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Research Article

Assessing Trends In Use Of Who Watch And Reserve Group Antibiotics: A Longitudinal Drug Utilization Review.

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Abstract

Background: The World Health Organization (WHO) developed the AWaRe tool to encourage the prudent application of antibiotics. Antibiotics are divided into three categories by this tool: Access, Watch, and Reserve group. Data on antibiotic prescriptions made by healthcare practitioners, categorized according to the AWaRe classification, are often challenging to obtain.
Objective: In this research work, we aimed to conduct the drug utilization review of some specific antibiotics from the watch and reserve group and check their compliance with WHO-defined guidelines.
Methods: This Prospective Longitudinal survey on antibiotic consumption was undertaken in Ghurki Trust Teaching Hospital. A total of 200 patients were taken by using a convenient sampling technique during the study period (Oct 2022 to November 2022). After passing the inclusion criteria, data were collected from the patient's medical file. A standardized data collection form was designed to conduct the current study & it includes the patient demographic data, Diagnosis of the patient, main indication of antibiotic use, Antibiotic consumption, total number of Antibiotics prescribed, total number of study drugs, dosage form, frequency, and main indication, date on which antibiotic prescribed & stopped, and compliance to WHO guidelines. SPSS was selected to analyze the data. The findings were displayed in tabular form as frequencies, percentages, means, and standard deviations.
Results: Of the 200 patients that were enrolled in this study, 54 (27%) were women and 146 (73%) were men. Out of 200 patients, majority of the patients were between the ages of 41 and 60 (41.5%), 63 (31.5%) patients had diabetes mellitus, and 103 (51.5%) patients had a previous history of surgery. From the Watch group of Antibiotics, a major number of patients were prescribed Piperacillin+Tazobactam i.e. 45 (22.5%). From the Reserve group of Antibiotics, a major number of patients were prescribed Tab Linezolid i.e. 20 (10%). Most of the antibiotics prescribed were for the infected wounds 69 (34.5%). Among the Watch group of antibiotics, out of 45 patients who were prescribed Piperacillin+Tazobactam, there were 13 prescriptions with rational prescribing while 32 prescriptions had irrational prescribing. Surprisingly Among the Reserve group of antibiotics, all the prescribing was irrational according to the WHO Essential Drug List.
Conclusion: Our findings raise serious concerns and emphasize the necessity of the hospital's improved antimicrobial stewardship and development of antibiotic guidelines. Antibiotics should be used with caution as they will lessen the burden of multi-drug resistance, allowing for better patient care and lowering the associated morbidity and mortality.

Keywords : *Drug Utilization Review, Watch/Reserve Group of Antibiotics, World Health Organization, anti-microbial resistance, Essential Drug List.*

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INTRODUCTION

Drug Utilization Review (DUR) is a systematic approach to assess the appropriate use of drugs. It is also termed as Drug Utilization Evaluation (DUE) or Medication Utilization Evaluation (MUE). It includes different aspects of the consumption of drugs. Firstly, whether a drug is approved for a particular illness or not. Secondly, is this drug recommended for use and is it a preferred choice or not. Thirdly, its dose, regimen, interactions, frequency, and side effects ratio are also evaluated (Chrischilles & Gondek, 1997).

DUR programs examine drug uses and their possible alternatives. These studies are quantitative and include collection, organization, and measurements of medicines. It compares new and old guidelines and also whether the ongoing practice is according to guidelines or not. According to WHO, DUR involves marketing, distribution, prescription, and the use of drugs in a society focusing on the resulting medical, social, and economic aspects (George, Joseph, Sujith, & Mohan, 2018).

Irrational use of drugs is an alarming global problem. International health agencies are working continuously on the rational use of drugs. For this purpose, many educational programs are conducted. It involves various techniques that focus on rationality, effectiveness, and cost of therapy. Hospital formulary & Medication utilization evaluation techniques help to obtain the above-mentioned objectives. A basic DUR program in a hospital comprises planning, Data collection, intervention, and finally evaluation of program. For example, antibiotics are prescription drugs and their wrong use can develop bacterial resistance in population. These studies can help in the appropriate use of antibiotics (Moore, Bykov, Savelli, & Zagorski, 1997).

The evaluation studies are performed on all categories of drugs like anti-epileptics, anti-hypertensive drugs, NSAIDS, antibiotics, anti-diabetics, and many more. Antibacterials are commonly used without appropriate advice. They are taken even in viral infections which increases their irrational use, and ultimately increases their resistance (Hersh, Shapiro, Pavia, & Shah, 2011; Istúriz & Carbon, 2000).

The first list of essential medicines was issued in 1977 by the World Health Organization. It was based on the need and importance of drugs in various countries. The list is updated frequently and covers the latest needs of population across the world (DOC). Up till now, 21 revisions have been made and 21st list was published in 2019 by WHO.

List is comprehensive and contains basic drugs that are required in a hospital. All drugs are arranged according to their therapeutic classes. A complementary list is also added with some drug classes. Prime objective of this updated list is the availability of life-saving drugs across the globe. Safety, efficacy, and cost-effectiveness of medicines are major inclusion criteria (Organization, 2019).

According to the Essential Medicine List, of all the therapeutic classes, antibiotics are an important class of drugs. Over the last decade, a lot of work has been done to curb the irrational use of antibiotics. Presently, it is an alarming issue and experts are working deliberately on it to control resistance against currently available antibiotics. Drug utilization reviews aid in antimicrobial stewardship campaigns and studies (Harbarth & Samore, 2005; Levy, 2005).

The 21st edition of essential drugs classifies antibiotics into three groups according to their spectrum of bacteria coverage in different pathological conditions. The main purpose of this classification is to ensure the optimal use of antibiotics. If the resistance is not controlled properly then the coming years are more challenging in this regard. Different recommendations were given by WHO working panels. They suggested first choice and second choice in different ailments keeping in view efficacy and resistance patterns (Organization, 2017a). Based on this priority option three categories were made namely Access, Watch, and Reserve groups. This grouping will help physicians while prescribing safe and most effective antibacterial agents.

The antibiotics of Access group are generally with narrow range and least adverse effects. This group of antibiotics covers twenty-one various diseases and pathological states. They are required in all healthcare settings with low prices. The first and second choice agents against bacterial infections are 19 in number and are termed as Access group according to Essential Medicine list of 2019 (Organization, 2019). Examples are Amikacin, Co-amoxiclav, Clindamycin, etc.

Some antibiotics have potential adverse effects and are more prone to resistance than Access group antibiotics. They are separately grouped as Watch group by the expert committee of WHO on antibiotics. These are broad-spectrum agents and their recommendation is for severe and complicated infections. These require more drug utilization studies. Some examples are Cefuroxime, Vancomycin, and Meropenem (Organization, 2019).

Reserve group includes highly sensitive antibiotics with targeted and broad spectrum. Some recent antibiotics are also categorized in this group. Regular stewardship programs are required to monitor and limit the use of these antibacterials. These should be used as last option against serious ailments and superbugs. The group includes Colistin, Linezolid, Plazomicin, Fosfomycin, and others (Organization, 2019).

A committee has been constituted by WHO to look into the implementation and repercussions of these groups of antibiotics. All these steps will optimize the use of antibacterials and better outcomes in serious illnesses with minimum adverse effects (Sharland et al., 2018).

We were planning to conduct the DUR of the following

antibiotics of Watch and Reserve group in a tertiary care healthcare setting to analyze their use according to essential medicine list of 2019 guidelines.

Watch group: Ceftriaxone,Ciprofloxacin,Piperacillin+Tazobactam and Meropenem.
Reserve group: Colistin, Fosfomycin, Linezolid.

Numerous studies have been conducted around the globe to assess the prudent use of antibiotics that are in the watch group and reserve group of the WHO essential drug list for 2019. As far as we are aware, no study has been conducted to investigate its compatibility with the WHO list of essential medications. We believe this is the first time this combination has been studied in Pakistan, and we feel the results can inform future antibiotic usage in this country's top tertiary hospital and elsewhere.

MATERIALS AND METHODS

Study Design

This Longitudinal observational study was conducted over a 2-month study period between Oct-2022 to Nov-2022 to observe the Drug utilization pattern of Reserve and Watch group of Specific antibiotics according to WHO Essential Drug List 2019 in a trust hospital, Lahore.

Study Location

This Prospective Longitudinal survey on antibiotic consumption was conducted in Ghurki Trust Teaching Hospital. The hospital is a nonprofit institution in Lahore, Pakistan. The hospital with 600 beds includes all major departments and services and has a specialty in Orthopedics.

Sampling Technique and Sample Size

Convenience sampling technique was used to conduct this study. Data from 200 patients were included in this study.

Inclusion Criteria

All the patients admitted to orthopedic ward, Medical Ward, Surgical ward, and ICU with complete medication records and who were receiving at least one or more antibiotics of study Drugs (Ceftriaxone, Meropenem, Piperacillin+Tazobactam, Ciprofloxacin, Colistin, Linezolid, Fosfomycin) of the hospital were included in the study. Patients were followed from initiation until discontinuation of the study drug.

Exclusion Criteria

This study excluded outpatients, patients admitted to other in-patient departments, and patients whose prescription records contained incomplete or irrelevant information.

Data Collection Form

The current study was conducted using a standardized data collection form that was divided into three primary sections. First part of the Performa included the patient demographic data i.e. Medical Registration No, Age, Gender, Ward, and Length of Hospitalization of patient. Second part of the Performa contained of Main Diagnosis of patient, Co-morbid condition, surgical procedure in Hospital, Main indication for antibiotic use, and treatment targeted according to culture reports. Third part was specified for Antibiotic consumption, total number of Antibiotics prescribed, total number of study drugs, dosage form, frequency, and main indication. This part included detailed information about all Antibiotics prescribed like class, strength, dose, route, dosing interval, date on which antibiotic was prescribed, date of stop of antibiotic, and compliance to WHO guidelines.

Data Collection Procedure

Data was collected on pre-designed Performa from the in-patients receiving study group of antibiotics (Watch Group= Ciprofloxacin, Ceftriaxone, Meropenem, Piperacillin+Tazobactam, Reserve Group= Linezolid, Fosfomycin, and Colistin). Enrolled patients who fulfilled the inclusion criteria were followed from initiation until discontinuation of treatment. Patients' demographics, Co-morbidities, and antibiotics prescribed were retrieved from the patient's files. Rationality of Antibiotics was evaluated according to the WHO Essential Drug List 2019.

Statistical Analysis

Statistical Process for Social Sciences (SPSS) was selected to analyze data obtained after the stated duration. As tabular representations, the results were displayed as frequency, percentages, mean, and standard deviation.

RESULTS

Demographic characteristics of patients

A total of 200 patients were enrolled in this study. Among 200 patients recruited for this study, 146 (73%) were males and 54 (27%) were females. Age of the patients was divided into 4 main categories and most of the patients were from the 41-60 years age group (41.5%). Out of 200 patients, 63 (31.5%) patients had diabetes mellitus. Among 200 patients, 103 (51.5%) patients had a previous history of surgery. Studied patients were taken from different wards and the majority of the patients were from orthopedic department as described in **Table 1**.

Table 1. Demographic characteristics of patients.

Gender	Number	Percentage
Male	146	73%
Female	54	27%
Age Group Division		
Less than 18 years	36	18%
19-40 year	61	30.5%
41-60 year	83	41.5%
61-85 year	20	10%
Ward		
Orthopedic	77	38.5%
Surgical	59	29.5%
ICU	34	17%
Medical	19	9.5%
Paeds	11	5.5%
Surgical Procedure in Hospital		
Yes	137	68.5%
No	63	31.5%
Culture Reports		
Yes	103	51.5%
No	97	48.5%
Co-morbidities		
Diabetes	63	31.5%
Hypertension	41	20.5%
Hepatitis C	7	3.5%
Ischemic Heart Disease	5	2.5%
Hepatitis B	3	1.5%

ICU= Intensive care unit

Antibiotics Prescribing Pattern

Table 2 shows the prescribing pattern of different studied groups of Antibiotics i.e. Watch group and Reserve group. From the Watch group of Antibiotics, a major number of patients were prescribed Piperacillin+Tazobactam i.e. 45 (22.5%). From the Reserve group of Antibiotics, a major number of patients were prescribed Tab Linezolid i.e. 20 (10%). There were a significant number of patients who were managed with Piperacillin +Tazobactam and ceftriaxone. Only a small number of patients were prescribed Fosfomycin and Colistin as described in **Table 2**.

Table 2. Antibiotics Prescribing Pattern.

Watch Group		
Inj Piperacillin+Tazobactam	45	22.5%
Inj Ceftriaxone	41	20.5%
Tab Ciprofloxacin	29	14.5%
Inj Meropenem	21	10.5%
Inj Ciprofloxacin	21	10.5%
Reserve Group		
Tab Linezolid	20	10%
Inj Linezolid	11	5.5%
Sachet Fosfomycin	5	2.5%
Inj Colistin	5	2.5%
Syp Linezolid	2	1%

Inj= Injection, Syp= Syrup, Tab= Tablet

Rationality of Antibiotics According to WHO essential drug list

Table 3 shows the rationality of Antibiotics According to WHO essential drug list. Among Watch group of antibiotics, out of 45 patients who were prescribed with Piperacillin+Tazobactam, there were 13 prescriptions with rational prescribing while 32 prescriptions had irrational prescribing. Out of 41 patients who prescribed Ceftriaxone, there were 32 prescriptions with rational prescribing while 9 prescriptions had irrational prescribing. Out of 29 patients who were prescribed Tab Ciprofloxacin, there were 2 prescriptions with rational prescribing while 27 prescriptions had irrational prescribing. Out of 21 patients who were prescribed Inj Meropenem, there were 12 prescriptions with rational prescribing while 9 prescriptions had irrational prescribing. Out of 21 patients who were prescribed Inj Ciprofloxacin, there were 9 prescriptions with rational prescribing while 12 prescriptions had irrational prescribing.

Surprisingly Among the Reserve group of antibiotics, all the prescribing was irrational according to WHO essential drug List as described in **Table 3**.

Table 3. Rationality of Antibiotics according to WHO essential drug list.

Watch Group	Yes	No
Inj Ceftriaxone	32 (78%)	9 (21%)
Inj Piperacillin+Tazobactam	13 (28%)	32 (71%)
Inj Meropenem	12 (57%)	9 (42%)
Inj Ciprofloxacin	9 (42%)	12 (58%)
Tab Ciprofloxacin	2 (6%)	27 (94%)
Reserve Group	Yes	No
Inj Colistin	0 (0%)	5 (100%)
Sachet Fosfomycin	0 (0%)	5 (100%)
Inj Linezolid	0 (0%)	11 (100%)
Syp Linezolid	0 (0%)	2 (100%)
Tab Linezolid	0 (0%)	20 (100%)

Inj= Injection, Syp= Syrup, Tab= Tablet

Main indication for Antibiotic Prescribing

Table 4 depicts that most of the antibiotics prescribed were for the infected wounds 69 (34.5%), followed by skin infections 40 (20%) and intra-abdominal infections 39 (19.5%). Fewer number of antibiotics were prescribed for other cases such as meningitis 19 (9.5%), respiratory tract infections 11 (5.5%), perianal abscess 10 (5%), enteric fever 8 (4%), urinary tract infections 2 (1%), Deep vein thrombosis (0.5%), & ischemic heart diseases 1 (0.5%).

Table 4. Main indication for Antibiotic Prescribing.

Indication	Number	Percentage
Infected wound	69	34.5%
Skin infection	40	20%
Intra-abdominal infection	39	19.5%
Meningitis	19	9.5%
Respiratory infection	11	5.5%
Perianal abscess	10	5%
Enteric fever	8	4%
UTI	2	1%
DVT	1	0.5%
IHD	1	0.5%

UTI= Urinary Tract Infection, DVT= Deep vein Thrombosis, IHD= Ischemic Heart Disease

DISCUSSION

The appropriate use of antibiotics is the key factor for the cost-effective treatment of infections and controlling the growing burden of anti-microbial resistance. Our study describes an overview of the rational and irrational use of antibiotics within a single healthcare setting. The rationality of the given antibiotics was determined by the WHO guidelines for prescribing antibiotics in essential medical lists (Organization, 2017b).

Among the watch group antibiotics given to the patients, Piperacillin+Tazobactam was the most widely used antibiotic (22.5%) with a high percentage of their irrational use (71%) as compared to its rational use (29%). The watch group antibiotics are those that are at higher risk of being resistant to the microbes but are a high priority for the treatment of most of the infections. Appropriate use of this group is the key factor in the never-ending battle against the developing resistance. Many recent studies also illustrate the increasingly irrational use of Piperacillin+Tazobactam in a tertiary care hospital in Pakistan with an irrationality percentage of more than 35% (Elahi et al.).

Apart from this, ciprofloxacin injection was comparatively less prescribed (14.5%) but was the most irrational usage (94%) among all the prescribed watch group antibiotics with only 6% of its rational usage. Same trend is followed by most of the healthcare settings in Pakistan regarding the usage of ciprofloxacin in Pakistan. Some studies describe the developing pattern of ciprofloxacin resistance in Pakistan and results illustrate that ciprofloxacin was 27% resistant to E. coli, 22% resistant to S .aureus, 17% resistant to S. typhi, 72% resistant to K. pneumoniae and 45% resistant to the P. aeruginosa due to its irrational and inappropriate usage (S. Q. Ali, Zehra, Naqvi, Shah, & Bushra, 2010). In our study, despite being the less prescribed antibiotic among the watch group antibiotics, ciprofloxacin in injection form was among the most irrationally used antibiotics with an irrationality percentage close to 58%. This suggests that irrespective of the dosage form, irrational usage of the ciprofloxacin is high as compared to the other watch group antibiotics.

In our study, ceftriaxone was also one of the most prescribed antibiotics among the watch group. However, many studies conducted in Pakistan reflect the overuse of ceftriaxone especially in medical prophylaxis which could possibly reflect its unnecessary prescription (Saleem et al., 2019). However, its usage was comparatively rational (78%). Meropenem prescription was a borderline case in our study among the watch group antibiotics. Its prescription was rational in 57% of the cases and irrational in 43% of the cases. However, a recent drug utilization review of Meropenem in Pakistan also highlights its high irrationality within tertiary healthcare settings (H. Ali et al., 2018b).

Within the reserve group antibiotics, our study shows that the most prescribed antibiotic was linezolid in tablet form (10%) followed by linezolid in injection form (5.5%), and then linezolid in syrup form (1%). However, when it comes to the rational use of this reserve group antibiotic, our data claims that its use was completely irrational (100%). The most recent studies conducted on the usage and sensitivity of linezolid in Pakistan also depict the developing resistance against that antibiotic due to its completely irrational use (A. Ali, Waseem, & Arif, 2019).

The other reserve group antibiotics follow the same irrationality pattern. Irrespective of their prescription, the usage of Colistin in injection form and Fosfomycin in sachet was completely irrational (100%). The irrational usage of Colistin may lead to the development of the Colistin resistant genes which could be a disastrous situation for the treatment of infectious diseases if the last reserve group of antibiotics starts showing resistance. The presence of Colistin resistant gene in Pakistan after China highlights this possibility of developing resistance to Colistin (Sample, 2017). Many recent studies also show the high development rates of Colistin and Fosfomycin leaving physicians with no other choice as the last group of reserve antibiotics is becoming resistant (Qamar et al., 2017).

Similarly, in our study, all the prescriptions of the reserve group antibiotics were irrational. This puts an image of the possible disaster situation we may have to face in the near future if all the reserve group antibiotics become resistant.

CONCLUSION

In our study, a high prescription of Watch group antibiotics was noted, and Piperacillin/Tazobactam was the most prescribed antibiotic (22.5%) with a high percentage of its irrational use (71%) as compared to its rational use (29%). Within the reserve group of antibiotics, the most prescribed antibiotic was linezolid in oral form. Overall, our study findings demonstrate high adherence to ceftriaxone according to who prescribed guidelines. However, when it comes to the rational use of this reserve group antibiotic, our data claims that its use was completely irrational (100%). These findings raise serious concerns and emphasize the necessity of the hospital's improved antimicrobial stewardship. Antibiotics should be used with caution as they will lessen the burden of multi-drug resistance, allowing for better patient care and lowering the associated morbidity and mortality.

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Ethical Review Committee

Ethical approval was obtained from the Hospital Ethical Review Committee before starting the study. The study was

performed according to hospital ethical standards and data were collected according to defined time duration.

Informed Consent Statement

Not Applicable

Data Availability Statement

The data are available on request from the author.

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Conflicts of Interest

The author declares no conflict of interest.

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