/ofloxacin and chloramphenicol.

On the quality control studies analyzed to access the compliance with standards, 92.86% of 42 tests analyzed passed the quality tests. However, a brand of ciprofloxacin tablets, and two brands of ceftriaxone injection failed the percentage content uniformity tests. Likewise, a brand of metronidazole infusion also failed pH test and another brand of cefuroxime tablet didn't pass the hardness test.

Comparing the quality tests with the resistance pattern, ciprofloxacin and ceftriaxone which failed the quality tests are among the antibiotics to which resistance developed. Studies have shown that use of sub-standard drugs with sub inhibitory concentrations can lead to high level resistance, increased mutation rate, and increased ability to acquire resistance to other antimicrobials¹³. The microorganisms most implicated are *Streptococcus spp*, *Staphylococcus spp*, *Klebsiella spp*, and *Escherichia coli*.

In our study, 74.3% of the physician attributed availability of antibiotics as a limiting factor for their inability to prescribe antibiotics to patient in line with the microbial culture and sensitivity (MCS) result. Another limiting factor that affects compliance with MCS result is the quality of the drug¹⁴. Even when the MCS result indicates the need for a particular antibiotic, clinically available data within a particular hospital, based on previous results obtained from using the

antibiotics might suggest failure of the intended choice to eradicate the causative microorganisms. This is in line with a research carried out in India where numerous drugs in government-owned hospitals failed the quality tests prescribed to ascertain the standard of drugs¹⁵. However, in this facility, of the 42 quality control tests carried out to ensure compliance with standards, 92.86% passed the quality tests except various brands of ceftriaxone injection and ciprofloxacin tablet, metronidazole infusion and cefuroxime tablet which failed percentage content uniformity, pH and hardness tests respectively. According to the resistance pattern ceftriaxone and ciprofloxacin are among the top antibiotics to which resistance is recorded.

A total of 97.1% of physicians in our study expressed willingness to prescribe antibiotics if they are made available within the facility, as they expressed confidence in the quality of antibiotics available due to the quality testing capacity of the laboratories. Also, despite the reduction in the circulation of fake and counterfeit drugs by the National Agency for Food Administration and Control (NAFDAC) by 23% from 2001 to 2005, about 10 million US dollars was lost to fake products in 2018¹⁶. This enormous peddling of fake and counterfeit drugs further heightens the trust of physicians in drugs. Our research strengthens the efforts put forth by the government and all affiliated agencies to ensure the availability of quality medications to patient, as 92.7% of the test carried out in the laboratory showed compliance of the antibiotics with standard value. The availability of drugs within a health facility influences the choice of drug that can be selected by a physician in the management of disease conditions. Particularly in public hospitals across low and middle income countries where resources are limited, the effect of availability on the prescribing power of physician is more pronounced than in private-owned hospitals¹⁷. In our study, we observed that the most resistance documented was associated with majority of the antibiotics available.

CONCLUSION

The findings of the study revealed that the quality and availability of antimicrobial may be predictive of the antimicrobial resistance pattern observed. Rational prescribing was largely

influenced by affordability and perceived quality of some brands of antimicrobials.

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