



Patterns of antibiotics prescriptions in two tertiary care hospitals of Peshawar, Pakistan

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Abstract:

Background: Inappropriate antibiotic use is a global concern, contributing to antibiotic resistance and jeopardizing the effectiveness of these life-saving medications. This study investigates prescribing patterns of antibiotics in two tertiary care hospitals located in Peshawar, Pakistan. Understanding these patterns can inform strategies to optimize antibiotic use and combat the rising tide of resistance in this region.

Methods: A two-month cross-sectional survey (September-October 2020) was conducted at two Peshawar hospitals using a convenient sampling method. Physicians across various specialties were included (general practitioners, pediatricians, etc.). Sample size calculation ensured a representative sample. A pilot questionnaire was initially distributed and refined for clarity and efficiency. Data was collected using a standardized questionnaire and analyzed with SPSS software.

Results: A two-month survey assessed antibiotic prescribing practices among 52 physicians at two Peshawar hospitals. While most physicians acknowledged the importance of proper antibiotic use, concerning trends were identified. Ten physicians believed antibiotics were harmless even when unnecessary, and 25% favored broad-spectrum antibiotics due to time constraints for cultures. Furthermore, 65% reported prescribing broad-spectrum antibiotics when unsure of the infection type, and 42% admitted to making mistakes with antibiotic prescriptions. These findings highlight the need for interventions to improve antibiotic stewardship and combat potential resistance issues in this healthcare setting.

Conclusion: The study identified worrying trends in antibiotic prescribing, but emphasizes the potential for improvement. Educational programs targeting both healthcare professionals and the public through various media channels are proposed

Keywords: Antibiotics, resistance, prescription.

INTRODUCTION:- Antimicrobials are the drugs used to prevent the pathogenicity of microorganisms[1]. Antimicrobials – including antibiotics, antivirals, antifungals and antiparasitics – are medicines used to prevent and treat infections in humans as well as in animals [2]. According to a study, the global consumption of antibiotics increased by 65% between 2000 and 2015, driven by increased

Patterns of antibiotics prescriptions in two tertiary care hospitals of Peshawar, Pakistan

consumption in low- and middle-income countries [LMICs] [3]. The LMICs with the highest antibiotic consumption were China, Pakistan, India, Brazil, and Russia [4,5]. Within the spectrum of antimicrobial resistance (AMR), antibiotic resistance refers to the ability of bacteria to survive in the presence of an antibiotic designed to kill or stop them from multiplying [6]. Over the past few years, unnecessarily overuse of antibiotics has led to the emergence of antimicrobial resistance worldwide mostly affecting low and middle income countries [1,2,7].

The two major factors contributing to resistance are the irrelevant use of antibiotics and insufficient infection control policies resulting in spread of resistant microbes. Okeke IN reported that approximately 30% of inpatient antibiotic use was unnecessary [8].

A study conducted in Indianapolis (US) found that many physicians accepted that antibiotics are overused, and many of them prescribed them even when clinical evidence of infection was uncertain [9]. The same study identified four points related to the culture of antibiotic prescription, which states that antibiotics are irrelevantly used and generally accepted; adverse effects of antibiotics have limited influence on physicians' prescribing attitudes; trainees are strongly influenced by the prescribing behavior of senior physicians; and other physicians' antibiotic prescribing decisions are cross-examined, but they are hesitant to provide any feedback or advice [9].

A systemic review published in 2013 identified physicians' antibiotic prescription behaviors [10]. This study presents inappropriate prescriptions in the context of both intrinsic and extrinsic factors. Extrinsic factors have a greater influence on antibiotic prescription, including: 1) patients' desire for antibiotics. 2) Increased time and money consumed in culture and sensitivity tests. 3) Increase patient volume. Intrinsic factors include the following: 1) Complacency, defined as physicians' desire to meet patients' expectations. 2) Fear of disease progression risk if antibiotics are not prescribed. 3) Fear of losing patients to other physicians. A study comparing knowledge and practice between doctors in France and Scotland showed that most doctors credit pharmaceutical companies, have poor infection control policies, and are veterinarians for antimicrobial resistance [11].

In Pakistan, the condition is the worst because, according to a national survey report, more than 70% of antibiotics are purchased privately without a doctor's prescription [12]. A study conducted in Karachi by students at Jinnah University for Women revealed that 74% of people prefer self-medication including antibiotics [12]. Commonly used self-medicated antibiotics included cefixime (40%), augmentin (30%), and kalaracid (4%). A study conducted on inpatient antibiotic pharmacology and physiology in HMC Peshawar showed that 35.7% of prescriptions were based on clinical proof of infection and were not dependent on culture results termed as empirical, while the remaining 64.3% were prescribed without proof of infection termed as prophylactic [13]. Antibiotics are the most commonly prescribed drugs, followed by analgesics, multivitamins, and cough preparations [13]. The most commonly prescribed antibiotics were penicillin (47.36%), tetracycline (43.1%), macrolides (4.2%), quinolones (3.1%), and cephalosporins (2.1%). The figure of antibiotic prescription was 46.11%, whereas according to the WHO, it should be 20-30% [14,15]. Pakistan does not have a comprehensive national surveillance program for monitoring antibiotic resistance. Additionally, there is a limited amount of research addressing the underlying causes of antibiotic resistance and the perspectives of general physicians in the country [16]. To the best of our knowledge, this type of study has not been conducted in Peshawar. Excessive use of antibiotics results in an increasing burden on the health system due to increased antimicrobial resistance and increased hospital stay, which is drastic for low-income countries such as Pakistan. Therefore, efforts should be made to control the injudicious use of antibiotics by health professionals and the general population by increasing awareness of antibiotics, their possible side effects, and antimicrobial resistance. The aim of this study was to identify the factors that influence physicians' antibiotic prescribing behavior and to determine their antibiotic prescription knowledge, attitude, and practice.

Patterns of antibiotics prescriptions in two tertiary care hospitals of Peshawar, Pakistan

MATERIAL AND METHODS:-

A cross-sectional survey was conducted using a convenient sampling technique at the Hayatabad Medical Complex and Rehman Medical Institute Peshawar over a period of 2 months (1st Sep-30thOct 2020).The study population included physicians, general physicians, Pediatricians, Pulmonologists, Gastroenterologists, Rheumatologists, Urologists, Nephrologists, Gynecologists, and obstetricians. Sample size was calculated using the following formula

(Daniel, 1999) $n = Z^2 p (1-p) / d^2$, n= sample size, Z= Z statistic for a level of confidence (1.96)

P= expected prevalence or proportion (in proportion of one; if 64%, P = 0.64) [9], d= precision (in proportion of one; if 15%, d = 0.15).

Initially, a test questionnaire was distributed (a pilot study was conducted) to eight physicians to check the response to the questionnaire pattern, time taken, and any discrepancies. First, the questionnaire was in descriptive form, which took a lot of time, and was difficult to understand by physicians; later, we changed the questionnaire to the grading form, which took much less time and was easy to understand and fill up. The new questionnaire was then distributed to 44 physicians. The total sample size was 52 patients. The final outcomes were noted and analyzed using the SPSS version 16 (SPSS Inc., Chicago (SPSS)).

Results:

The survey included 52 physicians (42 male and 10 female).Their ages ranged from 30 to 60 years with a mean age of 41.42.Working experience in hospitals ranged from 4 to 35 years, with a mean working experience of 14.62.Table 1.0 shows the number of medical specialists that took part in the survey.

Medical specialization

	Frequency	Percent	Valid Percent	Cumulative Percent
Valid General Physician	34	65.4	65.4	65.4
Pediatrician	4	7.7	7.7	73.1
Pulmonologist	3	5.8	5.8	78.8
Gastroenterologist	5	9.6	9.6	88.5
Gyne&Obs	2	3.8	3.8	92.3
Urologist/Nephrologist	3	5.8	5.8	98.1
Rheumatologist	1	1.9	1.9	100.0
Total	52	100.0	100.0	

Table 1.1 shows the type of service provided by the physicians.

Type of service

	Frequency	Percent	Valid Percent	Cumulative Percent
Valid Public practice	7	13.5	13.5	13.5

Patterns of antibiotics prescriptions in two tertiary care hospitals of Peshawar, Pakistan

Private practice	30	57.7	57.7	71.2
Both	15	28.8	28.8	100.0
Total	52	100.0	100.0	

Ten of 52 physicians thought that prescribing antibiotics did not cause damage when patients did not need them. Table 2.0 shows the frequency of physicians who think that one should wait for microbiological results before treating an infectious disease. In the neutral option, some physicians said that the decision depends on the condition of the patient; some said it depends on the case, and some said that it is preferable to prescribe prophylactic antibiotics and later change it on the basis of culture and sensitivity tests.

	Frequency	Percent	Valid Percent	Cumulative Percent
Valid Strongly Agree	1	1.9	1.9	1.9
Agree	9	17.3	17.3	19.2
Neutral	12	23.1	23.1	42.3
Disagree	20	38.5	38.5	80.8
Strongly Disagree	10	19.2	19.2	100.0
Total	52	100.0	100.0	

Table 3.0 shows the frequency of physicians prescribing antibiotics in situations where it is difficult for them to conduct systemic follow-up of the patient.

	Frequency	Percent	Valid Percent	Cumulative Percent
Valid Strongly Agree	1	1.9	1.9	1.9
Agree	19	36.5	36.5	38.5
Neutral	5	9.6	9.6	48.1
Disagree	18	34.6	34.6	82.7
Strongly Disagree	9	17.3	17.3	100.0
Total	52	100.0	100.0	

Of the 52 physicians, 46 thought that antibiotics should not be prescribed because patients insisted on it.

Patterns of antibiotics prescriptions in two tertiary care hospitals of Peshawar, Pakistan

Figure 1.0 displays that 25% of physicians think that wide-spectrum antibiotics should be prescribed because of the time and money consumed by culture and sensitivity tests.

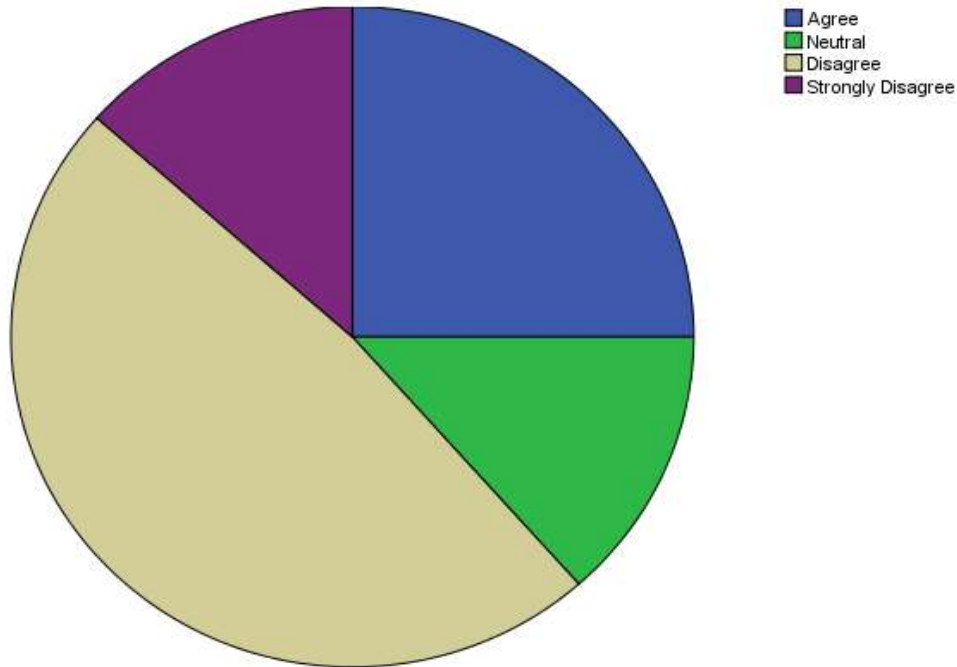


Figure 2.0 shows that 65.4% of physicians agreed that in case of doubt, it is preferable to prescribe broad-spectrum antibiotics to ensure that the patient is cured of an infection.

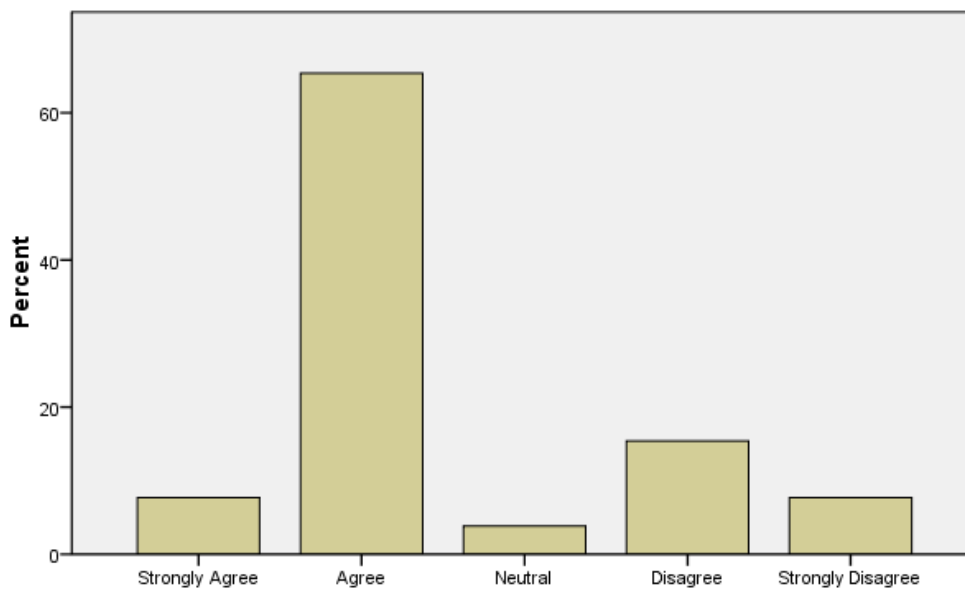


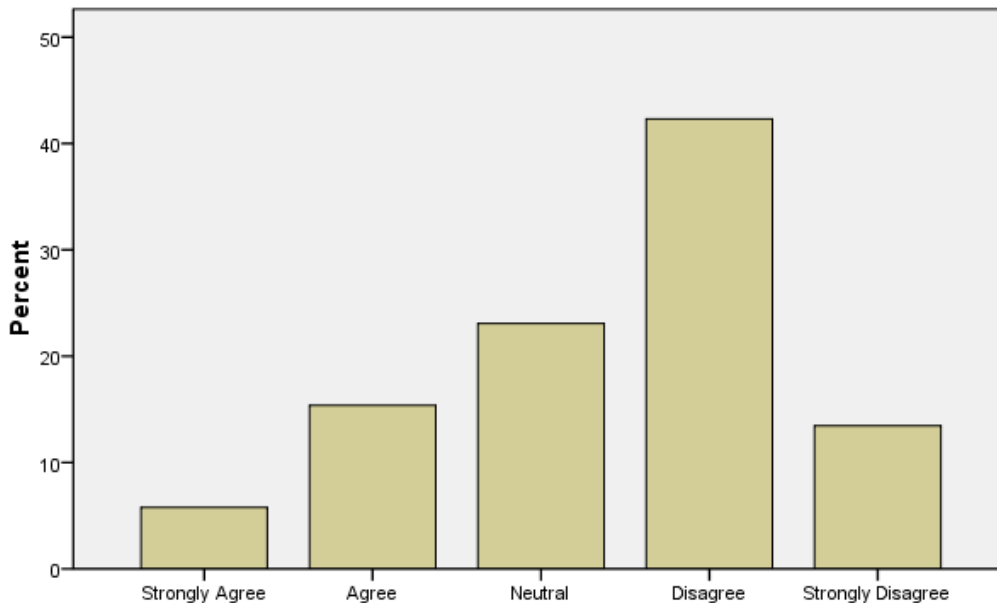
Table 4.0 shows that 78.8% of physicians agreed that if

they inherit a patient previously cared for by another doctor and they are already on antibiotics, they critically evaluate the decision.

Patterns of antibiotics prescriptions in two tertiary care hospitals of Peshawar, Pakistan

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Strongly Agree	16	30.8	30.8	30.8
	Agree	25	48.1	48.1	78.8
	Neutral	5	9.6	9.6	88.5
	Disagree	4	7.7	7.7	96.2
	Strongly Disagree	2	3.8	3.8	100.0
	Total	52	100.0	100.0	

Of the physicians, 32.7% agreed that they had never made wrong decisions about prescribing antibiotics, 42.3% agreed that they did make wrong decisions about prescribing antibiotics, and 25% marked this question as neutral. Figure 2.1 shows that 42.3% physicians disagree and 13.5% physicians strongly disagree that they prescribe antibiotics out of fear of what might happen if an infection is missed. Of the physicians, 15.4% agreed and 5.8% strongly agreed that they prescribe antibiotics out of fear of what might happen if an infection is missed. 23.1% physicians marked it as neutral and had different opinions; some said that they prescribe antibiotics not out of fear but out of care of the patient and some said that it depends on many factors such as the severity of the condition and prognosis of the disease.



22 physicians disagree and 28 strongly disagree that they prescribe antibiotics out of fear of losing patients to other physicians. Only 2 marked this question as neutral. Of the physicians, 48.1% agreed that they were more concerned about achieving a clinical cure for infection than about preventing potential adverse effects of antibiotics. Twenty physicians disagree and 26 physicians strongly disagree that

Patterns of antibiotics prescriptions in two tertiary care hospitals of Peshawar, Pakistan

antibiotics should be prescribed to patients so that they do not seem to colleagues, seniors, or patients' attendants that the patient is undertreated. Six physicians rated this question as neutral.

46 physicians marked amoxicillin as safe during pregnancy, whereas 6 marked ciprofloxacin as safe during pregnancy. 42 physicians marked metronidazole as the best agent against anaerobes, whereas nine marked ciprofloxacin, and one physician marked co-trimoxazole as the best agent against anaerobes. 43 physicians marked ceftriaxone as more effective in crossing the blood-brain barrier, eight marked vancomycin, and one physician marked clindamycin as more effective in crossing the blood-brain barrier. 42 physicians marked vancomycin as the drug of choice against methicillin-resistant *Staphylococcus aureus*, whereas seven marked ceftriaxone and three marked cefuroxime were the drugs of choice. Table 5.0 shows the response of physicians to woman complaining of 4 days of diarrhea with no history of fever

A 40 year old woman went to the emergency room complaining of 4 days of diarrhea (3 unformed stools per day).No history of fever. One month before she had UTI and took Ciprofloxacin. Which antibiotic will you recommend?

	Frequency	Percent	Valid Percent	Cumulative Percent
Valid Ciprofloxacin	6	11.5	11.5	11.5
Co-trimoxazole	7	13.5	13.5	25.0
No need of antibiotics	20	38.5	38.5	63.5
Oral rehydration	19	36.5	36.5	100.0
Total	52	100.0	100.0	

Figure 1.1 shows the response of physicians to 32 years old male who went to clinic complaining of fever, nasal discharge and throat pain for 3 days. Amoxicillin (38.5%), Clarithromycin (32.7%), Co-trimoxazole (7.7%) and no need of antibiotics (21%).

Patterns of antibiotics prescriptions in two tertiary care hospitals of Peshawar, Pakistan

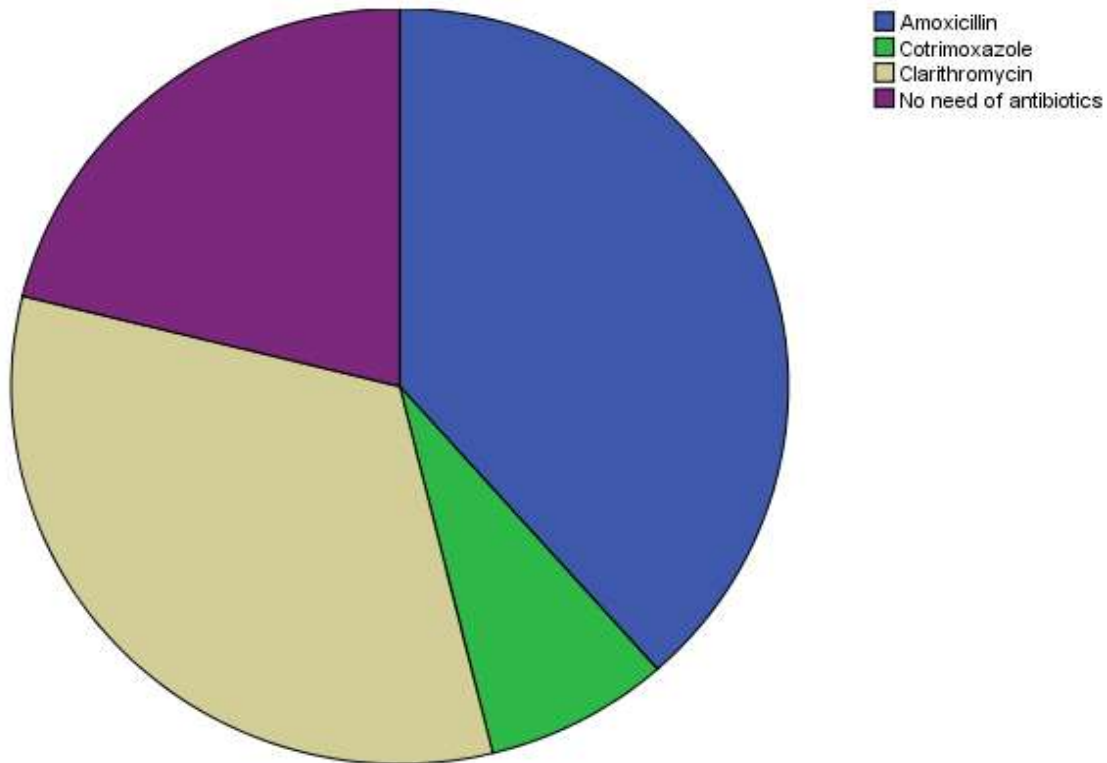


Table 6.0 shows the frequency of antibiotic prescription by physicians in the OPD, ward or emergency. 78.8% of physicians prescribe antibiotics more than once a day.

	Frequency	Percent	Valid Percent	Cumulative Percent
Valid More than once a day	41	78.8	78.8	78.8
Once a day	4	7.7	7.7	86.5
3-5 times per week	6	11.5	11.5	98.1
Less than once a week	1	1.9	1.9	100.0
Total	52	100.0	100.0	

Table 6.0

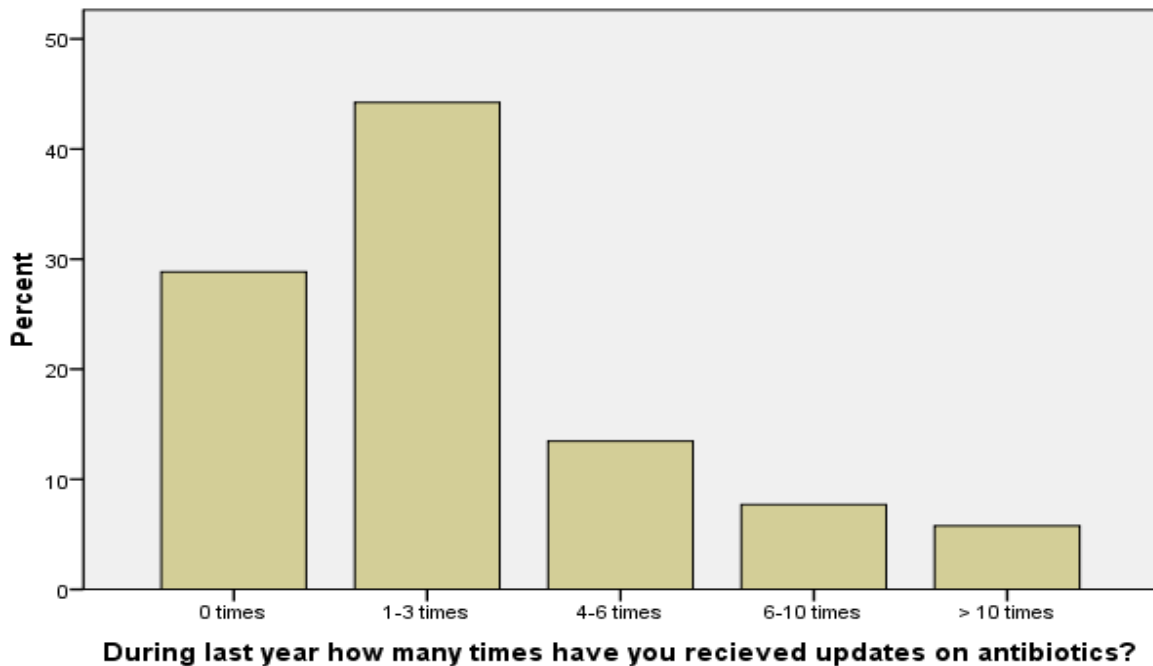
Table 7.0 shows that physicians use the Internet and antimicrobial guides/books as the main source of information about antibiotics as part of continuous medical education or when they have specific questions.

	Responses	
	N	Percent

Patterns of antibiotics prescriptions in two tertiary care hospitals of Peshawar, Pakistan

Sources of information	Information from senior colleagues	15	15.5%
	Information from colleagues of same rank	4	4.1%
	Internet sources	30	30.9%
	Antimicrobial guides/books	29	29.9%
	Medical representatives	14	14.4%
	Others	5	5.2%
Total		97	100.0%

Figure 2.2 shows that 28.8% of physicians had not received any update on antibiotics last year, whereas 44.2% physicians received update only 1-3 times during the previous year.



Discussion:

Antibiotic resistance is a worldwide problem but mostly affecting middle and low income countries [3,17,18]. In Pakistan, the condition is the worst because, according to a national survey, more than 70% of antibiotics are purchased privately without a doctor's prescription[19,20]. Even when doctors prescribe antibiotics, they are mostly based on clinical evidence, not on culture and sensitivity results. This injudicious use of antibiotics results in diseases that are resistant to most antibiotics, and the infective organisms become genetically altered with time to overcome the antibiotics, and the condition is worsening day by day [21].

Patterns of antibiotics prescriptions in two tertiary care hospitals of Peshawar, Pakistan

Regarding the finding that 46 out of 52 physicians thought that antibiotics should not be prescribed because patients insist on it or out of fear, but they prescribe antibiotics for the care of patients, this is consistent with the results of a study conducted in Palestine, which states that the majority of physicians indicated that they do not feel pressured by patients or family members to prescribe antibiotics (286, 90.5%) [22].

In this study, 48.1% of physicians agreed that they were more concerned about achieving a clinical cure for infection than about preventing potential adverse effects of antibiotics. Twenty physicians disagree and 26 physicians strongly disagree that antibiotics should be prescribed to patients so that they do not seem to colleagues, seniors, or the patient's attendant that the patient is being undertreated; however, these results are inconsistent with a study from Saudi Arabia, which stated that physicians do feel under pressure if the patient expects antibiotic prescription and if they do not get any, they are likely to express dissatisfaction [23].

In this study, 25% of the physicians thought that wide spectrum antibiotics should be prescribed because of the time and money consumed by culture and sensitivity tests, which is similar to other studies carried out in Pakistan and Iran, respectively, who stated that broad-spectrum antibiotics were considered a better treatment option, which is why they were prescribed as prophylactic agents. It should be noted that poor financial status and insufficient resources were considered the main reasons for not ordering culture tests [3,24].

This study states that 46 physicians marked Amoxicillin as safe drug during pregnancy, whereas 42 physicians marked Metronidazole as best agent against anaerobes. 43 physicians marked Ceftriaxone as more effective to cross blood brain barrier while 42 physicians marked Vancomycin as drug of choice against Methicillin Resistant Staphylococcus Aureus (MRSA)

Regarding the daily practice of antibiotic prescription, this study reported that 78.8% of physicians prescribe antibiotics more than once a day, which is inconsistent with the Palestinian study, which indicated that they prescribe antibiotics no more than once at a time with reference to guidelines [22].

This study shows that 28.8% of physicians have not received any update on antibiotics last year, whereas 44.2% physicians received update only 1-3 times during the last year, which is in contrast to a study from South Africa, which reported that their physicians are up-to-date with different information sources mentioned in decreasing order of frequency (textbooks 93%, professional/learned societies' guidelines 93%, WHO (World Health Organization) guidelines 81%, and smart phone apps 60%) [25].

Conclusion:

These results were alarming. However, it is not over yet, and through proper awareness and educational programs through print and social media for both public and medical professionals, we can make this condition better not only for ourselves but also for our coming generations so that they do not face the problems that we are facing now.

BIBLIOGRAPHY:-

1. BYJUS. What are Antimicrobial Agents? - Definition, Types with Examples & Videos. Accessed: September 13, 2023: <https://byjus.com/chemistry/antimicrobial-agents/>
2. World Health Organization. Antimicrobial resistance. Accessed: September 13, 2023: <https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance>

Patterns of antibiotics prescriptions in two tertiary care hospitals of Peshawar, Pakistan

3. Atif M, Ihsan B, Malik I, et al.: Antibiotic stewardship program in Pakistan: a multicenter qualitative study exploring medical doctors' knowledge, perception and practices. *BMC Infect Dis.* 2021, 21:374. 10.1186/s12879-021-06043-5
4. Klein EY, Van Boeckel TP, Martinez EM, et al.: Global increase and geographic convergence in antibiotic consumption between 2000 and 2015. *Proc Natl Acad Sci U S A.* 2018, 115:E3463-E3470. 10.1073/pnas.1717295115
5. Saleem Z, Hassali MA, Godman B, et al.: Sale of WHO AWaRe groups antibiotics without a prescription in Pakistan: a simulated client study. *J Pharm Policy Pract.* 2020, 13:26. 10.1186/s40545-020-00233-3
6. Bhuvaraghan A, King R, Larvin H, Aggarwal VR: Antibiotic Use and Misuse in Dentistry in India-A Systematic Review. *Antibiotics (Basel).* 2021, 10. 10.3390/antibiotics10121459
7. Ventola CL: The antibiotic resistance crisis: part 1: causes and threats. *P t.* 2015, 40:277-283.
8. Okeke IN: Poverty and Root Causes of Resistance in Developing Countries. *Antimicrobial Resistance in Developing Countries.* Sosa AdJ, Byarugaba DK, Amábile-Cuevas CF, Hsueh P-R, Kariuki S, Okeke IN (eds): Springer New York, New York, NY; 2010. 27-35. 10.1007/978-0-387-89370-9_3
9. Livorsi D, Comer A, Matthias MS, Perencevich EN, Bair MJ: Factors Influencing Antibiotic-Prescribing Decisions Among Inpatient Physicians: A Qualitative Investigation. *Infect Control Hosp Epidemiol.* 2015, 36:1065-1072. 10.1017/ice.2015.136
10. Teixeira Rodrigues A, Roque F, Falcao A, Figueiras A, Herdeiro MT: Understanding physician antibiotic prescribing behaviour: a systematic review of qualitative studies. *Int J Antimicrob Agents.* 2013, 41:203-212. 10.1016/j.ijantimicag.2012.09.003
11. Pulcini C, Williams F, Molinari N, Davey P, Nathwani D: Junior doctors' knowledge and perceptions of antibiotic resistance and prescribing: a survey in France and Scotland. *Clin Microbiol Infect.* 2011, 17:80-87. 10.1111/j.1469-0691.2010.03179.x
12. Ashraf Z, Amjad R: Survey of Non-Prescribed Use of Antibiotics in Respiratory Tract Infections and Role of Community Pharmacists to Enlighten the Society. *Journal of Bioequivalence & Bioavailability.* 2015, 08. 10.4172/jbb.1000258
13. Khan S, Shehzad A, Shehzad O, Al-Suhaimi EA: Inpatient antibiotics pharmacology and physiological use in Hayatabad medical complex, Pakistan. *Int J Physiol Pathophysiol Pharmacol.* 2013, 5:120-127.
14. Vance MA, Millington WR: Principles of irrational drug therapy. *Int J Health Serv.* 1986, 16:355-362. 10.2190/4X0T-4D2D-T00R-LNLH
15. Nathwani D, Davey P: Antibiotic prescribing--are there lessons for physicians? *QJM.* 1999, 92:287-292. 10.1093/qjmed/92.5.287
16. https://ecommons.aku.edu/cgi/viewcontent.cgi?article=1629&context=pakistan_fhs_mc_med_med
17. Jinks T, Lee N, Sharland M, et al.: A time for action: antimicrobial resistance needs global response. *Bull World Health Organ.* 2016, 94:558-558A. 10.2471/BLT.16.181743
18. Trikha S, Dalpath SK, Sharma M, Shafiq N: Antibiotic prescribing patterns and knowledge of antibiotic resistance amongst the doctors working at public health facilities of a state in northern India: A cross sectional study. *J Family Med Prim Care.* 2020, 9:3937-3943. 10.4103/jfmpe.jfmpe_367_20
19. Hussain T: Pakistan at the verge of potential epidemics by multi-drug resistant pathogenic bacteria. *Advancements in Life Sciences.* 2015, 2:46-47.
20. Imtiaz F, Hafeez A, Ashraf F, Imtiaz H: Antibiotic Dispensing & Prescription Pattern in Pharmacies of Islamabad & Rawalpindi: Pakistan. *International Journal of Collaborative Research on Internal Medicine & Public Health.* 2017, 9:683-692.
21. Atif M, Asghar S, Mushtaq I, et al.: What drives inappropriate use of antibiotics? A mixed methods study from Bahawalpur, Pakistan. *Infect Drug Resist.* 2019, 12:687-699. 10.2147/IDR.S189114

Patterns of antibiotics prescriptions in two tertiary care hospitals of Peshawar, Pakistan

22. Maraqa B, Nazzal Z, Hamshari S, et al.: Palestinian physicians' self-reported practice regarding antibiotic use for upper respiratory tract infections in primary healthcare. *Front Med (Lausanne)*. 2023, 10:1139871. 10.3389/fmed.2023.1139871
23. Alnemri AR, Almaghrabi RH, Alonazi N, Alfrayh AR: Misuse of antibiotic: A systemic review of Saudi published studies. *Curr Pediatr Res*. 2016, 20:169-173.
24. Sami R, Sadegh R, Fani F, Atashi V, Solgi H: Assessing the knowledge, attitudes and practices of physicians on antibiotic use and antimicrobial resistance in Iran: a cross-sectional survey. *J Pharm Policy Pract*. 2022, 15:82. 10.1186/s40545-022-00484-2
25. Domche Ngongang SC, Basera W, Mendelson M: Tertiary hospitals physician's knowledge and perceptions towards antibiotic use and antibiotic resistance in Cameroon. *BMC Infect Dis*. 2021, 21:1116. 10.1186/s12879-021-06792-3