



# A Study of Unnecessary Use of Antibiotics at a Tertiary care hospital: Urgent need to implement antimicrobial stewardship programs

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## ABSTRACT

**Background:** The resistant bacteria are on upward trend in the third world countries especially in Pakistan. One of the reasons is injudicious prescription of antibiotics. The aim of this study was to estimate the unnecessary use of antibiotics at a tertiary care hospital at Lahore Pakistan. **Methods and Material:** This is the descriptive, retrospective observational study. A total of 104 persons were recruited from an inpatient department of surgery, medicine and gynaecology in a tertiary care hospital were observed and data collected from June 2014 to July 2014 on the daily basis. The dose and the route of given antibiotics were observed in addition to their baseline tests like CBC (Complete Blood Count), urine complete examination, especially with respect to TLC (Total Leucocyte Count) and pus cells, and if any cultures were done along. Descriptive statistics was applied to data to inference results. **Results:** A total of 104 persons, consisting of 41% male and 59% female were included in the study. The mean age of total patients were  $43.97 \pm 18.3$  years. 9.61% patients were not receiving antibiotics. 90% patients received 143(100%) antimicrobials during the period of study with a range of 1-3 antimicrobials per patient. 30% antimicrobials were prescribed unnecessarily without any clinical evidence of infection. The most common prescribed antibiotic was ceftriaxone 30%. It was 88% of the prescription that were prescribed without ordering the culture test. 83 prescriptions were empiric, containing 29% of the unnecessary antibiotics. The unnecessarily prescribed antimicrobials cost 32,865 PKR per day to the sample population. **Conclusion:** Antimicrobials are being used unnecessarily, even empirical treatment are without significant sound clinical evidence. The antimicrobial resistance and emergence of new mutant strains can be attributable to injudicious use of antibiotics. Antimicrobial stewardship programs should be used to minimize this problem.

**Key words:** Antibiotic Resistance, Antimicrobial Stewardship, Bacteriological culture, Pre-authorization, Pakistan, Unnecessary use.

## INTRODUCTION

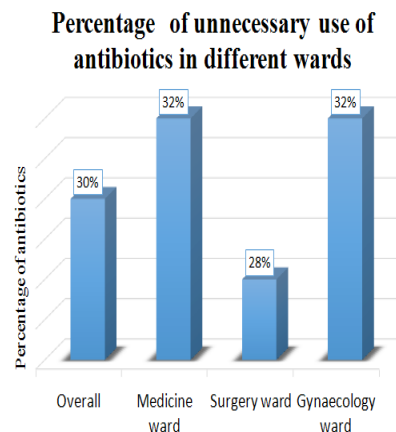
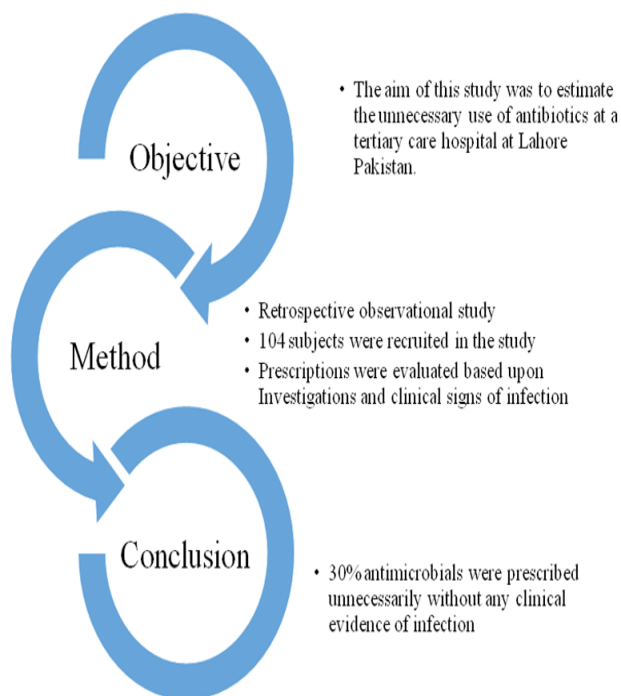
Antibiotics are among the most prescribed medicine in a hospital setting for treatment of infections. In Pakistan, the unnecessary use of antibiotics is very high and is one of the difficult task to overcome.<sup>1</sup> As a result, antimicrobial resistance is growing as the major challenge to the infectious disease control globally including Pakistan.<sup>2-5</sup> Literature reported the unnecessary or incorrect use of antimicrobials ranging from 9% to 64%.<sup>6</sup> This practice

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#### Graphical Abstract

apart from development of drug resistance results in higher morbidity, mortality, treatment cost and prolonged length of hospital stay with unnecessary exposure of patients to potentially harmful drugs.<sup>7-9</sup> Due to the rapid spread of multi-resistant microorganisms and decreasing accessibility of new antibiotics, resistance to antibiotics has become a major public health issue.<sup>10,11</sup> There is an evidence of increased in Extended Spectrum Beta Lactamase (ESBL) and carbapenem resistant *K. pneumoniae* in Pakistan.<sup>3</sup>

Antimicrobial stewardship programmes aim to optimize the use of antimicrobials in such way to prevent the emergence of resistance or other adverse effects, improving outcomes of care and reduce health care cost without compromising the quality of life. Antimicrobial stewardship programmes contain two basic strategies to reduce the unnecessary or inappropriate use of antimicrobials such as formulary restriction and prospective audit.<sup>12-14</sup> It also recommend that the bacteriological cultural should be available as early as possible before prescribing the broad spectrum antibiotics that result in removal of one or more antimicrobial agents.<sup>15,16</sup>

The unnecessary or incorrect use of antimicrobials have serious health hazard in present health care system of developing countries like Pakistan, in this context, the aim of this study was to estimate the unnecessary use of antibiotics in relation to parameter of infections at a tertiary care hospital.

## METHODS

This retrospective observational study was conducted at a tertiary care hospital, at Lahore, Pakistan. 104 subjects were recruited from an in-patient department of surgery, medicine, and gynaecology wards. The subjects not receiving antimicrobials were excluded from the study. The inclusion criteria was receiving antibiotics in the treatment regimen, having age more than 18 years and hospital stay more than 1 day. The CONSORT flow chart of the study was depicted in Figure 1. The study protocol was approved by the institutional ethical committee and informed consents were taken from the subject at the time of recruitment in the study. The data were collected regarding the use of oral and intravenous (I/V) antibiotics from June 2014 to July 2014 on the daily basis. A proforma was designed to collect the information about patient's age, gender, route of drug administration and different groups of antimicrobials according to "J" group of Anatomical Therapeutic Chemical (ATC) classification system from their medical sheets.<sup>17</sup> The diagnosis and therapy which were made by the medical officer (M.O), surgeon or physician were also recorded. The dose and the route of giving antibiotics was seen along with their baseline tests like Complete Blood examination (CBC), Urine complete examination, especially with respect to Total Leucocyte Count (TLC) or pus cells, and special emphasis was also given if any cultures were done along with sensitivity.

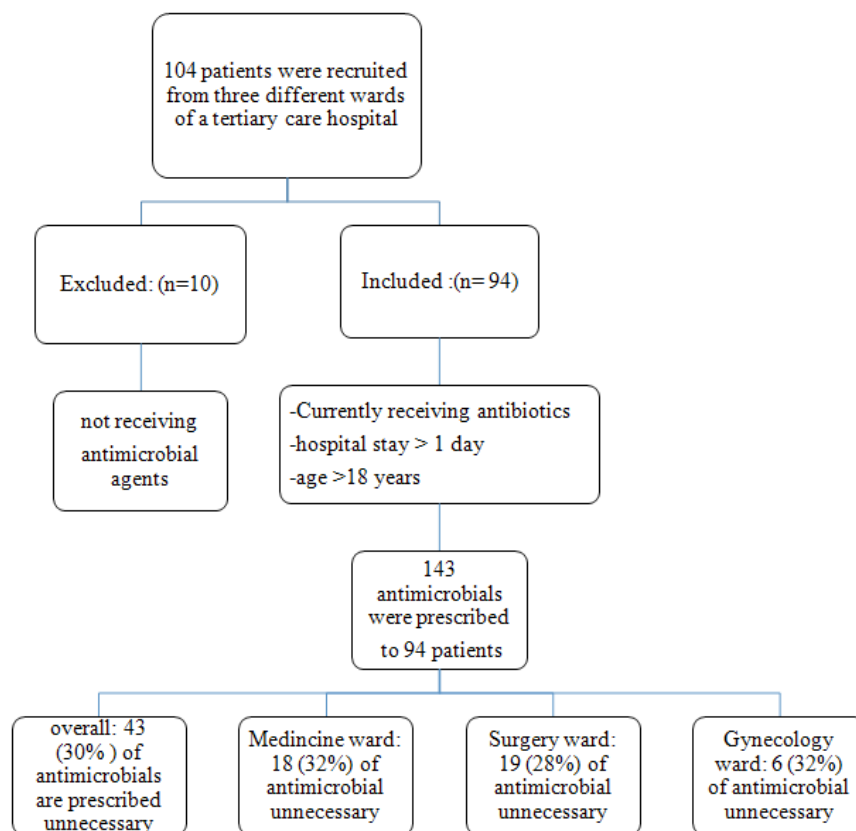


Figure 1: CONSORT flow chart of the study

An Infectious Disease (ID) specialist evaluated the case histories of the collected data based on the pathological investigation and clinical signs of infection including presence of fever, CBC with leukocytosis, urine complete examination and available culture sensitivity test. The local and international evidence based guidelines were also considered. The sample with TLC more than 11,000 cells/ $\mu$ l and urine sample with more than 0–4/hpf pus cells/WBCs was considered as clinical suspicion for infection.<sup>18</sup>

Based on ID expert recommendation, we declared the antimicrobial use as unnecessary, necessary, and empirical or evidence based. Antimicrobials were considered to be unnecessary when the subjects had no clinical sign of infection or indication for prophylaxis. The antimicrobials prescribed on the clinical suspicion of infection were recorded empirical and appropriate while the cultural sensitivity results were pending, whereas evidence based prescriptions are considered those which were prescribed after the bacteriological culture result.

For the estimation of cost for unnecessary antimicrobials, we considered the average cost (PKR) of at least three market leading brands of an antimicrobial agent. After getting the required data, we analysed the mean age,

frequently used antibiotics, frequent diagnosis and trend of antimicrobial prescription with reference to clinical evidence in medical, surgical and gynaecology ward using SPSS 21 version (Statistical Package for Social Sciences) for descriptive statistics.

## RESULTS

The patient characteristics are summarized in Table 1. A total of 104 persons, 46 (44%) consisting of 16 (35%) male and 30 (65%) female, from the medicine ward, while 41 (39%) consisting of 27 (66%) male and 14 (34%) from surgery ward and 17 (16%) female from gynaecology ward were included in the study. The mean age of total patients were  $43.97 \pm 18.3$  years. A sum of 94 patients (90%) received 143 antimicrobials during the period of study with the range of 1-3 antimicrobials per patient.

Table 2 listed the frequency of antibiotics prescribed to study population with ATC codes. The top five overall prescribed antibiotics were ceftriaxone (J01DD04) 43 (30%), ciprofloxacin (J01MA02) 19 (13%), metronidazole (J01XD01) 17 (12%) and cefuroxime (J01DC02) 10 (7%), co-amoxiclav J01CR02, 9 (6%). The consumption of ceftriaxone (J01DD04) was on top in all wards with 17

**Table 1: Subject characteristics**

Characteristics	Total	Medicine ward	Surgery ward	Gynaecology ward
<b>No. of evaluated patients (%)</b>	104 (100)	46 (44)	41 (39)	17 (16)
<b>Gender</b>				
Male	43 (41)	16 (35)	27 (66)	0 (0)
Female	61 (59)	30 (65)	14 (34)	17 (100)
<b>Mean age (M±SD)</b>	43.97 ± 18.3	51.22 ± 17.48	42.59 ± 17.84	27.71 ± 6.55
<b>Patients on antimicrobials (%)</b>	94 (90)	39 (85)	40 (98)	15 (88)
<b>no. of microbial agents prescribed</b>	143 (100)	56 (39)	68 (48)	19 (13)
single	48 (51)	22 (56)	15 (38)	11 (73)
Two	39 (41)	13 (33)	22 (55)	4 (27)
more than two	7 (7)	4 (10)	3 (8)	0 (0)

Data are represented as n (%) and M±SD where applicable. Numbers might not add to 100% because of rounding.

**Table 2: Frequency of antibiotics prescribed to study population**

Name of Antibiotics	ATC code	Total	Medicine ward	Surgery ward	Gynaecology ward
<b>Ceftriaxone</b>	J01DD04	43(30)	17(30)	16(24)	10(53)
<b>Ciprofloxacin</b>	J01MA02	19(13)	10(18)	9(13)	0(0)
<b>Metronidazole</b>	J01XD01	17(12)	6(11)	9(13)	2(11)
<b>Moxifloxacin</b>	J01MA14	4(3)	3(5)	1(1)	0(0)
<b>Levofloxacin</b>	J01MA12	4(3)	2(4)	1(1)	1(5)
<b>Imipenem + Cilastatin</b>	J01DH51	6(4)	3(5)	3(4)	0(0)
<b>Piperacillin + Tazobactam</b>	J01CR05	6(4)	3(5)	3(4)	0(0)
<b>Co-amoxiclave</b>	J01CR02	9(6)	2(4)	6(9)	1(5)
<b>Cefuroxime</b>	J01DC02	10(7)	2(4)	8(12)	0(0)
<b>Ceftazidime</b>	J01DD02	5(3)	1(2)	1(1)	3(16)
<b>Cefixime</b>	J01DD08	2(1)	0(0)	0(0)	2(11)
<b>Amikacin</b>	J01GB06	5(3)	0(0)	5(7)	0(0)
<b>Others</b>	-	13(9)	7(12)	6(9)	0(0)
<b>Total</b>	-	143(100)	56(100)	68(100)	19(100)

Data are represented as n (%).

**Table 3: Diagnosis and anti-biotics prescribed ward wise**

Indications	Total	Medicine ward	Surgery ward	Gynaecology ward
<b>Total no. of diagnoses</b>	94 (100)	39 (100)	40 (100)	15 (100)
<b>Respiratory tract infections</b>	6 (6)	6 (15)	0 (0)	0 (0)
<b>Gastroentology infections</b>	15 (16)	9 (23)	6 (15)	0 (0)
<b>CNS infections</b>	2 (2)	2 (5)	0 (0)	0 (0)
<b>Genito-urinary infections</b>	17 (18)	6 (15)	0 (0)	11 (73)
<b>Soft tissue infections</b>	8 (9)	1 (3)	7 (18)	0 (0)
<b>Musculo-skeletal infections</b>	11 (12)	0 (0)	11 (28)	0 (0)
<b>Other infections</b>	4 (4)	2 (5)	2 (5)	0 (0)
<b>No infections</b>	31 (33)	13 (33)	14 (35)	4 (27)

Data are represented as n (%).

**Table 4: Distribution of antimicrobial prescribed according to indication and wards**

	Unnecessary use												Total (All Wards)														
	Respiratory tract infection			CNS infection			Genito-urinary tract infection			Gastrointestinal infection				Skin and soft tissue infection			musculo-skeletal system infection			Other Infections			Total				
	M	S	G	M	S	G	M	S	G	M	S	G	M	S	G	M	S	G	M	S	G	M	S	G	M	S	G
<b>Total</b>	6	1	1	2	2	2	4	4	4	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
<b>Second-generation cephalosporin</b>	-	-	-	1(2)	-	-	-	-	-	1(2)	-	-	-	-	-	1(1)	-	-	6(9)	-	-	1(1)	-	-	2(1)	8(6)	-
<b>Third-generation cephalosporin</b>	20	6(11)	10	4(21)	2(4)	-	2(4)	-	4(7)	11	4(7)	4(6)	-	1(1)	-	1(1)	-	-	2(3)	-	-	-	-	-	18	17	15
<b>Co-amoxiclave</b>	4(3)	2(4)	1(1)	1(5)	-	-	-	-	-	-	-	-	-	2(3)	-	2(3)	-	-	2(3)	-	-	1(1)	-	-	6(4)	1(1)	9(6)
<b>Piperacillin-tazobactam</b>	2(1)	2(4)	-	-	-	-	-	-	-	-	1(1)	1(2)	1(1)	-	-	1(1)	-	-	1(1)	-	-	-	-	-	3(2)	3(2)	-
<b>Amino-glycosides</b>	-	-	-	-	-	-	-	-	-	-	1(1)	-	-	-	-	1(1)	-	-	3(4)	-	-	-	-	-	5(3)	-	5(3)
<b>Quinolones</b>	7(5)	4(7)	3(4)	-	6	(11)	-	-	1(2)	1(6)	4(7)	-	-	1(1)	-	1(1)	-	-	6(9)	-	-	1(1)	-	-	15	11	1(1)
<b>Carbapenems</b>	2(1)	2(4)	-	-	-	-	-	-	-	-	1(2)	1(1)	-	1(1)	-	1(1)	-	-	-	-	-	1(1)	-	-	3(2)	3(2)	-
<b>Metronidazole</b>	6(4)	1(2)	4(6)	1(5)	1(2)	-	-	-	1(6)	3(5)	3(4)	1(2)	2(3)	-	-	1(2)	2(3)	-	-	-	-	-	-	-	6(4)	9(6)	2(1)
<b>Other</b>	2(1)	1(2)	1(1)	-	-	-	2(4)	-	1(2)	-	-	1(1)	-	1(1)	-	1(1)	-	-	3(4)	-	3(5)	-	-	-	7(5)	6(4)	-
<b>Total</b>	43	18	19	6(32)	10	6(32)	10	0	4(7)	0	6(11)	0	13	13	11	0	2(4)	11	23	0	23	0	3(5)	4(6)	56	68	19
	(30)	(32)	(28)	(18)	(18)	(18)	(18)	(18)	(76)	(76)	(23)	(16)	(23)	(16)	(16)	(16)	(16)	(16)	(34)	(34)	(34)	0	3(5)	4(6)	(39)	(48)	(13)

Data are represented as n (%). Numbers might not add to 100% because of rounding, whereas MED stands for Medicine Ward, SGY stands for Surgery Ward, GYN stands for Gynaecology Ward, - stands for 0.

(30%) in medical ward, 16 (24%) of surgery ward and 10 (53%) of gynaecology ward respectively.

The diagnosis and indication of antibiotic prescribed were depicted in Table 3. The most common overall diagnosis were genito-urinary tract infections 17 (18%), gastroenterology tract infections 15 (16%), musculoskeletal infections 11 (12%), soft tissue infections 8 (9%), respiratory tract infections 6(6%) respectively. 31 (33%) patients were receiving antibiotics without an indication of infection. Table 3 also showed the ward wise distribution of all diagnosis.

Table 4 summarized the evaluation of antimicrobial prescribed and distribution of antimicrobial according to diagnosis. Overall, 43 (30%) of antimicrobial were prescribed unnecessarily, third generation cephalosporin is on top of list for unnecessary use with 20 (14%) of antimicrobial prescribed, Quinolone 7 (5%) are in second position for unnecessary usage.

Table 5 and Table 6 summarized the ward and indication wise diagnostic information with reference to use of antimicrobial in three wards and according to indications of antimicrobial respectively. 71 (76%) of the persons had TLC less than 11, 000 cells /  $\mu$ l and 93 (99%) persons had no fever. It was observed that 88% of the prescription were prescribed without ordering the culture test.

Table 7 showed the ward wise evidence based and empirical prescriptions. 83 (88%) prescription were empiric, containing 42 (29%) of the unnecessary antibiotics and even 1(1%) of the antimicrobial was unnecessary in evidence based prescriptions.

Table 8 table depicted the cost in Pakistani Rupees (PKR) of unnecessary antimicrobial prescribed. It was found that all unnecessarily prescribed antimicrobials cost 32,865 PKR per day or 350 PKR per day per person. The contribution of third generation cephalosporin is the highest with cost of 14093 PKR followed by Quinolone 6099 PKR and Carbapenem 4980 PKR per day therapy.

## DISCUSSION

The emergence of multi drug resistant organisms (MDROs) is a growing problem in developing countries. It is reported that  $\beta$ -lactam antibiotics resistant bacteria are present in almost 95% of adult population of India and Pakistan in contrast to that only 10% of New York adult population contain such organisms.<sup>19</sup>

The improper and unnecessary use of antibiotics are widely practiced athospital setting, may include inadequate dose, unnecessary prolonged surgical prophylaxis.<sup>20,21</sup> This is one of the study from developing country that describes

**Table 5: Diagnostic information with reference to use of antimicrobial in three wards**

Characteristics	Total	Medicine ward	Surgery ward	Gynaecology ward
<b>No. of patients on antimicrobial</b>	94(100)	39(41)	40(43)	15(16)
<b>Body temperature</b>				
Normal	93(99)	39(100)	39(98)	15(100)
Abnormal	1(1)	0(0)	1(2)	0(0)
<b>Urine with high pus cells/WBCs</b>				
Yes	13(14)	8(21)	2(5)	3(20)
No	17(18)	6(15)	3(8)	8(53)
Notdone	64(68)	25(64)	35(88)	4(27)
<b>CBC with high TLC</b>				
Yes	23(24)	13(33)	5(13)	5(33)
No	71(76)	26(67)	35(88)	10(67)
<b>Culture collected at start of antimicrobials</b>				
Positive	4(4)	3(8)	1(3)	0(0)
Negative	7(7)	5(13)	2(5)	0(0)
Notdone	83(88)	31(79)	37(93)	15(100)

Data are represented as n (%). Numbers might not add to 100% because of rounding.

**Table 6: Diagnostic information with reference to use of antimicrobials in three wards according to indications**

	Total	Genito-Urinary infections n=17	Gastrointestinal tract infections n=15	Musculo-skeletal infections n=11	Respiratory tractinfections n=6	Skin/ soft tissue infections n=8	CNS infections n=2	Others Infections n=4	no infections n=31
<b>Body temperature</b>									
Normal	93 (99)	17 (100)	15 (100)	11 (100)	6 (100)	8 (100)	2 (100)	3 (75)	31 (100)
Abnormal	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (25)	0 (0)
<b>Urine with high pus cells/WBCs</b>									
Yes	13 (14)	7 (41)	1 (7)	0 (0)	2 (33)	2 (25)	0 (0)	1 (25)	0 (0)
No	17 (18)	0 (0)	0 (0)	0 (0)	1 (17)	1 (13)	1 (50)	1 (25)	13 (42)
Notdone	64 (68)	10 (59)	14 (93)	11 (100)	3 (50)	5 (63)	1 (50)	2 (50)	18 (58)
<b>CBC with high TLC</b>									
Yes	23 (24)	9 (53)	8 (53)	2 (18)	0 (0)	3 (38)	1 (50)	0 (0)	0 (0)
No	71 (76)	8 (47)	7 (47)	9 (82)	6 (100)	5 (63)	1 (50)	4 (100)	31 (100)
<b>Culture collected at start of antimicrobials</b>									
Positive	4 (4)	3 (18)	0 (0)	0 (0)	0 (0)	1 (13)	0 (0)	0 (0)	0 (0)
Negative	6 (6)	2 (12)	1 (7)	0 (0)	0 (0)	2 (25)	1 (50)	0 (0)	1 (3)
Notdone	83 (88)	12 (71)	14 (93)	11 (100)	6 (100)	5 (63)	1 (50)	4 (100)	30 (97)

Data are represented as n (%). Numbers might not add to 100% because of rounding.

**Table 7: Evidence based and empirical prescriptions**

Therapy	Total	Medical wards	Surgical wards	Gynaecology ward
<b>Total no. of prescriptions</b>	94 (100)	39 (100)	40 (100)	15 (100)
<b>no. of unnecessary use of antibiotics</b>	43 (30)	18 (13)	19 (13)	6 (4)
<b>Empiric prescriptions</b>	83 (89)	31 (79)	37 (93)	15 (100)
<b>no. of unnecessary use of antibiotics</b>	42 (29)	17 (12)	19 (13)	6 (4)
<b>Evidence based prescriptions</b>	11 (12)	8 (21)	3 (8)	0 (0)
<b>no. of unnecessary use of antibiotics</b>	1 (1)	1 (1)	0 (0)	0 (0)

Data are represented as n (%). Numbers might not add to 100% because of rounding.

a trend of antibiotic use in indoor patient at a tertiary care centre and the results are very surprising that 30% of the antimicrobials were used unnecessarily while several studies showed the unnecessary or incorrect use of antimicrobials up to 64%.<sup>6</sup> While 89% of the prescription were prescribed empirically containing 29% unnecessary agents among all antimicrobial prescribed. Studies reported the major reason for an inappropriate use of antimicrobial is unnecessary usage.<sup>22,23</sup>

Furthermore, 88% prescriptions in this study contain antimicrobials without ordering bacteriological culture. It is evident that optimal antimicrobial use is linked with collection of cultures before prescribing the antimicrobial.<sup>24</sup> Another study demonstrated that timely bacteriological results are connected with decrease time to start effective therapy and reduction of 6 days in hospital stay.<sup>25</sup> By implementing this practice, a large number of inappropriate and unnecessary antibiotics could be avoided. In addition

**Table 8: Cost of unnecessary antimicrobial prescribed in Pakistani Rupees (PKR)**

Group of antimicrobial prescribed	Total	Unnecessary use	Cost of drug/day
Third-generation cephalosporin	50	20 (40)	14093
Co-amoxiclav	9	4 (44)	1347
Piperacillin-tazobactam	6	2 (33)	4722
Quinolones	27	7 (26)	6099
Carbapenems	6	2 (33)	4980
Metronidazole	17	6 (35)	1404
Other	13	2 (15)	220
<b>Total</b>	-	43 (30)	32865

Data are represented as n (%).

to this, extra healthcare burden in term of paying the cost of unnecessary antibiotics. According to a report, in Pakistan more than 58.7 million persons are living below the poverty line that means they earn less than 1.25\$ per day.<sup>26</sup> In this situation, extra cost of unnecessary medicine is an additional economic burden on health care system of Pakistan.

Most of European countries have implemented the antimicrobials stewardship program to compete with the unnecessary and overuse of antimicrobials along with the risk reduction with antibiotic overuse including emergence of resistance and toxicity. The tactics utilized by antimicrobial Stewardship Programs commonly include educating the prescriber, formulary optimization that is restricting specific antibiotics, preauthorization to use specific antibiotics, antibiotic use restrictions, prospective audit with intervention and feedback, optimization of dosing and administration, streamlining that is de-escalation of empiric therapy, switching early conversion from parenteral to oral route, sharing the appropriate duration of antibiotic therapy and the use of clinical guidelines to treatment infection with reference to local resistance.<sup>13</sup> Some developing countries have instituted these program.<sup>27,28</sup> and getting benefits from it and now it is recommended to implemented in Pakistan.

## CONCLUSION

It is concluded that most of the unnecessary use as well as to deal with growing problem of emerging resistant strains can be minimized with the initiation of bacteriological culture at the start or as early as possible before the antimicrobial use. In addition, antimicrobial stewardship has efficient strategies to balance the favourable clinical outcomes adverse clinical outcome and antimicrobial

resistance. It will further reduce the financial burden especially in developing countries like Pakistan.

## CONFLICTS OF INTEREST

The authors declare no conflicts of interests.

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## ABBREVIATION USED

<b>CBC:</b>	Complete Blood Count
<b>TLC:</b>	Total Leukocyte Count
<b>WBCs:</b>	White Blood Cells
<b>PKR:</b>	Pakistani Rupees
<b>ESBL:</b>	Extended Spectrum Beta Lactamase
<b>CONSORT:</b>	Consolidated standards of reporting trials
<b>I/V:</b>	Intravenous
<b>ATC:</b>	Anatomical Therapeutic Chemical Classification
<b>MO:</b>	Medical Officer
<b>ID:</b>	Infectious Disease
<b>MED:</b>	Medicine Ward
<b>SGY:</b>	Surgery Ward
<b>GYN:</b>	Gynaecology Ward
<b>CNS:</b>	Central Nervous System
<b>MDROs:</b>	Multi Drug Resistance Organisms



## Highlights of Paper

- A total of 104 persons were recruited consisting of 41% male and 59% female.
- 30% antimicrobials were prescribed unnecessarily without any clinical evidence of infection.
- The most common prescribed antibiotic was ceftriaxone 30%.
- It was 88% of the prescription that were prescribed without ordering the culture test.
- It was found that all unnecessarily prescribed antimicrobials cost 32,865 PKR per day.

## Author Profile



- **Prof Dr Bilal Bin Younis:** FRCP (E), FRCP (LON) Presently working as Medical Director and Professor of Medicine at Shalamar Medical and Dental College, Lahore, Pakistan. He is also the head of Sakina Institute of Diabetes and Endocrine Research (SiDER) at Shalamar Hospital. He has 11 nos. of journal paper; 1 international abstract; more than 40 invited talk national and international and 1 case report. Acting as PI in twelve (12) ongoing projects.
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