ABSTRACT

Background: A major danger to the health care system is the rise in antibiotic resistance. The aim of current Study is to evaluate the comparison defined daily dose (DDD) and prescribed daily dose (PDD) of macrolide and to evaluate the prescribing pattern of the drug, either it met the standards or not.

Methodology: Quantitative, retrospective study was carried out to measure the use of antibiotics specifically macrolide antibiotics in ENT outdoor department of teaching hospital Punjab, Pakistan. Study research from August 2021 to October 2021, the patient who was reported in OPD of ENT department during study period of 3 month retrospectively.

Results: Total 438 prescriptions were collected and reviewed to evaluate the prescribing pattern of macrolides in outdoor patients of ENT department. Out of 438 prescriptions only in one prescription 10 antibiotics was prescribe (polypharmacy) and in 19(4.3%) prescriptions only one antibiotic is prescribed. Drug prescribed by their generic were 438(100). Encounter with antibiotics 95%. All drug were prescribed from essential drug list (EDL). Azithromycin was the most commonly prescribed drug in ENT department, followed by clarithromycin.

Conclusion: Control bacterial resistance is become challenge to our health care system, major portion of our population is become resistance to majority classes of antibiotic if this practice will continue in future, it became difficult to control or treat infectious diseases. Irrational use of drugs, over prescribing of antibiotics and brand prescribing were observing during the study. Lack of knowledge and non-adherence to the prescribing indicators are the major factors that contribute towards the irrational drug prescribing that ultimately leads towards the antibiotics resistance.

Keywords: Macrolide, Azithromycin, Clarithromycin, Antibiotics resistance.
INTRODUCTION

According to World Health Organization drug utilization evaluation is defined as: An ongoing, systematic, criteria-based program of medicine evaluations that will help ensure appropriate medicine use. If therapy is determined to be inappropriate, interventions with providers or patients will be necessary to optimize pharmaceutical therapy. Antibiotics are discovered serendipitously while Alexander Fleming works on penicillin in 1929. This discovery helps to control major infectious outbreaks and tremendously safe mankind, revolution to health care system. It will be classified on different bases such as mechanism of action, Spectrum of activity and how it’s obtained (natural, semisynthetic, synthetic). Major Classification is cell wall synthesis inhibitors (Penicillins, Carbapenem, cephalosporins), protein synthesis inhibitors (Aminoglycoside’s, Tetra cyclins, Macrolides, Lincosamides), DNA topoisomerase, Folic acid synthesis inhibitors. In this study we primarily focus on the protein synthesis inhibitors subclass Macrolide antibiotics. In order to monitor the appropriate use of various medications, an effective method of Drug Utilization Evaluation (DUE) is used which is part of Pharmacy service provision. In relation to Guidelines or Standards the pattern of drug administration is analyzed by the Drug Utilization Evaluation process (1). All those medicines prescribing patterns will lead to the irrational use that are prescribed not according to indications and not complete duration of antibiotic use. In developing country like Pakistan, Patients are treated on hit and trial bases. Drug utilization as a research area make it possible the study of drug prescribing and its usage. In under developed countries, limited funds are available for health care system and drugs so for efficient or optimal use of our funds it’s really important to prescribe drug rationally. Drug utilization studies help to minimize all these issues, cost effectiveness by eradicated irrational use of medicine in current years DUE has become major tool that help in evaluation studies in medical system (2). In medical practices irrational use of drugs is utmost issue of health care system in both developed and underdeveloped countries. This irrational use of drugs leads to serious consequences such as development of resistance against antibiotics (3). According to World Health Organization WHO half of all drugs or medicines are prescribed medicine incorrectly, patient not administered accurate dose according to the guidelines. This irrational use of drugs leads to inappropriate medication outcomes, increase cost of treatment and increase mortality.
rate irrational use globally reason of economic burden. This problem is arisen due to polypharmacy, inappropriate use of antibiotics. A study which is conducted in India show that in prescription writing brand is mostly promoted this may be another cause of irrational use (4). The scientific use of the word antibiosis first expressed, in 1889, by Vuillemin in the following terms: "one creature destroying the life of another in order to sustain its own one being in unrestricted opposition to the life of the other". The word "antibiotic" means tending to prevent, or destroy life and other dictionaries define the term as "injurious to or destructive to living matter" (5).

According to Waksman, the term antibiotics is defined as: An antibiotic is a chemical substance produced by micro-organisms which has the capacity to inhibit the growth of and even to destroy bacteria and other micro-organisms. Antibiotics have both bacteriostatic and bactericidal effects it can stop the synthesis of cell wall, interrupt the synthesis of proteins by acting on the ribosome subunits and also act on RNA, DNA synthesis. The action of an antibiotic against micro-organisms is selective in nature, some organisms being affected and others not at all or only to a limited degree each antibiotic is thus characterized by a specific antimicrobial spectrum. The selective action of an antibiotic is also manifested against microbial vs. host cells. Antibiotics vary greatly in their physical and chemical properties and in their toxicity to animals (2-7). Because of these characteristics, some antibiotics have remarkable chemotherapeutic potentialities and can be used for the control of various microbial infections in man and in animals (5).

In field of medicine the discovery of antibiotics brought a revolution and become a major part of health care system. In developing countries bacterial infection control by use of antibiotic and decrease death rate due to bacterial infection (6). Antibiotics not only treat bacterial infections but also many major processes become possible by use of antibiotics like open heart surgery, organ transplant But misuse of these effective antibiotic lead to rapid rise in antimicrobial resistance (AMR) In golden age of antibiotics were synthesize by natural sources, every year new multiple classes of antibiotics were discover from natural sources over the time natural sources of antibiotic synthesis is diminish and antibiotics are synthesize in laboratory. In last few decades the bacteria acquire resistance against the antibiotics and this is due to misuse, overuse and underuse of antibiotics. Sub therapeutic doses of antibiotics long term use also major reason of antibiotic resistance which is completely wrong practices (7).
The most important scientific advances in human health is the discovery of antibiotics that open a new door of hope in era where bacterial infection is one of major cause of death but now the irrational use of antibiotics lead to the new resistance patterns that continuously emergence and become a threat to health care system. In 2013, the Centers for Disease Control and Prevention released a report that characterized the burden of antibiotic resistance; an estimated 2 million antibiotic-resistant illnesses and 23 000 deaths occur each year in the United States. (8-10)

They provide defense against microbial infections and cure a wide range of ailments or severe diseases. Antibiotics have both static and cidal effects inhibit the synthesis of protein by acting on the bacterial ribosome and also kill bacteria by acting on bacterial DNA. Antibiotic synthesis and resistance is existing side by side. Resistance is often in such a high degree that antibiotic becomes useless for several purposes for which it is used (11). Exposure of bacteria to sub therapeutic doses lead to develop resistance in bacteria and this resistance is genetic and transfer from one bacteria to other in same environment such as ground water (6) New development in antibiotic world is now in edge. We were lived in a bacterial world so we cannot stay ahead of mutation curve. In order to overcome and eliminate all these wrong practices DUE studies of antibiotics is conducted (12).

In the history of infectious diseases warned that the resistance about antibiotics rises once again and multiple new classes of antibiotics was generated in 1980 and think that infection is control but microbes are adapted in nature and become resistant against all known antibiotics. All natural resources of antibiotics are utilized till 20 century and post antibiotic era will become danger to health care system and become a major threat to human health (6).

Macrolide is belong to one of the most clinically used antibiotics that involve to treat the infections that caused by Gram positive bacteria such as Streptococcus species. Chemically macrolide is show as 14, 15, 16 membered lactone ring along with more than two or more sugar molecules (13). Macrolides are effective class of antibiotics that have wide pharmacological action and bactericidal activity against the streptococci and various anaerobes. Natural synthesize first macrolide is erythromycin, other major macrolides that are semisynthetic or synthetic are azithromycin, telithromycin, clarithromycin and solithromycin.

First row consists of first generation 14 membered ring erythromycin and second generation 14 membered ring clarithromycin and 15 membered ring azithromycin. Second row macrolide containing third generation macrolide such as Ketolides and third row macrolides are 16
membered ring drugs. Mechanism of action of macrolide is mapped by biochemical method and genetic method, which elucidate that macrolide bind to the larger subunit of ribosome which is responsible for all cellular protein synthesis and cause cell growth arrest by inhibiting the protein synthesis.

Erythromycin have bacteriostatic effect it act on 30S and 50S subunits of ribosome and stop the synthesis of amino acids, on 30 S it will act on A subunit and stop acylation and binding to A site while when it act on the 50S peptide bound formation stop and bacterial growth will stop.

Erythromycin was first used clinically, containing 14 membered lactone ring. Majority of antibiotics that prescribe in United States primary care centers are from macrolides class that for pharmacological relief of upper respiratory tract infections. Additionally, most of macrolide class antibiotics are prescribed for bacterial and viral illness such as influenza and rhino-sinusitis that are common diseases of winter season. Antibiotics are prescribed in the winter season. Antibiotics prescribing practice is quite difficult and complex process because its selection is depend upon various factors such as physician attitudes as every doctor as its own way to diagnose, patient sign and symptoms and time pressure s, severity of infection, region of infection and type of microbial and viral agent that cause infection.

It has been reported in various previously studies that macrolides antibiotics are inappropriate prescribe for various infections especially of viral origin and fluctuations in our result is also due to the these inappropriate prescribing practice and this practice is become one of the major reason of antibiotic resistance. Macrolide antibiotics are majorly prescribed in outpatient for various infectious treatment and counseling regarding the use duration and frequency is necessarily such as azithromycin is available in conveniently packaging that is usually prescribe for short duration of time and administered one daily if these protocols are not followed not mention to outdoor patient this will become lead to the antimicrobial resistance (14).

Erythromycin along with antimicrobial activity also provide local and systemic effect such as intestinal motility stimulator. Roxithromycin is new precursor of the erythromycin, have closely related pharmacological action in comparison to the erythromycin which is effective against skin and odontogenic infections (14-15).

Resistance against antibiotics is now globally emerging issues that become a major threat to human health and health care system in upcoming years[in order to maintain harmony to this resistance new development in the every class of antibiotic become necessity of our health
system but this is need high cost and modification in existing molecules and completely synthesize in laboratory to resolve all these issues and resistance we need amendments in the prescribing practice and need to follow or adapt drug utilization guidelines and standards (7). We conduct this study to ensure the rational use of antibiotic and develop those derivatives that minimize resistance and avoid those practices that become the reason of antibiotic resistance especially major classes that prescribe majorly. By conducting drug utilization study of antibiotic, we can minimize the factors that become major reason of antibiotic resistance. This study helps to eradicate the points and wrong practices resulting the proper use of antibiotics (16). Studies that conducted highlight the points that are underlying cause of resistance development in microbes (15).

Drug utilization evaluation play a vital role in interpret and evaluation by using this method we can permute the safe and effective prescription, administration and use of antibiotic. Those parameters will be eradicated and minimize from the health care system that cause irrational use. Inappropriate use of antibiotics and off label not only cause of antimicrobial resistance but also increase cost of medical care. This study describes that irrational use of antibiotic become major threat to health care system in future we stop these prescribing patterns and stick to the indication base treatment and complete duration of treatment so resistance not develope. Pakistan 70% population is resistance to the major classes to antibiotics this lead to very few choices to treat the infections. This study will maintain interventions that will improve patient outcomes. Results of this evaluation study of antibiotic become a source of highlighted points that become reason of irrational use and these wrong practices become will eliminated from health care system and bring optimum therapeutic outcome of respective antibiotic (14, 16)

Ensure that the pharmaceutical therapy is exact according the standard treatment protocol. Identified is there any need of further evaluation of specific medicine use problems Enhance the accountability in controlling the pharmaceutical product cost and medicine use process. Improve wrong prescribing behavior’s that cause medicine related problems. Drug utilization evaluation help to improve prescribing pattern and medicine use process. Enhancing the prevention of resistance among people by prescribing lower possible doses. Ensure that the antibiotics that prescribe are according to the ranges that mention in standard.
METHODOLOGY

Study design and setting
The present study was conducted in a Teaching Hospital of Punjab Lahore. A retrospective study design was adopted to carry out this study research from August 2021 to October 2021, the patient who was reported in OPD of ENT department during study period of 3 month.

Study Objective

General objectives
The utmost objective of this study is to evaluate the safe and effective use and prescribing patterns of macrolides are one of the causes of antibiotic resistance.

Specific objectives
- To ensure the rational use of antibiotics.
- Improve the wrong prescribing behavior that lead to medication problems.
- Extent of drug prescription in selected area.
- Identifying specific medicine use problems that require further evaluation
- Ensure safe and effective use.

Study population
Study was performed in patient of both genders who visited ENT department of hospital during study period who were receiving antibiotics of macrolide class for treatment or cure of the disease.

Inclusion criteria
The study involves all the patient of ENT ward that have respiratory tract infection.

Exclusion criteria
All the pediatric patient (newborn, infants) were excluded from the study.
All the patients were excluded from the study who visited the other departments.

Date collection and instrument
Prescriptions were collected from the ENT department of Social Security Hospital. For comparison in drug utilization amount of drug must be calculated by Defined daily dose DDD. Anatomical therapeutic classification system developed by WHO assign ATC code to different drugs. We calculated number of define daily doses per 1000 person/day for general population
that was included in study. Data that collected from prescription include drug name, dose and frequency. Collected data analyses by statistical tools.

**Data processing and analysis**
Comparison of prescribed daily dose and defined daily dose of macrolide was calculated by using ATC/DDD index 2018. Statistical analysis were calculated by applying student t test that calculate the means of data and give relation between different variables.

**Research Ethics**
The study protocol was approved by research and ethics committee of Chaudhary Muhammad Akram (CMA) teaching and research institute and Social Security Hospital, Lahore under the approval number of CMA/R&E-09-21/33.

**RESULTS**
438 patients in this study who received macrolide during the study period of 3 month. Most of the patients were male. It includes 301 (68.7%) males and 137 (31.2%) females. The percentage of males and females is in the following table 1.

<table>
<thead>
<tr>
<th>Table 1. Demographic description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Female</td>
</tr>
</tbody>
</table>

The utilization of macrolides antibiotics was evaluated by using WHO’s prescribing indicators. The first prescribing indicator was about to check the number of drugs per encounter or to check the number of drugs prescribed with macrolides. Minimum one drug prescribed to 19 (4.3%) patients while maximum ten drugs prescribed to 1 (0.22%) patient. The percentage of the number of drugs from 2-9 are given in the table 1.

<table>
<thead>
<tr>
<th>Table 2. Prescribing indicators:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prescribing indicator</td>
</tr>
<tr>
<td>------------------------</td>
</tr>
<tr>
<td>Number of drugs per encounter</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
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<td></td>
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</tbody>
</table>
The second prescribing indicator was related to check the number of drugs prescribed by generic. All the prescriptions were reviewed to check the number of drugs prescribed by generic and all the drug was prescribed by the generic name (438 prescriptions). The third prescribing indicator was encounter with antibiotics prescribed, during our study probation minimum one antibiotics was prescribed in 420 (95.8%) prescription, two antibiotics were in 18 (4.1%) prescription as given in the table 3.

The fourth prescribing indicator was encounter with the injection. Out of the 438 prescription that we received during our study period were 438 (100%), none of the prescription contained any injection as given in table 3. The last prescribing indicator was about to check the no. of drugs prescribed from the essential drug list. According to our data research/record in 438 prescription all the drugs that prescribed were present in essential drug list WHO-MHP-HPS-EML 2021.

Table 3. Prescribing Indicators

<table>
<thead>
<tr>
<th>Prescribing indicators</th>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drugs prescribed by generic name</td>
<td>438</td>
<td>0</td>
</tr>
<tr>
<td>Encounters with an antibiotic</td>
<td>1 (420)</td>
<td>2 out of 18</td>
</tr>
<tr>
<td>Encounters with an injection</td>
<td>0</td>
<td>438</td>
</tr>
<tr>
<td>Drugs from essential drugs list</td>
<td>438</td>
<td>0</td>
</tr>
</tbody>
</table>

After review all the prescription, we concluded that mostly prescribed anti-biotics from the class of Macrolides are Azithromycin rather than the clarithromycin. The total prescribed azithromycin is 385 out of 438 prescriptions, and clarithromycin is about 53 out of 438 as shown in table 4.
Table 4. Ratio of drug

<table>
<thead>
<tr>
<th>DRUG</th>
<th>COUNT</th>
<th>PERCENTAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azithromycin</td>
<td>385</td>
<td>87.7</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>53</td>
<td>12.1</td>
</tr>
</tbody>
</table>

Azithromycin was prescribed mostly in the Outdoor patient department of ENT. The Frequency of azithromycin is 385 out of 438 prescriptions, the prescribed azithromycin count in male is 265 (68.8%), and in female is 120 (31.1%). Same as, the frequency of clarithromycin is 53 out of 438. Prescribed clarithromycin count in male is 36 (67.9), and in female is 17 (32).

Table 5. Prescribed count in gender

<table>
<thead>
<tr>
<th>Gender</th>
<th>Drug</th>
<th>Count</th>
<th>% within gender</th>
<th>Drug</th>
<th>Count</th>
<th>% within gender</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>MALE</td>
<td>Azithromycin</td>
<td>265</td>
<td>88.0%</td>
<td>Clarithromycin</td>
<td>36</td>
<td>12.0%</td>
<td>301</td>
</tr>
<tr>
<td>FEMALE</td>
<td>Count</td>
<td>120</td>
<td>87.6%</td>
<td>Count</td>
<td>17</td>
<td>12.4%</td>
<td>137</td>
</tr>
<tr>
<td>Total</td>
<td>Count</td>
<td>385</td>
<td>87.9%</td>
<td>Total</td>
<td>53</td>
<td>12.1%</td>
<td>438</td>
</tr>
</tbody>
</table>

The comparison of define daily dose and prescribed daily dose is given in the table 6. The prescribed daily dose was obtained from the prescription while define daily dose was calculated by using WHO collaborating center for drug statistics methodology, ATC/DDD index. Where ATC means anatomical therapeutic classification.

ATC code for clarithromycin is J01FA09 and it define daily dose according to ATC/DDD index was 0.5 g and it was prescribed as 500 mg two times a day. ATC code for azithromycin is J01FA10 and its DDD was 0.3g while it was prescribed as 250mg two times a day as given in table 6.

Table 6. Comparison of DDD & PDD

<table>
<thead>
<tr>
<th>ATC Code</th>
<th>Name</th>
<th>DDD</th>
<th>PDD</th>
<th>Administration route</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>J01FA09</td>
<td>Clarithromycin</td>
<td>0.5</td>
<td>0.5</td>
<td>O</td>
<td>G</td>
</tr>
</tbody>
</table>
DISCUSSION

In the retrospective study, we observed the DUE of macrolides antibiotics. In this study we enrolled total 438 patients and reviewed their prescriptions to evaluate the prescribing patterns and utilization of macrolides among the outpatients. All the antibiotics Macrolides were prescribed by their brand as well as their generic name. It was also seen that the less costly brands were used (simultaneously mother brand and multinational brands also been prescribed).

In our study Azithromycin was the most frequently prescribed macrolides followed by Clarithromycin. Several studies were conducted previously in developing countries shows that 35 to 60% clinical practitioner prescribe antibiotics out of which only less than 20 % were appropriate prescribing (6). Hogerzeil et al., 1993 performed comparative analysis studies in twelve developing countries show that (25-70%) patients was received antibiotics unnecessary during their clinical visit. One of major reason of antibiotic resistance is non-rational use of antibiotics in recent practice it is common to prescribe antibiotics even if it’s not patient need. Such wrong practices become a major reason of antibiotic resistance and it will become threshold to all mankind because development of antibiotic already on its edge (7).

A study conducted in Outpatient Emergency Clinics at Queen Rania Al Abdullah II Children's Hospital, Jordan, 2013 show that out of 4530 prescriptions macrolide class azithromycin is prescribed in 1357 (36%) prescriptions 53.3 % azithromycin is prescribed for upper urinary tract infections while our study show azithromycin is majorly prescribed antibiotic among the macrolide class (15).

A study conducted in the outpatient pediatrics population: analysis of surveys published during 2000–2005 reported that azithromycin is prescribed in 7.8% prescription in Netherlands (1998), 9% in Canada (2000) during their study period (16).

A cross sectional research were conducted in Khartoum states for irrational use of antibiotics included 300 patients out of which 70% were females and 30 % males which reported that 56 percent patient repeat the same antibiotic without symptoms and 34% believe due to the incorrect prescription. Out of 300 patient’s 39 percent patient were taken azithromycin (17).
Antibiotic utilization evaluation is estimated by using variables like Prescribe daily dose (PDD) and define daily dose (DDD) that is usually deviate from the prescribe daily dose when analysis is conducted in groups of patients.

The studies conducted in 130 US hospitals on 59 antimicrobial agents that prescribe in adult that discharge from hospital show that out of 1795504 patients, 1074174 patients prescribed at least one dose of antibiotic (18).

A study conducted by the Pharmacoepidemiology and drug safety on macrolide and cephalosporin class in order to evaluate and check the safety profile of these antibiotics regarding heart diseases result reveals that the macrolide class azithromycin report 375 ADRs and clarithromycin report 302 ADRs (19).

During our study probation minimum one antibiotics was prescribed in 420 prescriptions out of 438 prescription and 18% prescriptions contain 2 antibiotics. According to our data research and record in 438 prescriptions all the drugs that prescribed were present in the Essential drug list 2020 (20).

A study published by World Journal of pharmaceutical that was conducted in tertiary care Hospital surgical department in order to evaluate the use of antibiotics in surgical patients the analyses and evaluation is performed by using two variables number of antibiotics prescribed in preoperative patients and percentage of antibiotics used in postoperative patients, 50.27% male and 49.7% females were involved in study out of which 84.53% patients prescribed antibiotics preoperative state out of which 87.2% antibiotics that prescribed in preoperative patients are cephalosporins and no antibiotics were prescribed from the macrolide class. A study conducted in tertiary care hospital in order to evaluate the drug utilization evaluation of antibiotics that use various prescription indicators such as average number of antibiotics in each prescription, Number of antibiotics that prescribed in injection form, percentage of antibiotics that are from Essential drug list and percentage of antibiotics that are prescribed by their generic names and percentage of drugs that are prescribed by their brands name. While our study also used that prescription indicator for evaluation of use of macrolide antibiotics in outdoor patient of teaching hospital in 438 prescriptions, these prescriptions are evaluated by using various indicators as used in above study. All prescriptions were reviewed to check the number of drugs prescribed by their generic name and all the drugs was prescribed by the generic names 438 prescriptions (21).
CONCLUSION
Above all discussion clearly describe that control bacterial resistance is become challenge to our health care system major portion of our population is become resistance to majority classes of antibiotic if this practice will continue in future, it became difficult to control or treat infectious diseases. The most widely prescribed macrolides recommended were observed to be Azithromycin followed by clarithromycin. We have observed Erythromycin was not being prescribed by the physician in the ENT department of outdoor patients. All the macrolides are prescribed as per the WHO prescribing indicator. We also calculate the DDD/PDD of the drug. Polypharmacy, brand prescribing and over-prescribing of antibiotics are the major thing that ultimately causing resistance against antibiotic.

Authors’ contributions
MN conceptualized and designed the study. AHG and ZA contributed in collecting the data and the arrangement of materials required to complete the project. MQZ and MHA performed the literature survey. SA and JA interpreted the results, edited and formatted article. All the authors have contributed equally and approved the final manuscript.

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DECLARATIONS

Ethics approval
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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