Drug Utilization Evaluation of Levofloxacin at a Secondary Care Center in Hyderabad, India

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ABSTRACT

Drug use evaluation is 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. A DUE can be structured so that it will assess the actual process of administering or dispensing a medicine (i.e., appropriate indications, dose, and medicine interactions) or assess the outcomes. Empirical therapy forms the basis of treatment in India mostly and it is the responsibility of DTC (Drugs and therapeutics committee) to organize a DUE study and adopt suitable protocol for controlling irrational drug use. In our study we have developed a data collection form based upon WHO guidelines for conducting a DUE study on Levofloxacin use evaluation. Ours is a retrospective study conducted from the dates corresponding to 1-8-2015 to 31-7-2016. A total of 62 case records were obtained containing Levofloxacin as one of the drug in the prescription. The gender distribution of case sheets were male- 24, female- 38. Indication wise the distribution of case sheets were - Lower respiratory tract infections = 26, Pulmonary Kochs = 06, Cystitis = 02, Non indicated = 18, Upper respiratory tract infection = 04, Urinary tract infection = 06. The minimum dose administered was 35 mg/day and the maximum dose administered per day was 2000 mg/day. The minimum number of days of treatment was 1 day and the maximum number of days of treatment was 38 days. All patient folders evaluated with regards to UTI, CAP, KOCHS were found to meet the standard criteria appropriate for Levofloxacin use with respect to dose, and dose frequency. However, in the case of dose duration the evaluation was found to be largely inappropriate for all the justified indications. In addition, twenty nine percentage of Levofloxacin use for unjustified indications was noted. This means that Levofloxacin has been deviated from standard treatment guidelines hence it facilitates the development of resistant strains to Levofloxacin and of no use in the near future, and it also effect the patient economically.

Key words: DUE, Levofloxacin, WHO, Secondary care center, Hyderabad.

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INTRODUCTION

Drug use evaluation is 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. A DUE can be structured so that it will assess the actual process of administering or dispensing a medicine (i.e., appropriate indications, dose, medicine interactions) or assess the outcomes. The following eight steps outline the basic information necessary to start and maintain a DUE Program.

Establish Responsibility

Responsibility falls to the DTC or a subcommittee of the DTC that functions only to monitor DUEs In the hospital or clinic. The DTC should undertake this responsibility with considerable interest,

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because this process can solve many medicine use problems, as has proven to be the Case in many countries where this quality assurance function has been fully utilized.

The DTC or a subcommittee must establish procedures that will govern the committee in its activities concerning medicine use review and evaluation. As part of the responsibility of the DUE function, the DTC must establish a plan, outlining which medicines will be a part of the DUE process. This plan needs to be updated and evaluated each year.

Develop Scope of Activities

The DTC should assess and identify medicine use problems and using this information to develop a scope of activity for the DUE program. The scope can be extensive, or it can focus on a single aspect of pharmaceutical therapy. Methods to identify medicine use problems include and ABC or vital, essential, nonessential (VEN) analysis, defined daily dose analysis, ADR reports, medication error reports, antibiotic sensitivity results, procurement studies, hospital and primary care clinic indicator studies, patient complaints or feedback, and staff feedback. These screening mechanisms serve to provide the DTC with information concerning medicine use that would need further evaluation in a DUE.

Establish Criteria, Define and Establish Thresholds

Criteria are statements that define correct medicine use. Establishing criteria is the single most important procedure in a DUE. Criteria for the use of any medicine should be established by the DTC using relevant evidence-based literature sources and recognized international and local experts. The criteria for any DUE should reflect what is in the country's STGs (assuming that they have been developed correctly) and any medicine-use protocols that exist. Credibility of the DUE relies on criteria that are based on evidence-based medicine. Criteria must be developed with and accepted by the medical staff for the process to be credible.

Criteria should be developed for three to five of the most important indicators for each aspect of medicine use. Reviewing larger numbers of indicators will make for a more difficult DUE process and may significantly impair the outcomes of the review. This is not to say that more extensive use of indicators should not be reviewed, only that results are more easily obtained and possibly more meaningful when the scope is narrowed to include only the most important aspects of care.

After developing criteria, the DTC must establish a threshold or standard (benchmark) against which the criteria will be judged. A threshold refers to the percentage of charts or records that will meet or exceed the established criteria for the medicine. Ideally, this threshold will be 100 percent, but realistically, a smaller percentage will be more appropriate to account for exceptions to routine medicine prescribing. Therefore, a threshold of 90 to 95 percent is typically used for many criteria, but each instance must be carefully analyzed before reaching a conclusion.

Collect Data and Organize Results.

DUEs can be accomplished as prospective evaluations, or they can be performed retrospectively. A prospective analysis involves the collection of data as the medicine is being prepared or dispensed to the patient. Retrospective analysis is done using chart reviews or other data sources to review medicine use according to indicators and criteria prepared in advance. The advantage of a prospective review is that the pharmacist (or other reviewer) can intervene at the time the medicine is dispensed to prevent errors in, for example, dosage, indications, or interactions. Retrospective evaluation, which may involve more of the reviewer's time or require access to medical records, is best accomplished when the reviewer has time away from the patient care areas and distractions.

Analyze Data

Data are collected, tabulated, and analyzed to see if criteria and thresholds are met. The following important steps should be completed when analyzing data—

- Tabulate results for each indicator
- Analyze results to see if the criteria are met and the thresholds are not exceeded
- Determine why thresholds are not met
- Analyze data quarterly or more frequently

If a threshold is not met, it may indicate a medicine use problem that requires the attention of the DTC.

Develop Recommendations and Action Plan

After completing the data analysis, information is presented to the DTC and a decision is made as to the appropriateness of the information in the DUE. The DTC also must decide on whether

to continue, discontinue, or expand the functions of the DUE in question. All medicines that do not meet the thresholds must be evaluated carefully and plans must be made to improve the use of the medicine relative to the criteria.

Recommendations should be prepared for the DTC to address the following—

- Inappropriate medicine use
- Unacceptable patient outcomes
- Methods to resolve any medicine use problem

Recommendations should include specific steps to correct any medicine use problem that is evident from performing the DUE. For example, if a specific medicine is being prescribed at a high dose, then the recommendations need to reflect this and how the DTC might improve the dosing of this medicine. Interventions to improve medicine use might include—

- Education, including letters to practitioners, in-service education, workshops, newsletters, and face-to-face discussions
- Implementation of medicine order forms
- Prescribing restrictions
- Formulary manual changes
- Change (or better enforcement) of the STGs.

Conduct DUE Follow-up

Follow-up in every DUE is critical to ensure resolution of any unresolved medicine use problems. The DUE may have identified new problems that need to be resolved within the health care system. If the problems are not resolved, then the DUE will have little usefulness to the health care system. As a part of a follow-up plan, the DTC must assess the need to continue, modify, or stop the DUE activity depending on the results of each specific medicine review.

A DUE should be an ongoing process in which medicine-related problems are regularly addressed. Medicine review should be considered a long-term program, one that is continuously updated and revised to reflect current situations and needs within the health care institution.

All programs within the DTC should be evaluated yearly. This complete evaluation is necessary to look comprehensively at the entire program and analyze its merits and its utility in improving medicine use. Programs that do not have a significant impact on medicine use should be redesigned so that they can provide measurable improvements. Without improvements in medicine use and patient outcomes, the time spent on DUE will be of no value. It must be stressed that indicators and criteria for a DUE can be highly individualized depending on the specific needs of the health care facility.[1,2]

MATERIALS AND METHODS

Study Design: Retrospective Drug Utilization Evaluation Study.

Study Site: A Secondary Care Center at Hyderabad, India.

Study Duration: 4 months.

Source of Data: A Data-collection form was developed based on WHO Guidelines.

Sample Size: 62.

Study Procedure: Since it is a retrospective study, we have collected all the case records from the medical record department from 1-08-2015 to 31-7-2016 that contained Levofloxacin in the prescription. A total of 62 case records were obtained containing Levofloxacin as a drug in the prescription. During the process of evaluation, the prescriptions were analyzed for correct indication, correct dose, frequency, ADRs, Drug-Drug interactions, and contra-indications. The criteria established was adopted from standard treatment guidelines as formulated by FDA. The Threshold was developed by taking into consideration, the prescribing habits (KAP) of the doctors at these centers, the indicators are assigned with a threshold of 90-100%.[3]

Statistical analysis: Descriptive statistical analysis has been carried out in the present study where ever necessary.

RESULTS

A total of 62 case sheets were obtained that contained Levofloxacin as one of the drug in the treatment plan during the course of their stay at hospital. The 62 number of cases were obtained from the following dates : 1-8-15 to 31-7-16. Month wise the number of case sheets that contained Levofloxacin are as follows:

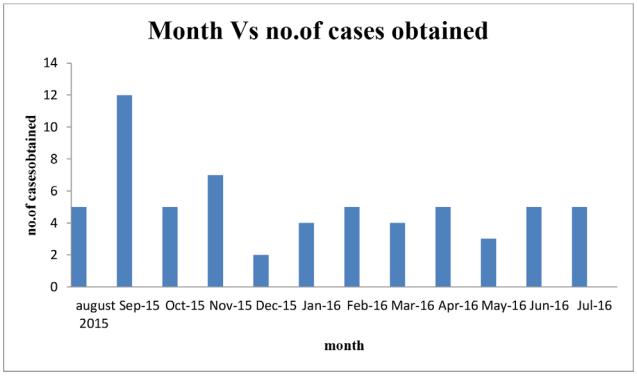

Figure 1: Month wise the number of Levofloxacin cases obtained.

Month	No. of Cases
August/2015	05
September/2015	12
October/2015	05
November/2015	07
December/2015	02
January/2016	04
February/2016	05
March/2016	04
April/2016	05
May/2016	03
June/2016	05
July/2016	05

Age wise the number of case sheets that contained Levofloxacin are as follows:

AGE	NO OF CASES
0-10	01
11-20	05
21-30	10
31-40	03
41-50	06
51-60	08
61-70	09
71-80	06
81-90	05
91-100	03

Gender wise the number of case sheets that contained Levofloxacin are as follows:

Males = 24

Female = 38

Indication wise number of case sheets that contained Levofloxacin are as follows:

Lower respiratory tract infections = 26

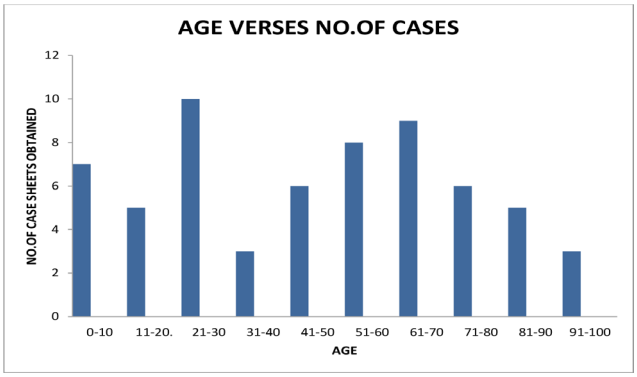

Figure 2: Age wise the number of cases obtained.

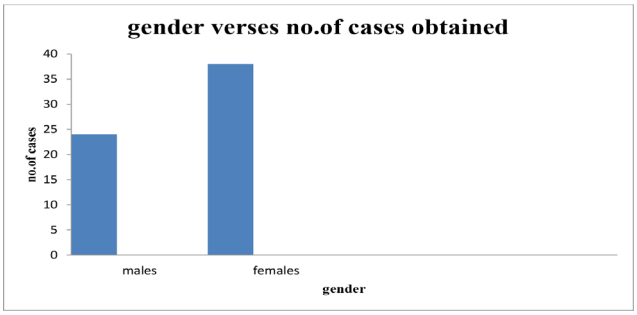

Figure 3: Gender wise the number of cases obtained.

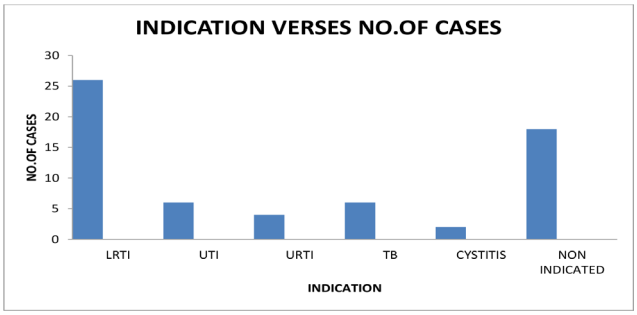

Figure 4: Indication wise the number of cases obtained.

Pulmonary Kochs = 06

Cystitis = 02

Non-indicated = 18

Upper respiratory tract infection = 04

Urinary tract infection = 06

DISCUSSION

Levofloxacin is a fluoroquinolone antibacterial agent with a broad spectrum of activity against Gram-positive and Gram-negative bacteria and atypical respiratory pathogens. Indications are acute bacterial sinusitis (ABS), acute bacterial exacerbations of chronic

Parameters	Sample size(N)	Min.	Max.	Mean	Standard Deviation	Variance	Median
Age	62	0.2500	96.0000	48.3540	±27.5700	760.1023	50.5000
Dose	62	35.0000	2000.0	552.6613	±286.3904	82019.44	500.00
Frequency	62	1.0000	2.0000	1.2903	±0.4576	0.2094	1.0000
Duration of therapy	62	1.0000	38.0000	5.0806	±5.3233	28.3377	4.0000
Interaction with Levofloxacin	62	0	6.000	1.3387	±1.2139	1.4736	1.0000

Table depicting the results of statistical analysis.

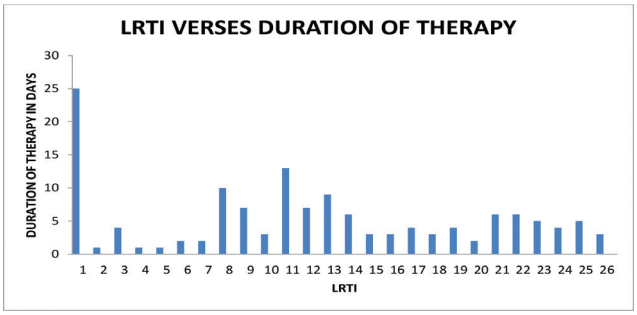

Figure 5: Estimate of duration of therapy in LRTI.

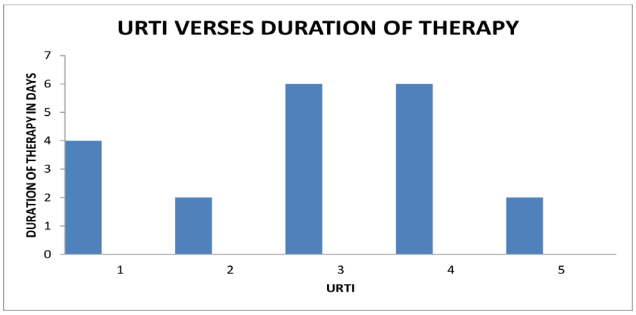

Figure 8: Estimate of duration of therapy in URTI.

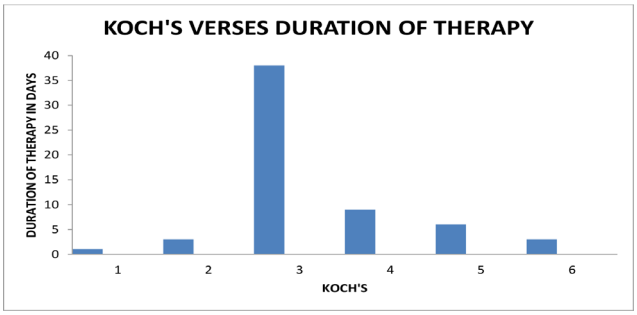

Figure 6: Estimate of duration of therapy in Koch's.

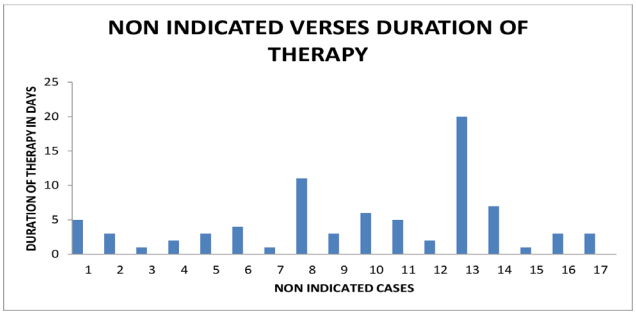

Figure 9: Estimate of duration of therapy in non-indicated cases.

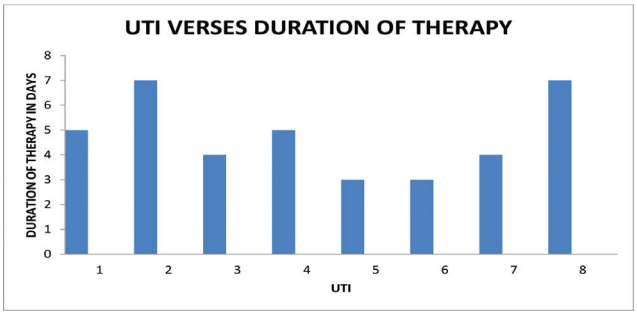

Figure 7: Estimate of duration of therapy in UTI.

bronchitis (ABECB), nosocomial or community-acquired pneumonia (CAP), UTIs, acute pyelonephritis, chronic bacterial prostatitis, skin and skin structure infections and inhalation anthrax.

The development of resistance by microorganisms is of global concern. This is because microorganisms that were susceptible to some anti-infective agents have now become resistant. Unfortunately, irrational prescribing is a global problem. Studies on medicine prescribing in India have concluded that much of it is irrational. Making a prescribing decision is vital in the prevention of morbidity and mortality. The physician's prescribing decision is the result of input from patients, commercial sources, professional colleagues, academic literature, and government regulations. Ineffective use of these sources of information can result in a wide variety of prescribing errors. Medicine utilization review is the most common and structured approach used to examine patterns of medicine use and to determine levels of appropriateness in prescribing. Medicine usage reviews are essential to establish the extent of rational and irrational prescribing and to deliver better healthcare services. Antimicrobials, like any other medicines, may be used inappropriately.

A prescriber may choose an inappropriate type of antimicrobial, taking into account the clinical condition,

resistance patterns and cost. Continuing antimicrobial misuse leads not only to poor patient outcome, unnecessary adverse reactions and wasted resources, but also to emerging resistance of bacteria to antimicrobials. Antimicrobials can also be very expensive, and in most facilities, they constitute a major portion of the drug budget. The phenomenon of resistance is seen not only in bacteria and mycobacteria (multidrug resistant TB, for example), but also in protozoal infections (resistance to chloroquine as an antimalarial) and viral infections (HIV and antiretrovirals).

This study provides the data on the use of Levofloxacin at a secondary care centre in hyderabad. The considered parameters are age, gender, indication, dose, frequency, duration of therapy, contraindications and drug interacting with Levofloxacin.

A total of 62 cases of Levofloxacin use were identified between the period from 1/8/15 - 31/7/16 patient. The distribution of cases on gender basis is 24 males (38.07%) and 38 females (61.3%).

The age range was between 3 months and 94 years. The usage pattern of Lefloxacin among various age groups are as follows: of 0-10(11.3%), 11-20(8.06%), 21-30yrs (16.13%) and 31-40(4.8%), 41-50(9.7%), 51-60(13%), 61-70(14.55%), 71-80(9.7%), 81-90(8.06%) and 91-100(4.8%).

As per STGs, the percentage of Levofloxacin used among 9 paediatric (<18yrs) patients is 14.5% and it has not met the established criteria, and the rest 53 patients (85.4%) met the criteria.

In our study, Levofloxacin usage percentage according to indications are:-

Lower respiratory tract infections(bronchitis, pnuemonitis) is 41.9% (26 cases)

Urinary tract infections are 9.7%9% (05 cases) & Cystitis is 3.25% (02 cases)

Pulmonary koch's is 9.7% (06 cases)

Upper respiratory tract infection is 6.45% (04 cases)

Other indications for which the drug was used unjustifiably to an insignificant level were pregnancy-4.84% (03 cases) and Other cases - 24.2% (15 cases)

Out of 62 cases 44 (71%) has met the established criteria, and the remaining 18 (29.03%) cases have not met the criteria as per STGs.

illness most frequently treated with Levofloxacin is LRTI.

In this research, the criteria of appropriateness of Levofloxacin use at the dose, dose frequency, dose duration were

1. The **dose** of Levofloxacin based on indication and duration given was **500 mg or 750 mg OD.** In all the indications studied, they met the benchmark requirement of 95%. Therefore, Levofloxacin was used appropriately as far as dose was concerned.

2. Out of 62 cases, **dose frequencies** were twelve hours and twenty-four hours in 17 cases (27.41%) and 45 cases (72.58%) respectively.

3. **Dose durations were mostly inappropriate for all the justified indications studied**. According to STGs for **UTI** average duration of therapy is five days, results showed minimum of three days and maximum of seven days were given, on an average the results are appropriately meeting the STGs (100%).

   In case of **upper respiratory tract infections** results showed minimum of two days and maximum of six days given with an average of four days, as per STGs average duration is ten days hence, it deviated from STGs with - 60%.

In our study, six case sheets were diagnoised with **pulmonary koch's** for that Levofloxacin was prescribed for the period of minimum one day and maximum of 38 days which is inappropriate.

As per standards, the duration of therapy with Levofloxacin in koch's is four months hence duration of therapy fails to meet the standards. There would be a lot of carriers in the system and the disease would continue to be transmitted from person to person. Hence, it facilitates the development of resistant strains to Levofloxacin.

Suggestion

A 3 months old baby diagnoised with pulmonary koch's for that Levofloxacin 35mg is prescribed for 38 days which is contraindicated in pediatric patient because it got a severe adverse reaction of inducing osteochondritis thus reducing proliferation of bone, hence other alternative drugs are better option in pediatrics suffering with koch's.

In case of **lower respiratory tract infection (ABS, ABECB, CAP)** the duration of treatment was a minimum of one day and maximum of thirteen days with

an average of seven days, as per STGs average duration of therapy is eleven days hence it fails to meet standards and had deviated from STG by -33%.

Drug interactions

The potential for Levofloxacin interaction with multivalent cations (MVC) was quite minimal as only four cases received prescriptions with MVC 8.8%. If the MVCs are required, then they should be administered not within two hours after or six hours prior to the next Levofloxacin dose. Out of 62 cases (100%), 17 cases (27%) are reported without any potential interaction and 45 cases (72.58%) reported with interaction.

Drugs interacting with Levofloxacin are

Calcium cations – 8.88%(04 cases)
Iron - 4.4%(02 cases)
Aluminium complex – 2.2%(01 case)
Ondansetron-35%(16 cases)
Metronidazole-20%(09 cases)
Anti-diabetic(sulfonylureas)-13.33%(6 cases)
NSAIDS-13.33%(09 cases)
Corticosteroid-11.11%(05 cases)
Insulin-8.88%(04 cases)
Aminoglycosides(azithromycin,clarithromycin)-6.6% (03 cases)
Fluroquinolones(ofloxacin)-2.2%(01 cases).

Drug utilization pattern according to contraindication

As per STGs, Levofloxacin is contraindicated in pregnancy and peadiatrics(<18years).

In our study, out of 62 cases, 14 cases (22.58%) are contraindicated and met the threshold of 100% of which 11(78.5%) and 03(21.4%) cases were peadiatrics and pregnancy respectively.

Outcomes

In case of UTI (8 Cases), The complaints were subsided receiving Levofloxacin (75%) and negative in 2 subjects (25%). Twenty six patients were receiving Levofloxacin for LRTI the outcomes were positive in 22 (84.61. %) subjects and the rest (15.39%) are negative. Six cases of pulmonary koch's treated with Levofloxacin out of which five were (83.33) positive and rest (15.67%). In case of URTI (04 cases), complaints were reduced in 75% (03 cases).

CONCLUSION

All patient folders evaluated with regards to UTI, CAP, KOCHS were found to meet the standard criteria appropriate for Levofloxacin use with respect to dose, and dose frequency.

However, in the case of dose duration the evaluation was found to be largely inappropriate for all the justified indications. In addition**,** twenty-nine percentage of Levofloxacin use for unjustified indications was noted. This means that Levofloxacin has been deviated from standard treatment guidelines hence it facilitates the development of resistant strains to Levofloxacin and of no use in the near future, and it also effect the patient economically.

ACKNOWLEDGEMENT

We would like to express our gratitude to everyone who was instrumental in this study.

CONFLICT OF INTEREST

No conflict of interest is declared.

ABBREVIATIONS USED

ABECB – Acute bacterial exacerbation of chronic bronchitis ; **ABS** – Acute bacterial sinusitis ; **ADR** – Adverse drug reactions ; **CAP** – Community acquired pneumonia ; **COPD** – chronic obstructive pulmonary disease ; **DDD** – Defined daily dose ; **DTC** – Drug therapeutic committee ; **DUE** – Drug utilization evaluation ; **DUR** – Drug utilization Review ; **FDA** – Food drug administration ; **FQs** – Fluroquinolones ; **LRTI** - – Lower respiratory tract infections ; **MDRSP** – Multiple drug resistance streptococcus pneumonia ; **MVC** – Monovalent cations ; **STG** – Standard treatment guidlines ; **TB** - Tuberculosis ; **URTI** – Upper respiratory tract infection ; **UTI** – Urinary Tract Infection ; **VEN** – Vital Essential Non-essential anlaysis ; **WHO** – World health organization

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